ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS
1. NAME OF THE MEDICINAL PRODUCT

REYATAZ 100 mg hard capsules

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains 100 mg of atazanavir (as sulphate)

Excipient: 54.79 mg of lactose per capsule.

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Hard capsule
Opaque blue and white capsule printed with white and blue inks, with "BMS 100 mg" on one half and with "3623" on the other half.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

REYATAZ capsules, co-administered with low dose ritonavir, are indicated for the treatment of HIV-1 infected adults and paediatric patients 6 years of age and older in combination with other antiretroviral medicinal products.

Based on available virological and clinical data from adult patients, no benefit is expected in patients with strains resistant to multiple protease inhibitors (≥ 4 PI mutations). There are very limited data available from children aged 6 to less than 18 years (see sections 4.4 and 5.1).

The choice of REYATAZ in treatment experienced adult and paediatric patients should be based on individual viral resistance testing and the patient’s treatment history (see sections 4.4 and 5.1).

4.2 Posology and method of administration

Therapy should be initiated by a physician experienced in the management of HIV infection.

_Adults:_ the recommended dose of REYATAZ capsules is 300 mg once daily taken with ritonavir 100 mg once daily and with food. Ritonavir is used as a booster of atazanavir pharmacokinetics (see sections 4.5 and 5.1).

_Paediatric patients (6 years to less than 18 years of age):_ The dose of REYATAZ capsules for paediatric patients is based on body weight as shown in Table 1 and should not exceed the recommended adult dose. REYATAZ capsules must be taken with ritonavir and have to be taken with food.
Table 1: Dose for Paediatric Patients (6 years to less than 18 years of age) for REYATAZ capsules with ritonavir

<table>
<thead>
<tr>
<th>Body Weight (kg)</th>
<th>REYATAZ dose</th>
<th>ritonavir dose&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>15 to less than 20</td>
<td>150 mg</td>
<td>100 mg&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>20 to less than 40</td>
<td>200 mg</td>
<td>100 mg</td>
</tr>
<tr>
<td>at least 40</td>
<td>300 mg</td>
<td>100 mg</td>
</tr>
</tbody>
</table>

<sup>a</sup> Ritonavir capsules, tablets or oral solution.

<sup>b</sup> Ritonavir oral solution no lower than 80 mg and not more than 100 mg may be used for paediatric patients from 15 kg to less than 20 kg who cannot swallow ritonavir capsules/tablets.

The available data do not support the use of REYATAZ in combination with low dose ritonavir in paediatric patients weighing less than 15 kg.

*Paediatric patients (less than 6 years of age):* REYAYAZ is not recommended in paediatric patients less than 6 years of age due to insufficient data on pharmacokinetics, safety, and efficacy. REYATAZ has not been studied in children less than 3 months of age and is not recommended especially taking into account the potential risk of kernicterus.

*Patients with renal impairment:* no dosage adjustment is needed. REYATAZ with ritonavir is not recommended in patients undergoing haemodialysis (see sections 4.4 and 5.2).

*Patients with hepatic impairment:* REYATAZ with ritonavir has not been studied in patients with hepatic impairment. REYATAZ with ritonavir should be used with caution in patients with mild hepatic impairment. REYATAZ must not be used in patients with moderate to severe hepatic impairment (see sections 4.3, 4.4, and 5.2).

*Method of administration:* for oral administration. The capsules should be swallowed whole. REYATAZ oral powder is available for adult patients who are unable to swallow capsules (see Summary of Product Characteristics for REYATAZ oral powder). REYATAZ oral powder must not be used in paediatric patients unable to swallow capsules due to insufficient data on pharmacokinetics, safety, and efficacy.

### 4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients (see section 6.1).

Patients with moderate to severe hepatic insufficiency (see sections 4.2 and 4.4).

Combination of rifampicin and REYATAZ with concomitant low-dose ritonavir is contraindicated (see section 4.5).

REYATAZ with ritonavir must not be used in combination with medicinal products that are substrates of the CYP3A4 isoform of cytochrome P450 and have narrow therapeutic windows (e.g., astemizole, terfenadine, cisapride, pimozide, quinidine, bepridil, triazolam, midazolam administered orally (for caution on parenterally administered midazolam, see section 4.5), and ergot alkaloids, particularly, ergotamine, dihydroergotamine, ergonovine, methylergonovine) (see section 4.5).

REYATAZ must not be used in combination with products containing St. John’s wort (*Hypericum perforatum*) (see section 4.5).

### 4.4 Special warnings and precautions for use

Patients should be advised that current antiretroviral therapy has not been proven to prevent the risk of transmission of HIV to others through blood or sexual contact. Appropriate precautions should continue to be employed.
Co-administration of REYATAZ with ritonavir at doses greater than 100 mg once daily has not been clinically evaluated. The use of higher ritonavir doses may alter the safety profile of atazanavir (cardiac effects, hyperbilirubinaemia) and therefore is not recommended. Only when atazanavir with ritonavir is co-administered with efavirenz, a dose increase of ritonavir to 200 mg once daily could be considered. In this instance, close clinical monitoring is warranted (see Interaction with other Medicinal Products below).

Patients with coexisting conditions
Atazanavir is primarily hepatically metabolised and increased plasma concentrations were observed in patients with hepatic impairment (see sections 4.2 and 4.3). The safety and efficacy of REYATAZ has not been established in patients with significant underlying liver disorders. Patients with chronic hepatitis B or C and treated with combination antiretroviral therapy are at an increased risk for severe and potentially fatal hepatic adverse reactions. In case of concomitant antiviral therapy for hepatitis B or C, please refer also to the relevant Summary of Product Characteristics for these medicinal products (see section 4.8).

Patients with pre-existing liver dysfunction, including chronic active hepatitis, have an increased frequency of liver function abnormalities during combination antiretroviral therapy and should be monitored according to standard practice. If there is evidence of worsening liver disease in such patients, interruption or discontinuation of treatment must be considered.

No dosage adjustment is needed in patients with renal impairment. However, REYATAZ with ritonavir is not recommended in patients undergoing haemodialysis (see sections 4.2 and 5.2).

Dose related asymptomatic prolongations in PR interval with REYATAZ have been observed in clinical studies. Caution should be used with medicinal products known to induce PR prolongations. In patients with pre-existing conduction problems (second degree or higher atrioventricular or complex bundle-branch block), REYATAZ should be used with caution and only if the benefits exceed the risk (see section 5.1). Particular caution should be used when prescribing REYATAZ in association with medicinal products which have the potential to increase the QT interval and/or in patients with pre-existing risk factors (bradycardia, long congenital QT, electrolyte imbalances (see sections 4.8 and 5.3).

There have been reports of increased bleeding, including spontaneous skin haematomas and haemarthroses, in type A and B haemophiliac patients treated with protease inhibitors. In some patients additional factor VIII was given. In more than half of the reported cases, treatment with protease inhibitors was continued or reintroduced if treatment had been discontinued. A causal relationship has been suggested, although the mechanism of action has not been elucidated. Haemophiliac patients should therefore be made aware of the possibility of increased bleeding.

Fat redistribution and metabolic disorders
Combination antiretroviral therapy has been associated with the redistribution of body fat (lipodystrophy) in HIV patients. The long-term consequences of these events are currently unknown. Knowledge about the mechanism is incomplete. A connection between visceral lipomatosis and protease inhibitors and lipoatrophy and nucleoside reverse transcriptase inhibitors has been hypothesised. A higher risk of lipodystrophy has been associated with individual factors such as older age, and with drug related factors such as longer duration of antiretroviral treatment and associated metabolic disturbances. Clinical examination should include evaluation for physical signs of fat redistribution.

Combination antiretroviral therapy (CART), including REYATAZ (with or without ritonavir)-based CART, is associated with dyslipidaemia. Consideration should be given to the measurement of fasting serum lipids and blood glucose. Lipid disorders should be managed as clinically appropriate (see section 4.8).

In clinical studies, REYATAZ (with or without ritonavir) has been shown to induce dyslipidaemia to a lesser extent than comparators. The clinical impact of such findings has not been demonstrated in the
absence of specific studies on cardiovascular risk. The selection of antiretroviral therapy must be
guided principally by antiviral efficacy. Consultation with standard guidelines for management of
dyslipidaemia is recommended.

**Hyperglycaemia**
New onset diabetes mellitus, hyperglycaemia, and exacerbation of existing diabetes mellitus have been
reported in patients receiving protease inhibitors. In some of these, the hyperglycaemia was severe and
in some cases also associated with ketoacidosis. Many patients had confounding medical conditions,
some of which required therapy with medicinal products that have been associated with development
of diabetes or hyperglycaemia.

**Hyperbilirubinaemia**
Reversible elevations in indirect (unconjugated) bilirubin related to inhibition of UDP-glucuronosyl
transferase (UGT) have occurred in patients receiving REYATAZ (see section 4.8). Hepatic
transaminase elevations that occur with elevated bilirubin in patients receiving REYATAZ should be
evaluated for alternative etiologies. Alternative antiretroviral therapy to REYATAZ may be
considered if jaundice or scleral icterus is unacceptable to a patient. Dose reduction of atazanavir is not
recommended because it may result in a loss of therapeutic effect and development of resistance.

Indinavir is also associated with indirect (unconjugated) hyperbilirubinaemia due to inhibition of
UGT. Combinations of REYATAZ and indinavir have not been studied and co-administration of these
medicinal products is not recommended (see section 4.5).

**Nephrolithiasis**
Nephrolithiasis has been reported in patients receiving REYATAZ (see section 4.8). If signs or
symptoms of nephrolithiasis occur, temporary interruption or discontinuation of treatment may be
considered.

**Immune reactivation syndrome**
In HIV-infected patients with severe immune deficiency at the time of institution of combination
antiretroviral therapy (CART), an inflammatory reaction to asymptomatic or residual opportunist
pathogens may arise and cause serious clinical conditions, or aggravation of symptoms. Typically,
such reactions have been observed within the first few weeks or months of initiation of CART.
Relevant examples are cytomegalovirus retinitis, generalised and/or focal mycobacterial infections,
and Pneumocystis carinii pneumonia. Any inflammatory symptoms should be evaluated and treatment
instituted when necessary.

**Osteonecrosis**
Although the etiology is considered to be multifactorial (including corticosteroid use, alcohol
consumption, severe immunosuppression, higher body mass index), cases of osteonecrosis have been
reported particularly in patients with advanced HIV-disease and/or long-term exposure to combination
antiretroviral therapy (CART). Patients should be advised to seek medical advice if they experience
joint aches and pain, joint stiffness or difficulty in movement.

**Interactions with other medicinal products**
Co-administration of REYATAZ with simvastatin or lovastatin is not recommended (see section 4.5).

Co-administration of REYATAZ with nevirapine or efavirenz is not recommended (see section 4.5).
If the co-administration of REYATAZ with an NNRTI is required, an increase in the dose of both
REYATAZ and ritonavir to 400 mg and 200 mg, respectively, in combination with efavirenz could be
considered with close clinical monitoring.

Atazanavir is metabolised principally by CYP3A4. Co-administration of REYATAZ with ritonavir
and medicinal products that induce CYP3A4 is not recommended (see sections 4.3 and 4.5).

Co-administration of voriconazole and REYATAZ with ritonavir is not recommended unless an
assessment of the benefit/risk justifies the use of voriconazole (see section 4.5).
Concomitant use of REYATAZ/ritonavir and fluticasone or other glucocorticoids that are metabolized by CYP3A4 is not recommended unless the potential benefit of treatment outweighs the risk of systemic corticosteroid effects, including Cushing's syndrome and adrenal suppression (see section 4.5).

The absorption of atazanavir may be reduced in situations where gastric pH is increased irrespective of cause.

Co-administration of REYATAZ with proton pump inhibitors is not recommended (see section 4.5). If the combination of REYATAZ with a proton pump inhibitor is judged unavoidable, close clinical monitoring is recommended in combination with an increase in the dose of REYATAZ to 400 mg with 100 mg of ritonavir; doses of proton pump inhibitors comparable to omeprazole 20 mg should not be exceeded.

Co-administration of REYATAZ/ritonavir in combination with tenofovir and an H2-receptor antagonist should be avoided (see section 4.5).

Lactose
Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

**Paediatric population**

**Safety:**
Asymptomatic PR interval prolongation was more frequent in paediatric patients than adults. Asymptomatic first- and second-degree AV block was reported in paediatric patients (see section 4.8). Caution should be used with medicinal products known to induce PR prolongations. In paediatric patients with pre-existing conduction problems (second degree or higher atrioventricular or complex bundle-branch block), REYATAZ should be used with caution and only if the benefits exceed the risk. Cardiac monitoring is recommended based on the presence of clinical findings (e.g., bradycardia).

**Efficacy**
Atazanavir/ritonavir is not effective in viral strains harbouring multiple mutations of resistance. While in adults no benefit can be expected in patients with ≥4 PI mutations, in treatment experienced children even lower numbers of PI mutations may be predictive of a lack of benefit (see section 5.1).

**4.5 Interaction with other medicinal products and other forms of interaction**

When REYATAZ and ritonavir are co-administered, the metabolic drug interaction profile for ritonavir may predominate because ritonavir is a more potent CYP3A4 inhibitor than atazanavir. The Summary of Product Characteristics for ritonavir must be consulted before initiation of therapy with REYATAZ and ritonavir.

Atazanavir is metabolised in the liver through CYP3A4. It inhibits CYP3A4. Therefore, REYATAZ with ritonavir is contraindicated with medicinal products that are substrates of CYP3A4 and have a narrow therapeutic index: astemizole, terfenadine, cisapride, pimozide, quinidine, bepridil, triazolam, orally administered midazolam, and ergot alkaloids, particularly ergotamine and dihydroergotamine (see section 4.3).

**Other interactions**
Interactions between atazanavir/ritonavir and protease inhibitors, antiretroviral agents other than protease inhibitors, and other non-antiretroviral medicinal products are listed in the tables below (increase is indicated as “↑”, decrease as “↓”, no change as “↔”, twice daily as “BID” and once daily as “QD”). If available, 90% confidence intervals (CI) are shown in parentheses. The studies presented in Table 2 were conducted in healthy subjects unless otherwise noted. Of importance, many studies were conducted with unboosted atazanavir, which is not the approved regimen of atazanavir.
Table 2: Interactions between REYATAZ and other medicinal products

<table>
<thead>
<tr>
<th>Co-administered medicinal products (dose in mg)</th>
<th>Medicinal product assessed</th>
<th>AUC (90% CI)</th>
<th>Cmax (90% CI)</th>
<th>Cmin (90% CI)</th>
<th>Recommendations concerning co-administration</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ANTI-INFECTIVES</strong></td>
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<tr>
<td>Antiretrovirals</td>
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<tr>
<td><strong>Protease inhibitors:</strong></td>
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</tr>
<tr>
<td>Ritonavir 100 mg QD (atazanavir 300 mg QD)</td>
<td>atazanavir</td>
<td>↑3.50*</td>
<td>↑2.20*</td>
<td>↑8.13*</td>
<td>Ritonavir 100 mg once daily is used as a booster of atazanavir pharmacokinetics.</td>
</tr>
<tr>
<td>studies conducted in HIV-infected patients</td>
<td></td>
<td>(2.44, 5.03)</td>
<td>(1.56, 3.11)</td>
<td>(4.59, 14.39)</td>
<td></td>
</tr>
<tr>
<td>* In a combined analysis, atazanavir 300 mg and ritonavir 100 mg (n=33) was compared to atazanavir 400 mg without ritonavir (n=28). The mechanism of interaction between atazanavir and ritonavir is CYP3A4 inhibition.</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Indinavir</td>
<td>Indinavir is associated with indirect unconjugated hyperbilirubinaemia due to inhibition of UGT.</td>
<td></td>
<td></td>
<td></td>
<td>Co-administration of REYATAZ/ritonavir and indinavir is not recommended (see section 4.4).</td>
</tr>
<tr>
<td><strong>Nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs)</strong></td>
<td></td>
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<tr>
<td>Lamivudine 150 mg BID + didanosine 300 mg BID (atazanavir 400 mg QD)</td>
<td>No significant effect on lamivudine and didanosine concentrations was observed.</td>
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<td></td>
<td></td>
<td>Based on these data and because ritonavir is not expected to have a significant impact on the pharmacokinetics of NRTIs, the co-administration of REYATAZ/ritonavir with these medicinal products is not expected to significantly alter the exposure of the co-administered drugs.</td>
</tr>
<tr>
<td>Abacavir</td>
<td>The co-administration of REYATAZ/ritonavir with abacavir is not expected to significantly alter the exposure of abacavir.</td>
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</tr>
<tr>
<td>Didanosine (buffered tablets) 200 mg/stavudine 40 mg, both single dose (atazanavir 400 mg single dose)</td>
<td>atazanavir, simultaneous administration with ddI+d4T (fasted)</td>
<td>↓0.13*</td>
<td>↓0.11*</td>
<td>↓0.16*</td>
<td>Didanosine should be taken at the fasted state 2 hours after REYATAZ/ritonavir taken with food. The co-administration of REYATAZ/ritonavir with stavudine is not expected to significantly alter the exposure of stavudine.</td>
</tr>
<tr>
<td></td>
<td>atazanavir, dosed 1 hr after ddI+d4T (fasted)</td>
<td>↔1.03*</td>
<td>↑1.12*</td>
<td>↔1.03*</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>(0.64, 1.67)</td>
<td>(0.67, 1.98)</td>
<td>(0.61, 1.73)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Atazanavir concentrations were greatly decreased when co-administered with didanosine (buffered tablets) and stavudine. The mechanism of interaction is a reduced solubility of atazanavir with increasing pH related to the presence of anti-acid agent in didanosine buffered tablets. No significant effect on didanosine and stavudine concentrations was observed.</td>
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<td></td>
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<td></td>
</tr>
<tr>
<td>Didanosine (enteric coated capsules) 400 mg single dose (atazanavir 300 mg QD with ritonavir 100 mg QD)</td>
<td>Didanosine (with food)</td>
<td>↓0.66*</td>
<td>↓0.62*</td>
<td>↑1.25*</td>
<td>No significant effect on atazanavir concentrations was observed when administered with enteric-coated didanosine, but administration with food decreased didanosine concentrations.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(0.59, 0.73)</td>
<td>(0.52, 0.74)</td>
<td>(0.92, 1.69)</td>
<td></td>
</tr>
<tr>
<td>Tenofovir disoproxil fumarate 300 mg QD (atazanavir 300 mg QD with ritonavir 100 mg QD) studies conducted in HIV-infected patients</td>
<td>atazanavir</td>
<td>↓0.78*</td>
<td>↓0.84*</td>
<td>↓0.77*</td>
<td>* In a combined analysis from several clinical studies, atazanavir/ritonavir 300/100 mg co-administered with tenofovir</td>
</tr>
</tbody>
</table>
Co-administered medicinal products (dose in mg) | Medicinal product assessed (mg) | AUC (90% CI) | C<sub>max</sub> (90% CI) | C<sub>min</sub> (90% CI) | Recommendations concerning co-administration
---|---|---|---|---|---
disoproxil fumarate 300 mg (n=39) was compared to atazanavir/ritonavir 300/100 mg (n=33). The efficacy of REYATAZ/ritonavir in combination with tenofovir in treatment-experienced patients has been demonstrated in clinical study 045 and in treatment naive patients in clinical study 138 (see sections 4.8 and 5.1). The mechanism of interaction between atazanavir and tenofovir is unknown.

Tenofovir disoproxil fumarate 300 mg QD (atazanavir 300 mg QD with ritonavir 100 mg QD) was assessed. The results are as follows:

<table>
<thead>
<tr>
<th>Medicinal product assessed</th>
<th>AUC (90% CI)</th>
<th>C&lt;sub&gt;max&lt;/sub&gt; (90% CI)</th>
<th>C&lt;sub&gt;min&lt;/sub&gt; (90% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>tenofovir disoproxil fumarate</td>
<td>↑1.37 (1.30, 1.45)</td>
<td>↑1.34 (1.20, 1.51)</td>
<td>↑1.29 (1.21, 1.36)</td>
</tr>
</tbody>
</table>

Patients should be closely monitored for tenofovir-associated adverse events, including renal disorders.

Non-nucleoside reverse transcriptase inhibitors (NNRTIs)

<table>
<thead>
<tr>
<th>Non-nucleoside reverse transcriptase inhibitors (NNRTIs)</th>
<th>Atazanavir (pm):</th>
<th>Recommendations concerning co-administration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Efavirenz 600 mg QD (atazanavir 400 mg QD with ritonavir 100 mg QD)</td>
<td>all administered with food</td>
<td>↔1.00* (0.91, 1.10)</td>
</tr>
<tr>
<td>Efavirenz 600 mg QD (atazanavir 400 mg QD with ritonavir 200 mg QD)</td>
<td>all administered with food</td>
<td>↔1.06%/** (0.90, 1.26)</td>
</tr>
<tr>
<td>Nevirapine 200 mg BID (atazanavir 400 mg QD with ritonavir 100 mg QD) study conducted in HIV infected patients</td>
<td>nevirapine</td>
<td>↑1.26 (1.17, 1.36)</td>
</tr>
<tr>
<td>Nevirapine 200 mg BID (atazanavir 400 mg QD with ritonavir 100 mg QD) study conducted in HIV infected patients</td>
<td>atazanavir</td>
<td>↑1.50 (1.11, 1.32)</td>
</tr>
</tbody>
</table>

Efavirenz, like other NNRTIs, is a potent inhibitor as well as a substrate of CYP3A4. Based on data obtained with other boosted PIs and ketoconazole, where ketoconazole AUC showed a 3-fold increase, REYATAZ/ritonavir is expected to increase efavirenz concentrations. Co-administration of efavirenz with REYATAZ/ritonavir is not recommended (see section 4.4).

Antibiotics

<table>
<thead>
<tr>
<th>Antibiotics</th>
<th>Atazanavir (pm):</th>
<th>Recommendations concerning co-administration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clarithromycin 500 mg BID (atazanavir 400 mg QD)</td>
<td>clarithromycin</td>
<td>↑1.94 (1.75, 2.16)</td>
</tr>
<tr>
<td>Clarithromycin 500 mg BID (atazanavir 400 mg QD)</td>
<td>14-OH clarithromycin</td>
<td>↓0.30 (0.26, 0.34)</td>
</tr>
<tr>
<td>Clarithromycin 500 mg BID (atazanavir 400 mg QD)</td>
<td>atazanavir</td>
<td>↑1.28 (1.16, 1.43)</td>
</tr>
</tbody>
</table>

A dose reduction of clarithromycin may result in subtherapeutic concentrations of 14-OH clarithromycin. The mechanism of the clarithromycin/atazanavir interaction is CYP3A4 inhibition. No recommendation regarding dose reduction can be made; therefore, caution should be exercised if REYATAZ/ritonavir is co-administered with clarithromycin.

Antifungals

<table>
<thead>
<tr>
<th>Antifungals</th>
<th>Recommendations concerning co-administration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ketoconazole 200 mg QD (atazanavir 400 mg QD)</td>
<td>No significant effect on atazanavir concentrations was observed. Ketoconazole and itraconazole should be used cautiously with REYATAZ/ritonavir. High doses of ketoconazole and itraconazole (&gt;200 mg/day) are not recommended.</td>
</tr>
<tr>
<td>Itraconazole</td>
<td>Itraconazole, like ketoconazole, is a potent inhibitor as well as a substrate of CYP3A4. Based on data obtained with other boosted PIs and ketoconazole, where ketoconazole AUC showed a 3-fold increase, REYATAZ/ritonavir is expected to increase ketoconazole or itraconazole concentrations. Co-administration of REVATAZ/ritonavir and voriconazole has not been studied. Co-administration of voriconazole and REYATAZ/ritonavir is not recommended unless an assessment of the benefit/risk to...</td>
</tr>
</tbody>
</table>

Voriconazole | Co-administration of REVATAZ/ritonavir and voriconazole has not been studied. Co-administration of voriconazole and REYATAZ/ritonavir is not recommended unless an assessment of the benefit/risk to... |
<table>
<thead>
<tr>
<th>Co-administered medicinal products (dose in mg)</th>
<th>Medicinal product assessed</th>
<th>AUC (90% CI)</th>
<th>C&lt;sub&gt;max&lt;/sub&gt; (90% CI)</th>
<th>C&lt;sub&gt;min&lt;/sub&gt; (90% CI)</th>
<th>Recommendations concerning co-administration</th>
</tr>
</thead>
<tbody>
<tr>
<td>(90% CI) by an average of 24% (19% to 36%) and 39% (22% to 52%), respectively. Administration of voriconazole resulted in a minor decrease in steady state C&lt;sub&gt;max&lt;/sub&gt; and AUC of ritonavir (90% CI) with an average of 24% (16% to 39%) and 14% (26% to 1%), respectively. the patient justifies the use of voriconazole (see section 4.4). Patients should be carefully monitored for adverse events and/or loss of efficacy during the co-administration of voriconazole and REYATAZ/ritonavir.</td>
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<tr>
<td>Fluconazole 200 mg QD (atazanavir 300 mg and ritonavir 100 mg QD)</td>
<td>Atazanavir and fluconazole concentrations were not significantly modified when REYATAZ/ritonavir was co-administered with fluconazole.</td>
<td>No dosage adjustments are needed for REYATAZ/ritonavir and fluconazole.</td>
<td></td>
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<tr>
<td>Antimycobacterial</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Rifabutin 150 mg twice weekly (atazanavir 300 mg and ritonavir 100 mg QD)</td>
<td>rifabutin</td>
<td>↑1.48 **</td>
<td>↑2.49 **</td>
<td>↑1.40 **</td>
<td>When given with REYATAZ/ritonavir, the recommended dose of rifabutin is 150 mg 3 times per week on set days (for example Monday-Wednesday-Friday). Increased monitoring for rifabutin-associated adverse reactions including neutropenia and uveitis is warranted due to an expected increase in exposure to rifabutin. Further dosage reduction of rifabutin to 150 mg twice weekly on set days is recommended for patients in whom the 150 mg dose 3 times per week is not tolerated. It should be kept in mind that the twice weekly dosage of 150 mg may not provide an optimal exposure to rifabutin thus leading to a risk of rifamycin resistance and a treatment failure. No dose adjustment is needed for REYATAZ/ritonavir.</td>
</tr>
<tr>
<td>25-O-desacetyl-rifabutin</td>
<td>25-O-desacetyl-rifabutin</td>
<td>↑10.90 **</td>
<td>↑7.77 **</td>
<td>↑11.45 **</td>
<td>** When compared to rifabutin 150 mg QD alone. Total rifabutin and 25-O-desacetyl-rifabutin AUC: ↑2.19 (1.78, 2.69). In previous studies, the pharmacokinetics of atazanavir was not altered by rifabutin.</td>
</tr>
<tr>
<td>Rifampicin</td>
<td>Rifampicin is a strong CYP3A4 inducer and has been shown to cause a 72% decrease in atazanavir AUC which can result in virological failure and resistance development. During attempts to overcome the decreased exposure by increasing the dose of REYATAZ or other protease inhibitors with ritonavir, a high frequency of liver reactions was seen.</td>
<td>The combination of rifampicin and REYATAZ with concomitant low-dose ritonavir is contraindicated (see section 4.3).</td>
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</tr>
<tr>
<td>ACID REDUCING AGENTS</td>
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<td></td>
</tr>
<tr>
<td>H&lt;sub&gt;2&lt;/sub&gt;-Receptor antagonists</td>
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<td></td>
</tr>
<tr>
<td>Without Tenofovir</td>
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</tr>
<tr>
<td>In HIV-infected patients with atazanavir/ritonavir at the recommended dose 300/100 mg QD</td>
<td>atazanavir</td>
<td>↓0.82 (0.75, 1.01)</td>
<td>↓0.80 (0.68, 0.93)</td>
<td>↔0.99 (0.84, 1.18)</td>
<td>For patients not taking tenofovir, if REYATAZ 300 mg/ritonavir 100 mg and H&lt;sub&gt;2&lt;/sub&gt;-receptor antagonist</td>
</tr>
<tr>
<td>- famotidine 20 mg BID</td>
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<td></td>
</tr>
</tbody>
</table>

**Tenofovir**
<table>
<thead>
<tr>
<th>Co-administered medicinal products (dose in mg)</th>
<th>Medicinal product assessed</th>
<th>AUC (90% CI)</th>
<th>C\textsubscript{max} (90% CI)</th>
<th>C\textsubscript{min} (90% CI)</th>
<th>Recommendations concerning co-administration</th>
</tr>
</thead>
<tbody>
<tr>
<td>- famotidine 40 mg BID</td>
<td>atazanavir</td>
<td>↓ 0.77</td>
<td>↓ 0.77</td>
<td>↓ 0.80</td>
<td>antagonists are co-administered, a dose equivalent to famotidine 20 mg BID should not be exceeded. If a higher dose of an H\textsubscript{2}-receptor antagonist is required (eg, famotidine 40 mg BID or equivalent) an increase of the REYATAZ/ritonavir dose from 300/100 mg to 400/100 mg can be considered.</td>
</tr>
</tbody>
</table>

In Healthy volunteers with atazanavir/ritonavir at an increased dose of 400/100 mg QD

- famotidine 40 mg BID atazanavir ↓ 0.77 (0.68, 0.86) ↓ 0.77 (0.67, 0.88) ↓ 0.80 (0.69, 0.92)       |

With Tenofovir 300 mg QD

In HIV-infected patients with atazanavir/ritonavir at the recommended dose of 300/100 mg QD

- famotidine 20 mg BID atazanavir ↓ 0.79* (0.66, 0.96) ↓ 0.79* (0.64, 0.96) ↓ 0.81* (0.63, 1.05)       |
- famotidine 40 mg BID atazanavir ↓ 0.76* (0.64, 0.89) ↓ 0.77* (0.64, 0.92) ↓ 0.75* (0.53, 1.07)       |

* When compared to atazanavir 300 mg QD with ritonavir 100 mg QD and tenofovir disoproxil fumarate 300 mg all as a single dose with food. When compared to atazanavir 300 mg with ritonavir 100 mg without tenofovir, atazanavir concentrations are expected to be additionally decreased by about 20%. The mechanism of interaction is decreased solubility of atazanavir as intra-gastric pH increases with H\textsubscript{2} blockers.

Proton pump inhibitors

<table>
<thead>
<tr>
<th>Medicinal product assessed</th>
<th>AUC (90% CI)</th>
<th>C\textsubscript{max} (90% CI)</th>
<th>C\textsubscript{min} (90% CI)</th>
<th>Recommendations concerning co-administration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Omeprazole 40 mg QD (atazanavir 400 mg QD with ritonavir 100 mg QD) atazanavir (am): 2 hr after omeprazole</td>
<td>↓ 0.39</td>
<td>↓ 0.44</td>
<td>↓ 0.35</td>
<td>Co-administration of REYATAZ/ritonavir with proton pump inhibitors is not recommended. If the combination of REYATAZ/ritonavir with a proton pump inhibitor is judged unavoidable, close clinical monitoring is recommended in combination with an increase in the dose of REYATAZ to 400 mg with 100 mg of ritonavir; doses of proton pump inhibitors comparable to omeprazole 20 mg should not be exceeded (see section 4.4).</td>
</tr>
<tr>
<td>Omeprazole 20 mg QD (atazanavir 400 mg QD with ritonavir 100 mg QD) atazanavir (am): 1 hr after omeprazole</td>
<td>↓ 0.70*</td>
<td>↓ 0.69*</td>
<td>↓ 0.69*</td>
<td>The decrease in AUC, C\textsubscript{max}, and C\textsubscript{min} was not mitigated when an increased dose of REYATAZ/ritonavir (400/100 mg once daily) was temporally separated from omeprazole by 12 hours. Although not studied, similar results are expected with other proton pump inhibitors. This decrease in atazanavir exposure might negatively impact the efficacy of atazanavir. The mechanism of interaction is decreased solubility of atazanavir as intra-gastric pH increases with proton pump inhibitors.</td>
</tr>
</tbody>
</table>

* When compared to atazanavir 300 mg QD with ritonavir 100 mg QD

Antacids

<table>
<thead>
<tr>
<th>Medicinal product assessed</th>
<th>AUC (90% CI)</th>
<th>C\textsubscript{max} (90% CI)</th>
<th>C\textsubscript{min} (90% CI)</th>
<th>Recommendations concerning co-administration</th>
</tr>
</thead>
</table>
| Antacids and medicinal products containing buffers | Reduced plasma concentrations of atazanavir may be the consequence of increased gastric pH if antacids, including buffered medicinal products, are administered with REYATAZ/ritonavir. | REYATAZ/ritonavir should be administered 2 hours before or 1 hour after antacids or
<table>
<thead>
<tr>
<th>Co-administered medicinal products (dose in mg)</th>
<th>Medicinal product assessed</th>
<th>AUC (90% CI)</th>
<th>C_{max} (90% CI)</th>
<th>C_{min} (90% CI)</th>
<th>Recommendations concerning co-administration</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ANTICOAGULANTS</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>buffered medicinal products.</td>
</tr>
<tr>
<td>Warfarin</td>
<td>Co-administration with REYATAZ/ritonavir has the potential to produce a decrease or, less often, an increase in INR (International Normalised Ratio).</td>
<td></td>
<td></td>
<td></td>
<td>It is recommended that the INR be monitored carefully during treatment with REYATAZ/ritonavir, especially when commencing therapy.</td>
</tr>
<tr>
<td><strong>ANTINEOPLASTICS AND IMMUNOSUPPRESSANTS</strong></td>
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<tr>
<td><strong>Antineoplastics</strong></td>
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<tr>
<td>Irinotecan</td>
<td>Atazanavir inhibits UGT and may interfere with the metabolism of irinotecan, resulting in increased irinotecan toxicities.</td>
<td></td>
<td></td>
<td></td>
<td>If REYATAZ/ritonavir is co-administered with irinotecan, patients should be closely monitored for adverse events related to irinotecan.</td>
</tr>
<tr>
<td><strong>Immunosuppressants</strong></td>
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<tr>
<td>Cyclosporin</td>
<td>Concentrations of these immunosuppressants may be increased when co-administered with REYATAZ/ritonavir due to CYP3A4 inhibition.</td>
<td></td>
<td></td>
<td></td>
<td>More frequent therapeutic concentration monitoring of these medicinal products is recommended until plasma levels have been stabilised.</td>
</tr>
<tr>
<td>Tacrolimus</td>
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<tr>
<td>Sirolimus</td>
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</tr>
<tr>
<td><strong>CARDIOVASCULAR AGENTS</strong></td>
<td></td>
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</tr>
<tr>
<td><strong>Antiarrhythmics</strong></td>
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<tr>
<td>Amiodarone</td>
<td>Concentrations of these antiarrhythmics may be increased when co-administered with REYATAZ/ritonavir. The mechanism of amiodarone or systemic lidocaine/atazanavir interaction is CYP3A inhibition. Quinidine has a narrow therapeutic window and is contraindicated due to potential inhibition of CYP3A by REYATAZ/ritonavir.</td>
<td></td>
<td></td>
<td></td>
<td>Caution is warranted and therapeutic concentration monitoring is recommended when available. The concomitant use of quinidine is contraindicated (see section 4.3).</td>
</tr>
<tr>
<td>Systemic lidocaine, Quinidine</td>
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<tr>
<td><strong>Calcium channel blockers</strong></td>
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<tr>
<td>Bepridil</td>
<td>REYATAZ/ritonavir should not be used in combination with medicinal products that are substrates of CYP3A4 and have a narrow therapeutic index.</td>
<td></td>
<td></td>
<td></td>
<td>Co-administration with bepridil is contraindicated (see section 4.3).</td>
</tr>
<tr>
<td>Diltiazem 180 mg QD (atazanavir 400 mg QD)</td>
<td>diltiazem: ↑2.25 (2.09, 2.41)</td>
<td>↑1.98 (1.78, 2.19)</td>
<td>↑2.42 (2.14, 2.73)</td>
<td></td>
<td>An initial dose reduction of diltiazem by 50% is recommended, with subsequent titration as needed and ECG monitoring.</td>
</tr>
<tr>
<td></td>
<td>desacetyl-diltiazem: ↑2.65 (2.45, 2.87)</td>
<td>↑2.72 (2.44, 3.03)</td>
<td>↑2.21 (2.02, 2.42)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>No significant effect on atazanavir concentrations was observed. There was an increase in the maximum PR interval compared to atazanavir alone. Co-administration of diltiazem and REYATAZ/ritonavir has not been studied. The mechanism of diltiazem/atazanavir interaction is CYP3A4 inhibition.</td>
<td></td>
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</tr>
<tr>
<td>Verapamil</td>
<td>Serum concentrations of verapamil may be increased by REYATAZ/ritonavir due to CYP3A4 inhibition.</td>
<td></td>
<td></td>
<td></td>
<td>Caution should be exercised when verapamil is co-administered with REYATAZ/ritonavir.</td>
</tr>
<tr>
<td><strong>CORTICOSTEROIDS</strong></td>
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<tr>
<td>Fluticasone propionate intranasal 50 µg 4 times daily for 7 days (ritonavir 100 mg capsules BID)</td>
<td>The fluticasone propionate plasma levels increased significantly, whereas the intrinsic cortisol levels decreased by approximately 86% (90% confidence interval 82-89%). Greater effects may be expected when fluticasone propionate is inhaled. Systemic corticosteroid effects</td>
<td></td>
<td></td>
<td></td>
<td>Co-administration of REYATAZ/ritonavir and these glucocorticoids is not recommended.</td>
</tr>
</tbody>
</table>
including Cushing’s syndrome and adrenal suppression have been reported in patients receiving ritonavir and inhaled or intranasally administered fluticasone propionate; this could also occur with other corticosteroids metabolized via the P450 3A pathway, e.g., budesonide. The effects of high fluticasone systemic exposure on ritonavir plasma levels are yet unknown. The mechanism of interaction is CYP3A4 inhibition.

**Recommended** unless the potential benefit of treatment outweighs the risk of systemic corticosteroid effects (see section 4.4). A dose reduction of the glucocorticoid should be considered with close monitoring of local and systemic effects or a switch to a glucocorticoid, which is not a substrate for CYP3A4 (e.g., beclomethasone). Moreover, in case of withdrawal of glucocorticoids, progressive dose reduction may have to be performed over a longer period.

**ERECTILE DYSFUNCTION**

**PDE5 Inhibitors**

<table>
<thead>
<tr>
<th>Co-administered medicinal products (dose in mg)</th>
<th>Medicinal product assessed</th>
<th>AUC (90% CI)</th>
<th>Cmax (90% CI)</th>
<th>Cmin (90% CI)</th>
<th>Recommendations concerning co-administration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sildenafil with REYATAZ/ritonavir</td>
<td>Sildenafil</td>
<td>↓0.81 (0.75, 0.87)</td>
<td>↓0.84 (0.74, 0.95)</td>
<td>↓0.63 (0.55, 0.71)</td>
<td>Patients should be warned about these possible side effects.</td>
</tr>
<tr>
<td>St. John's wort (Hypericum perforatum)</td>
<td>St. John's wort with REYATAZ/ritonavir</td>
<td>↓1.85 (1.67, 2.05)</td>
<td>↓1.68 (1.51, 1.88)</td>
<td>↓2.02 (1.77, 2.31)</td>
<td>Co-administration of REYATAZ/ritonavir with products containing St. John's wort is contraindicated.</td>
</tr>
</tbody>
</table>

**HERBAL PRODUCTS**

Concomitant use of St. John's wort with REYATAZ/ritonavir may be expected to result in significant reduction in plasma levels of atazanavir. This effect may be due to an induction of CYP3A4. There is a risk of loss of therapeutic effect and development of resistance (see section 4.3).

**HORMONAL CONTRACEPTIVES**

<p>| Ethinyloestradiol 25 μg + norgestimate (atazanavir 300 mg QD with ritonavir 100 mg QD) | Ethinyloestradiol | ↓0.81 (0.77, 0.87) | ↓0.84 (0.74, 0.95) | ↓0.63 (0.55, 0.71) | If an oral contraceptive is administered with REYATAZ/ritonavir, it is recommended that the oral contraceptive contain at least 30 μg of ethinyloestradiol and that the patient be reminded of strict compliance with this contraceptive dosing regimen. Co-administration of REYATAZ/ritonavir with other hormonal contraceptives or oral contraceptives containing progestogens other than norgestimate has not been studied, and therefore should be avoided. An alternate reliable method of contraception is recommended. |
| ethinyloestradiol norgestimate | ↑1.85 (1.67, 2.05) | ↑1.68 (1.51, 1.88) | ↑2.02 (1.77, 2.31) | While the concentration of ethinyloestradiol was increased with atazanavir given alone, due to both UGT and CYP3A4 inhibition by atazanavir, the net effect of atazanavir/ritonavir is a decrease in ethinyloestradiol levels because of the inducing effect of ritonavir. The increase in progestin exposure may lead to related side-effects (e.g. insulin resistance, dyslipidemia, acne and spotting), thus possibly affecting the compliance. |</p>
<table>
<thead>
<tr>
<th>Co-administered medicinal products (dose in mg)</th>
<th>Medicinal product assessed</th>
<th>AUC (90% CI)</th>
<th>C&lt;sub&gt;max&lt;/sub&gt; (90% CI)</th>
<th>C&lt;sub&gt;min&lt;/sub&gt; (90% CI)</th>
<th>Recommendations concerning co-administration</th>
</tr>
</thead>
<tbody>
<tr>
<td>LIPID LOWERING AGENTS</td>
<td></td>
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<tr>
<td>HMG-CoA reductase inhibitors</td>
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<tr>
<td>Simvastatin and lovastatin</td>
<td>Simvastatin and lovastatin are highly dependent on CYP3A4 for their metabolism and co-administration with REYATAZ/ritonavir may result in increased concentrations.</td>
<td></td>
<td></td>
<td></td>
<td>Co-administration of simvastatin or lovastatin with REYATAZ/ritonavir is not recommended due to an increased risk of myopathy including rhabdomyolysis. The use of another HMG-CoA reductase inhibitor which does not undergo metabolism by CYP3A such as pravastatin or fluvastatin is recommended.</td>
</tr>
<tr>
<td>Atorvastatin</td>
<td>The risk of myopathy including rhabdomyolysis may also be increased with atorvastatin, which is also metabolised by CYP3A4.</td>
<td></td>
<td></td>
<td></td>
<td>Caution should be exercised.</td>
</tr>
<tr>
<td>OPIOIDS</td>
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<tr>
<td>Buprenorphine, QD, stable maintenance dose, (atazanavir 300 mg QD with ritonavir 100 mg QD)</td>
<td>buprenorphine ↑1.67 ↑1.37 ↑1.69 norbuprenorphine ↑2.05 ↑1.61 ↑2.01</td>
<td></td>
<td></td>
<td></td>
<td>Co-administration warrants clinical monitoring for sedation and cognitive effects. A dose reduction of buprenorphine may be considered.</td>
</tr>
<tr>
<td>Methadone, stable maintenance dose (atazanavir 400 mg QD)</td>
<td>No significant effect on methadone concentrations was observed. Given that low dose ritonavir (100 mg twice daily) has been shown to have no significant effect on methadone concentrations, no interaction is expected if methadone is co-administered with REYATAZ and ritonavir, based on these data.</td>
<td></td>
<td></td>
<td></td>
<td>No dosage adjustment is necessary if methadone is co-administered with REYATAZ and ritonavir.</td>
</tr>
<tr>
<td>SEDATIVES</td>
<td></td>
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</tr>
<tr>
<td>Benzodiazepines</td>
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<tr>
<td>Midazolam</td>
<td>Midazolam and triazolam are extensively metabolized by CYP3A4. Co-administration with REYATAZ/ritonavir may cause a large increase in the concentration of these benzodiazepines. No drug interaction study has been performed for the co-administration of REYATAZ/ritonavir with benzodiazepines. Based on data for other CYP3A4 inhibitors, plasma concentrations of midazolam are expected to be significantly higher when midazolam is given orally. Data from concomitant use of parenteral midazolam with other protease inhibitors suggest a possible 3-4 fold increase in midazolam plasma levels.</td>
<td></td>
<td></td>
<td></td>
<td>REYATAZ/ritonavir should not be co-administered with triazolam or orally administered midazolam (see section 4.3), whereas caution should be used with co-administration of REYATAZ/ritonavir and parenteral midazolam. If REYATAZ is co-administered with parenteral midazolam, it should be done in an intensive care unit (ICU) or similar setting which ensures close clinical monitoring and appropriate medical management in case of respiratory depression and/or prolonged sedation. Dosage adjustment for midazolam should be considered, especially</td>
</tr>
</tbody>
</table>
4.6 Pregnancy and lactation

There are no adequate data from the use of atazanavir in pregnant women. Studies in animals have not shown evidence of selective developmental toxicity or effects on reproductive function and fertility (see section 5.3). REYATAZ should be used during pregnancy only if the potential benefit justifies the potential risk.

It is not known whether REYATAZ administered to the mother during pregnancy will exacerbate physiological hyperbilirubinaemia and lead to kernicterus in neonates and infants. In the prepartum period, additional monitoring and alternative therapy to REYATAZ should be considered.

It is not known whether atazanavir is excreted in human milk. Studies in rats have demonstrated that atazanavir is excreted in the milk. It is therefore recommended that mothers being treated with REYATAZ not breast-feed their infants. As a general rule, it is recommended that HIV infected women not breast-feed their infants in order to avoid transmission of HIV.

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed. Patients should be informed that dizziness has been reported during treatment with regimens containing REYATAZ (see section 4.8).

4.8 Undesirable effects

REYATAZ has been evaluated for safety in combination therapy with other antiretroviral medicinal products in controlled clinical trials in 1,806 adult patients receiving REYATAZ 400 mg once daily (1,151 patients, 52 weeks median duration and 152 weeks maximum duration) or REYATAZ 300 mg with ritonavir 100 mg once daily (655 patients, 96 weeks median duration and 108 weeks maximum duration).

Adverse reactions were consistent between patients who received REYATAZ 400 mg once daily and patients who received REYATAZ 300 mg with ritonavir 100 mg once daily, except that jaundice and elevated total bilirubin levels were reported more frequently with REYATAZ plus ritonavir.

Among patients who received REYATAZ 400 mg once daily or REYATAZ 300 mg with ritonavir 100 mg once daily, the only adverse reactions of any severity reported very commonly with at least a possible relationship to regimens containing REYATAZ and one or more NRTIs were nausea (20%), diarrhoea (10%), and jaundice (13%). Among patients receiving REYATAZ 300 mg with ritonavir 100 mg, the frequency of jaundice was 19%. In the majority of cases, jaundice was reported within a few days to a few months after the initiation of treatment (see section 4.4).

Combination antiretroviral therapy has been associated with redistribution of body fat (lipodystrophy) in HIV patients, including loss of peripheral and facial subcutaneous fat, increased intra-abdominal and visceral fat, breast hypertrophy, and dorsocervical fat accumulation (buffalo hump).

Combination antiretroviral therapy has been associated with metabolic abnormalities such as hypertriglyceridaemia, hypercholesterolaemia, insulin resistance, hyperglycaemia, and hyperlactataemia (see sections 4.4 and 5.1).
**Adult patients**
The following adverse reactions of moderate intensity or greater with at least a possible relationship to regimens containing REYATAZ and one or more NRTIs have also been reported. The frequency of adverse reactions listed below is defined using the following convention: very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1,000 to < 1/100), rare (≥ 1/10,000 to < 1/1,000), or very rare (< 1/10,000). Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

<table>
<thead>
<tr>
<th>Medical Category</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cardiac disorders:</strong></td>
<td>rare: oedema, palpitation</td>
</tr>
<tr>
<td><strong>Nervous system disorders:</strong></td>
<td>common: headache; uncommon: peripheral neuropathy, syncope, amnesia, dizziness, somnolence, dysgeusia</td>
</tr>
<tr>
<td><strong>Eye disorders:</strong></td>
<td>common: ocular icterus</td>
</tr>
<tr>
<td><strong>Respiratory, thoracic and mediastinal disorders:</strong></td>
<td>uncommon: dyspnoea</td>
</tr>
<tr>
<td><strong>Gastrointestinal disorders:</strong></td>
<td>common: vomiting, diarrhoea, abdominal pain, nausea, dyspepsia; uncommon: pancreatitis, gastritis, abdominal distension, stomatitis aphthous, flatulence, dry mouth</td>
</tr>
<tr>
<td><strong>Renal and urinary disorders:</strong></td>
<td>uncommon: nephrolithiasis, hematuria, proteinuria, pollakiuria; rare: kidney pain</td>
</tr>
<tr>
<td><strong>Skin and subcutaneous tissue disorders:</strong></td>
<td>common: rash; uncommon: urticaria, alopecia, pruritus; rare: vesiculobullous rash, eczema, vasodilatation</td>
</tr>
<tr>
<td><strong>Musculoskeletal and connective tissue disorders:</strong></td>
<td>uncommon: muscle atrophy, arthralgia, myalgia; rare: myopathy</td>
</tr>
<tr>
<td><strong>Metabolism and nutrition disorders:</strong></td>
<td>uncommon: weight decreased, weight gain, anorexia, appetite increased</td>
</tr>
<tr>
<td><strong>Vascular disorders:</strong></td>
<td>uncommon: hypertension</td>
</tr>
<tr>
<td><strong>General disorders and administration site conditions:</strong></td>
<td>common: lipodystrophy syndrome, fatigue; uncommon: chest pain, malaise, pyrexia, asthenia; rare: gait disturbance</td>
</tr>
<tr>
<td><strong>Immune system disorders:</strong></td>
<td>uncommon: hypersensitivity</td>
</tr>
<tr>
<td><strong>Hepatobiliary disorders:</strong></td>
<td>common: jaundice; uncommon: hepatitis; rare: hepatosplenomegaly</td>
</tr>
<tr>
<td><strong>Reproductive system and breast disorders:</strong></td>
<td>uncommon: gynaecomastia</td>
</tr>
<tr>
<td><strong>Psychiatric disorders:</strong></td>
<td>uncommon: depression, disorientation, anxiety, insomnia, sleep disorder, abnormal dream</td>
</tr>
</tbody>
</table>
In HIV-infected patients with severe immune deficiency at the time of initiation of combination antiretroviral therapy (CART), an inflammatory reaction to asymptomatic or residual opportunistic infections may arise (see section 4.4).

Cases of osteonecrosis have been reported, particularly in patients with generally acknowledged risk factors, advanced HIV disease or long-term exposure to combination antiretroviral therapy (CART). The frequency of this is unknown (see section 4.4).

**Laboratory abnormalities**
The most frequently reported laboratory abnormality in patients receiving regimens containing REYATAZ and one or more NRTIs was elevated total bilirubin reported predominantly as elevated indirect [unconjugated] bilirubin (87% Grade 1, 2, 3, or 4). Grade 3 or 4 elevation of total bilirubin was noted in 37% (6% Grade 4). Among experienced patients treated with REYATAZ 300 mg once daily with 100 mg ritonavir once daily for a median duration of 95 weeks, 53% had Grade 3-4 total bilirubin elevations. Among naive patients treated with REYATAZ 300 mg once daily with 100 mg ritonavir once daily for a median duration of 96 weeks, 48% had Grade 3-4 total bilirubin elevations (see section 4.4).

Other marked clinical laboratory abnormalities (Grade 3 or 4) reported in ≥ 2% of patients receiving regimens containing REYATAZ and one or more NRTIs included: elevated creatine kinase (7%), elevated alanine aminotransferase/serum glutamic-pyruvic transaminase (ALT/SGPT) (5%), low neutrophils (5%), elevated aspartate aminotransferase/serum glutamic-oxaloacetic transaminase (AST/SGOT) (3%), and elevated lipase (3%).

Two percent of patients treated with REYATAZ experienced concurrent Grade 3-4 ALT/AST and Grade 3-4 total bilirubin elevations.

**Patients co-infected with hepatitis B and/or hepatitis C virus**
Among 1,151 patients receiving atazanavir 400 mg once daily, 177 patients were co-infected with chronic hepatitis B or C, and among 655 patients receiving atazanavir 300 mg once daily with ritonavir 100 mg once daily, 97 patients were co-infected with chronic hepatitis B or C. Co-infected patients were more likely to have baseline hepatic transaminase elevations than those without chronic viral hepatitis. No differences in frequency of bilirubin elevations were observed between these patients and those without viral hepatitis. The frequency of treatment emergent hepatitis or transaminase elevations in co-infected patients was comparable between REYATAZ and comparator regimens (see section 4.4).

**Paediatric population**
In clinical studies, paediatric patients 3 months to less than 18 years of age had a mean duration of treatment with REYATAZ of 115 weeks. The safety profile in these studies was overall comparable to that seen in adults. Both asymptomatic first-degree (23%) and second-degree (1%) atrioventricular block were reported in paediatric patients. The most frequently reported laboratory abnormality in paediatric patients receiving REYATAZ was elevation of total bilirubin (≥ 2.6 times ULN, Grade 3-4) which occurred in 45% of patients.

**Postmarketing experience**
There have been postmarketing reports of unknown frequency for torsades de pointes, QTc prolongation, diabetes mellitus, hyperglycaemia, nephrolithiasis, and gallbladder disorders including cholelithiasis, cholecystitis, and cholestasis.

### 4.9 Overdose

Human experience of acute overdose with REYATAZ is limited. Single doses up to 1,200 mg have been taken by healthy volunteers without symptomatic untoward effects. At high doses that lead to high drug exposures, jaundice due to indirect (unconjugated) hyperbilirubinaemia (without associated liver function test changes) or PR interval prolongations may be observed (see sections 4.4 and 4.8).
Treatment of overdose with REYATAZ should consist of general supportive measures, including monitoring of vital signs and electrocardiogram (ECG), and observations of the patient's clinical status. If indicated, elimination of unabsorbed atazanavir should be achieved by emesis or gastric lavage. Administration of activated charcoal may also be used to aid removal of unabsorbed drug. There is no specific antidote for overdose with REYATAZ. Since atazanavir is extensively metabolised by the liver and is highly protein bound, dialysis is unlikely to be beneficial in significant removal of this medicinal product.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: protease inhibitor, ATC code: J05AE08

Mechanism of action: atazanavir is an azapeptide HIV-1 protease inhibitor (PI). The compound selectively inhibits the virus-specific processing of viral Gag-Pol proteins in HIV-1 infected cells, thus preventing formation of mature virions and infection of other cells.

Antiviral activity in vitro: atazanavir exhibits anti-HIV-1 (including all clades tested) and anti-HIV-2 activity in cell culture.

Resistance

Antiretroviral treatment naive adult patients
In clinical trials of antiretroviral treatment naive patients treated with unboosted atazanavir, the I50L substitution, sometimes in combination with an A71V change, is the signature resistance substitution for atazanavir. Resistance levels to atazanavir ranged from 3.5- to 29-fold without evidence of phenotypic cross resistance to other PIs. In clinical trials of antiretroviral treatment naive patients treated with boosted atazanavir, the I50L substitution did not emerge in any patient without baseline PI substitutions. The N88S substitution has been rarely observed in patients with virologic failure on atazanavir (with or without ritonavir). While it may contribute to decreased susceptibility to atazanavir when it occurs with other protease substitutions, in clinical studies N88S by itself does not always lead to phenotypic resistance to atazanavir or have a consistent impact on clinical efficacy.

Table 3. De novo substitutions in treatment naive patients failing therapy with atazanavir + ritonavir (Study 138, 96 weeks)

<table>
<thead>
<tr>
<th>Frequency</th>
<th>de novo PI substitution (n=26)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;20%</td>
<td>none</td>
</tr>
<tr>
<td>10-20%</td>
<td>none</td>
</tr>
</tbody>
</table>

* Number of patients with paired genotypes classified as virological failures (HIV RNA ≥ 400 copies/ml).

The M184I/V substitution emerged in 5/26 REYATAZ/ritonavir and 7/26 lopinavir/ritonavir virologic failure patients, respectively.

Antiretroviral treatment experienced adult patients
In antiretroviral treatment experienced patients from Studies 009, 043, and 045, 100 isolates from patients designated as virological failures on therapy that included either atazanavir, atazanavir + ritonavir, or atazanavir + saquinavir were determined to have developed resistance to atazanavir. Of the 60 isolates from patients treated with either atazanavir or atazanavir + ritonavir, 18 (30%) displayed the I50L phenotype previously described in naive patients.

Table 4. De novo substitutions in treatment experienced patients failing therapy with atazanavir + ritonavir (Study 045, 48 weeks)

<table>
<thead>
<tr>
<th>Frequency</th>
<th>de novo PI substitution (n=35)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;20%</td>
<td>M36, M46, I54, A71, V82</td>
</tr>
<tr>
<td>10-20%</td>
<td>L10, I15, K20, V32, E35, S37, F53, I62, G73, I84, L90</td>
</tr>
</tbody>
</table>

* Number of patients with paired genotypes classified as virological failures (HIV RNA ≥ 400 copies/ml).
Ten patients had baseline phenotypic resistance to atazanavir + ritonavir (fold change [FC]>5.2). FC susceptibility in cell culture relative to the wild-type reference was assayed using PhenoSense™ (Monogram Biosciences, South San Francisco, California, USA).

None of the de novo substitutions (see Table 4) are specific to atazanavir and may reflect re-emergence of archived resistance on atazanavir + ritonavir in Study 045 treatment-experienced population.

The resistance in antiretroviral treatment experienced patients mainly occurs by accumulation of the major and minor resistance substitutions described previously to be involved in protease inhibitor resistance.

**Clinical results**

*In antiretroviral naive adult patients*

Study 138 is an international randomised, open-label, multicenter, prospective trial of treatment naïve patients comparing REYATAZ/ritonavir (300 mg/100 mg once daily) to lopinavir/ritonavir (400 mg/100 mg twice daily), each in combination with fixed dose tenofovir/emtricitabine (300 mg/200 mg tablets once daily). The REYATAZ/ritonavir arm showed similar (non-inferior) antiviral efficacy compared to the lopinavir/ritonavir arm, as assessed by the proportion of patients with HIV RNA < 50 copies/ml at week 48 (Table 5). Analyses of data through 96 weeks of treatment demonstrated durability of antiviral activity (Table 5).
In antiretroviral experienced adult patients

**Study 045** is a randomised, multicenter trial comparing REYATAZ/ritonavir (300/100 mg once daily) and REYATAZ/saquinavir (400/1,200 mg fixed dose combination twice daily), each in combination with tenofovir (see sections 4.5 and 4.8) and one NRTI, in patients with virologic failure on two or more prior regimens containing at least one PI, NRTI, and NNRTI. For randomised patients, the mean time of prior antiretroviral exposure was 138 weeks for PIs, 281 weeks for NRTIs, and 85 weeks for NNRTIs. At baseline, 34% of patients were receiving a PI and 60% were receiving an NNRTI. Fifteen of 120 (13%) patients in the REYATAZ + ritonavir treatment arm and 17 of 123 (14%) patients in the lopinavir + ritonavir arm had four or more of the PI substitutions L10, M46, I54, V82, I84, and L90. Thirty-two percent of patients in the study had a viral strain with fewer than two NRTI substitutions.

The primary endpoint was the time-averaged difference in change from baseline in HIV RNA through 48 weeks (Table 6).

---

**Table 5: Efficacy Outcomes in Study 138**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>REYATAZ/ritonavir&lt;sup&gt;b&lt;/sup&gt; (300 mg/100 mg once daily)</th>
<th>Lopinavir/ritonavir&lt;sup&gt;c&lt;/sup&gt; (400 mg/100 mg twice daily)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n=440</td>
<td>n=443</td>
</tr>
<tr>
<td>Week 48</td>
<td>Week 96</td>
<td>Week 48</td>
</tr>
<tr>
<td>HIV RNA &lt;50 copies/ml, %</td>
<td></td>
<td></td>
</tr>
<tr>
<td>All patients&lt;sup&gt;d&lt;/sup&gt;</td>
<td>78</td>
<td>74</td>
</tr>
<tr>
<td>Difference estimate [95% CI]&lt;sup&gt;d&lt;/sup&gt;</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Week 48: 1.7% [-3.8%, 7.1%]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Week 96: 6.1% [0.3%, 12.0%]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Per protocol analysis&lt;sup&gt;e&lt;/sup&gt;</td>
<td>86</td>
<td>91</td>
</tr>
<tr>
<td>(n=392&lt;sup&gt;f&lt;/sup&gt;)</td>
<td>(n=352)</td>
<td>(n=372)</td>
</tr>
<tr>
<td>HIV RNA &lt;50 copies/ml, % by Baseline Characteristic&lt;sup&gt;d&lt;/sup&gt;</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HIV RNA &lt;100,000 copies/ml</td>
<td>82 (n=217)</td>
<td>75 (n=217)</td>
</tr>
<tr>
<td>≥100,000 copies/ml</td>
<td>74 (n=223)</td>
<td>74 (n=223)</td>
</tr>
<tr>
<td>CD4 count &lt;50 cells/mm&lt;sup&gt;3&lt;/sup&gt;</td>
<td>78 (n=58)</td>
<td>78 (n=58)</td>
</tr>
<tr>
<td>50 to &lt;100 cells/mm&lt;sup&gt;3&lt;/sup&gt;</td>
<td>76 (n=45)</td>
<td>71 (n=45)</td>
</tr>
<tr>
<td>100 to &lt;200 cells/mm&lt;sup&gt;3&lt;/sup&gt;</td>
<td>75 (n=106)</td>
<td>71 (n=106)</td>
</tr>
<tr>
<td>≥200 cells/mm&lt;sup&gt;3&lt;/sup&gt;</td>
<td>80 (n=222)</td>
<td>76 (n=222)</td>
</tr>
<tr>
<td>HIV RNA Mean Change from Baseline, log&lt;sub&gt;10&lt;/sub&gt; copies/ml</td>
<td></td>
<td></td>
</tr>
<tr>
<td>All patients</td>
<td>-3.09 (n=397)</td>
<td>-3.21 (n=360)</td>
</tr>
<tr>
<td>CD4 Mean Change from Baseline, cells/mm&lt;sup&gt;3&lt;/sup&gt;</td>
<td></td>
<td></td>
</tr>
<tr>
<td>All patients</td>
<td>203 (n=370)</td>
<td>268 (n=336)</td>
</tr>
<tr>
<td>HIV RNA &lt;100,000 copies/ml</td>
<td>179 (n=183)</td>
<td>243 (n=163)</td>
</tr>
<tr>
<td>≥100,000 copies/ml</td>
<td>227 (n=187)</td>
<td>291 (n=173)</td>
</tr>
</tbody>
</table>

<sup>a</sup> Mean baseline CD4 cell count was 214 cells/mm<sup>3</sup> (range 2 to 810 cells/mm<sup>3</sup>) and mean baseline plasma HIV-1 RNA was 4.94 log<sub>10</sub> copies/ml (range 2.6 to 5.88 log<sub>10</sub> copies/ml)

<sup>b</sup> REYATAZ/RTV with tenofovir/emtricitabine (fixed dose 300 mg/200 mg tablets once daily).

<sup>c</sup> Lopinavir/RTV with tenofovir/emtricitabine (fixed dose 300 mg/200 mg tablets once daily).

<sup>d</sup> Intent-to-treat analysis, with missing values considered as failures.

<sup>e</sup> Per protocol analysis: Excluding non-completers and patients with major protocol deviations.

<sup>f</sup> Number of patients evaluable.

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In antiretroviral experienced adult patients

Study 045 is a randomised, multicenter trial comparing REYATAZ/ritonavir (300/100 mg once daily) and REYATAZ/saquinavir (400/1,200 mg fixed dose combination twice daily), each in combination with tenofovir (see sections 4.5 and 4.8) and one NRTI, in patients with virologic failure on two or more prior regimens containing at least one PI, NRTI, and NNRTI. For randomised patients, the mean time of prior antiretroviral exposure was 138 weeks for PIs, 281 weeks for NRTIs, and 85 weeks for NNRTIs. At baseline, 34% of patients were receiving a PI and 60% were receiving an NNRTI. Fifteen of 120 (13%) patients in the REYATAZ + ritonavir treatment arm and 17 of 123 (14%) patients in the lopinavir + ritonavir arm had four or more of the PI substitutions L10, M46, I54, V82, I84, and L90. Thirty-two percent of patients in the study had a viral strain with fewer than two NRTI substitutions.

The primary endpoint was the time-averaged difference in change from baseline in HIV RNA through 48 weeks (Table 6).

Table 6: Efficacy Outcomes at Week 48<sup>a</sup> and at Week 96 (Study 045)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>ATV/RTV&lt;sup&gt;b&lt;/sup&gt; (300 mg/100 mg once daily) n=120</th>
<th>LPV/RTV&lt;sup&gt;c&lt;/sup&gt; (400 mg/100 mg twice daily) n=123</th>
<th>Time-averaged difference ATV/RTV-LPV/RTV&lt;sup&gt;d&lt;/sup&gt; [97.5% CI]&lt;sup&gt;e&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Week 48</td>
<td>Week 96</td>
<td>Week 48</td>
</tr>
<tr>
<td>HIV RNA Mean Change from Baseline, log&lt;sub&gt;10&lt;/sub&gt; copies/ml</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All patients</td>
<td>-1.93 (n=90)</td>
<td>-2.29 (n=64)</td>
<td>-1.87 (n=99)</td>
</tr>
<tr>
<td>HIV RNA &lt;50 copies/ml, %&lt;sup&gt;f&lt;/sup&gt; (responder/evaluable)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All patients</td>
<td>36 (43/120)</td>
<td>32 (38/120)</td>
<td>42 (52/123)</td>
</tr>
<tr>
<td>HIV RNA &lt;50 copies/ml by select baseline PI substitutions,&lt;sup&gt;g&lt;/sup&gt; %&lt;sup&gt;f&lt;/sup&gt; (responder/evaluable)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0-2</td>
<td>44 (28/63)</td>
<td>41 (26/63)</td>
<td>56 (32/57)</td>
</tr>
<tr>
<td>3</td>
<td>18 (2/11)</td>
<td>9 (1/11)</td>
<td>38 (6/16)</td>
</tr>
<tr>
<td>≥4</td>
<td>27 (12/45)</td>
<td>24 (11/45)</td>
<td>28 (14/50)</td>
</tr>
</tbody>
</table>

CD4 Mean Change from Baseline, cells/mm<sup>3</sup>

<table>
<thead>
<tr>
<th>Parameter</th>
<th>All patients</th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Week 48</td>
<td>Week 96</td>
<td>Week 48</td>
<td>Week 96</td>
<td>Week 48</td>
<td>Week 96</td>
</tr>
<tr>
<td>HIV RNA Mean Change from Baseline, log&lt;sub&gt;10&lt;/sub&gt; copies/ml</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All patients</td>
<td>110 (n=83)</td>
<td>122 (n=60)</td>
<td>121 (n=94)</td>
<td>154 (n=60)</td>
<td>NA</td>
<td>NA</td>
</tr>
</tbody>
</table>

<sup>a</sup>The mean baseline CD4 cell count was 337 cells/mm<sup>3</sup> (range: 14 to 1,543 cells/mm<sup>3</sup>) and the mean baseline plasma HIV-1 RNA level was 4.4 log<sub>10</sub> copies/ml (range: 2.6 to 5.88 log<sub>10</sub> copies/ml).

<sup>b</sup>ATV/RTV with tenofovir/emtricitabine (fixed dose 300 mg/200 mg tablets once daily).

<sup>c</sup>LPV/RTV with tenofovir/emtricitabine (fixed dose 300 mg/200 mg tablets once daily).

<sup>d</sup>Confidence interval.

<sup>e</sup>Number of patients evaluable.

<sup>f</sup>Intent-to-treat analysis, with missing values considered as failures. Responders on LPV/RTV who completed treatment before Week 96 are excluded from Week 96 analysis. The proportion of patients with HIV RNA < 400 copies/ml were 53% and 43% for ATV/RTV and LPV/RTV at weeks 48 and 96 respectively.

<sup>g</sup>Select substitutions include any change at positions L10, K20, L24, V32, L33, M36, M46, G48, I50, I54, L63, A71, G73, V82, I84, and L90 (0-2, 3, 4 or more) at baseline.

NA = not applicable.

Through 48 weeks of treatment, the mean changes from baseline in HIV RNA levels for REYATAZ + ritonavir and lopinavir + ritonavir were similar (non-inferior). Consistent results were obtained with the last observation carried forward method of analysis (time-averaged difference of 0.11, 97.5% confidence interval [-0.15, 0.36]). By as-treated analysis, excluding missing values, the proportions of patients with HIV RNA < 400 copies/ml (<50 copies/ml) in the REYATAZ + ritonavir arm and the lopinavir + ritonavir arm were 55% (40%) and 56% (46%), respectively.

Through 96 weeks of treatment, mean HIV RNA changes from baseline for REYATAZ + ritonavir and lopinavir + ritonavir met criteria for non-inferiority based on observed cases. Consistent results were obtained with the last observation carried forward method of analysis. By as-treated analysis, excluding missing values, the proportions of patients with HIV RNA < 400 copies/ml (<50 copies/ml) for REYATAZ + ritonavir were 84% (72%) and for lopinavir + ritonavir were 82% (72%). It is important to note that at time of the 96-week analysis, 48 % of patients overall remained on study.

REYATAZ + saquinavir was shown to be inferior to lopinavir + ritonavir.

**Paediatric population**

Assessment of the pharmacokinetics, safety, tolerability, and efficacy of REYATAZ is based on data from the open-label, multicenter clinical trial PACTG 1020A conducted in patients from 3 months to 21 years of age. Overall in this study, 182 paediatric patients (81 antiretroviral-naive and 101 antiretroviral-experienced) received once daily REYATAZ (capsule or powder formulation), with or without ritonavir, in combination with two NRTIs.

The clinical data derived from this study are inadequate to support the use of atazanavir (with or without ritonavir) in children below 6 years of age.

Efficacy data observed in the 41 paediatric patients aged 6 years to less than 18 years that received REYATAZ capsules with ritonavir are presented in Table 7. For treatment-naive paediatric patients, the mean baseline CD4 cell count was 344 cells/mm<sup>3</sup> (range: 2 to 800 cells/mm<sup>3</sup>) and mean baseline
plasma HIV 1 RNA was 4.67 log10 copies/ml (range: 3.70 to 5.00 log10 copies/ml). For treatment-experienced paediatric patients, the mean baseline CD4 cell count was 522 cells/mm³ (range: 100 to 1157 cells/mm³) and mean baseline plasma HIV 1 RNA was 4.09 log10 copies/ml (range: 3.28 to 5.00 log10 copies/ml).

Table 7: Efficacy Outcomes (paediatric patients 6 years to less than 18 years of age) at Week 48 (Study PACTG 1020A)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Treatment-Naive REYATAZ Capsules/ritonavir (300 mg/100 mg once daily) n=16</th>
<th>Treatment-Experienced REYATAZ Capsules/ritonavir (300 mg/100 mg once daily) n=25</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV RNA &lt;50 copies/ml, % a</td>
<td>All patients 81 (13/16)</td>
<td>24 (6/25)</td>
</tr>
<tr>
<td>HIV RNA &lt;400 copies/ml, % a</td>
<td>All patients 88 (14/16)</td>
<td>32 (8/25)</td>
</tr>
<tr>
<td>CD4 Mean Change from Baseline, cells/mm³</td>
<td>All patients 293 (n=14 b)</td>
<td>229 (n=14 b)</td>
</tr>
<tr>
<td>HIV RNA &lt;50 copies/ml by select baseline PI substitutions, c % (responder/evaluable d)</td>
<td>0-2 NA 27 (4/15)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>3 NA -</td>
<td></td>
</tr>
<tr>
<td></td>
<td>≥4 NA 0 (0/3)</td>
<td></td>
</tr>
</tbody>
</table>

a Intent-to-treat analysis, with missing values considered as failures.
b Number of patients evaluable.
c PI major L24I, D30N, V32I, L33F, M46IL, 147AV, G48V, 150LV, F53LY, I54ALMSTV, L76V, V82AFLST, I84V, N88DS, L90M; PI minor: L10CFIRV, V11I, E35G, K43T, Q58E, A71ILTV, G73ACST, T74P, N83D, L89V.
d Includes patients with baseline resistance data.
NA = not applicable.

Data in the paediatric population are very limited. Available data do suggest that atazanavir in combination with ritonavir may not be effective in treatment experienced children even with very few (<3) PI mutations.

5.2 Pharmacokinetic properties

The pharmacokinetics of atazanavir were evaluated in healthy adult volunteers and in HIV-infected patients; significant differences were observed between the two groups. The pharmacokinetics of atazanavir exhibit a non-linear disposition. In healthy subjects, the AUC of atazanavir from the capsules and oral powder were similar.

Absorption: in HIV-infected patients (n=33, combined studies), multiple dosing of REYATAZ 300 mg once daily with ritonavir 100 mg once daily with food produced a geometric mean (CV%) for atazanavir, Cmax of 4466 (42%) ng/ml, with time to Cmax of approximately 2.5 hours. The geometric mean (CV%) for atazanavir Cmin and AUC was 654 (76%) ng/ml and 44185 (51%) ng•h/ml, respectively.

Food effect: co-administration of REYATAZ and ritonavir with food optimises the bioavailability of atazanavir. Co-administration of a single 300-mg dose of REYATAZ and 100-mg dose of ritonavir with a light meal resulted in a 33% increase in the AUC and a 40% increase in both the Cmax and the 24-hour concentration of atazanavir relative to the fasting state. Co-administration with a high-fat meal did not affect the AUC of atazanavir relative to fasting conditions and the Cmax was within 11% of fasting values. The 24-hour concentration following a high fat meal was increased by approximately 33% due to delayed absorption; the median Tmax increased from 2.0 to 5.0 hours. Administration of REYATAZ with ritonavir with either a light or a high-fat meal decreased the coefficient of variation.
of AUC and C\textsubscript{max} by approximately 25% compared to the fasting state. To enhance bioavailability and minimise variability, REYATAZ is to be taken with food.

**Distribution:** atazanavir was approximately 86% bound to human serum proteins over a concentration range of 100 to 10,000 ng/ml. Atazanavir binds to both alpha-1-acid glycoprotein (AAG) and albumin to a similar extent (89% and 86%, respectively, at 1,000 ng/ml). In a multiple-dose study in HIV-infected patients dosed with 400 mg of atazanavir once daily with a light meal for 12 weeks, atazanavir was detected in the cerebrospinal fluid and semen.

**Metabolism:** studies in humans and *in vitro* studies using human liver microsomes have demonstrated that atazanavir is principally metabolised by CYP3A4 isozyme to oxygenated metabolites. Metabolites are then excreted in the bile as either free or glucuronidated metabolites. Additional minor metabolic pathways consist of N-dealkylation and hydrolysis. Two minor metabolites of atazanavir in plasma have been characterised. Neither metabolite demonstrated *in vitro* antiviral activity.

**Elimination:** following a single 400-mg dose of $^{14}$C-atazanavir, 79% and 13% of the total radioactivity was recovered in the faeces and urine, respectively. Unchanged drug accounted for approximately 20% and 7% of the administered dose in the faeces and urine, respectively. Mean urinary excretion of unchanged drug was 7% following 2 weeks of dosing at 800 mg once daily. In HIV-infected adult patients (n=33, combined studies) the mean half-life within a dosing interval for atazanavir was 12 hours at steady state following a dose of 300 mg daily with ritonavir 100 mg once daily with a light meal.

**Special populations**

**Paediatric patients:** The pharmacokinetics of atazanavir in paediatric patients exhibit an increased absorption rate compared to adults. There is a slight trend toward a higher clearance in younger children when normalised for body weight. As a result, greater peak to trough ratios are observed. The geometric mean AUC values in paediatric patients at recommended doses are expected to be similar to those observed in adults, with higher geometric mean C\textsubscript{max} (13-17%) and lower geometric mean C\textsubscript{min} (up to 30%) values compared to those in adults. The variability of pharmacokinetic parameters in younger children is higher.

**Impaired renal function:** in healthy subjects, the renal elimination of unchanged atazanavir was approximately 7% of the administered dose. There are no pharmacokinetic data available for REYATAZ with ritonavir in patients with renal insufficiency. REYATAZ (without ritonavir) has been studied in adult patients with severe renal impairment (n=20), including those on haemodialysis, at multiple doses of 400 mg once daily. Although this study presented some limitations (i.e., unbound drug concentrations not studied), results suggested that the atazanavir pharmacokinetic parameters were decreased by 30% to 50% in patients undergoing haemodialysis compared to patients with normal renal function. The mechanism of this decrease is unknown. (See sections 4.2 and 4.4.)

**Impaired hepatic function:** atazanavir is metabolised and eliminated primarily by the liver. The effects of hepatic impairment on the pharmacokinetics of atazanavir after a 300 mg dose with ritonavir have not been studied. Concentrations of atazanavir with or without ritonavir are expected to be increased in patients with moderately or severely impaired hepatic function (see sections 4.2, 4.3, and 4.4).

**Age/Gender:** a study of the pharmacokinetics of atazanavir was performed in 59 healthy male and female subjects (29 young, 30 elderly). There were no clinically important pharmacokinetic differences based on age or gender.

**Race:** a population pharmacokinetic analysis of samples from Phase II clinical trials indicated no effect of race on the pharmacokinetics of atazanavir.
5.3 Preclinical safety data

In repeat-dose toxicity studies, conducted in mice, rats, and dogs, atazanavir-related findings were generally confined to the liver and included generally minimal to mild increases in serum bilirubin and liver enzymes, hepatocellular vacuolation and hypertrophy, and, in female mice only, hepatic single-cell necrosis. Systemic exposures of atazanavir in mice (males), rats, and dogs at doses associated with hepatic changes were at least equal to that observed in humans given 400 mg once daily. In female mice, atazanavir exposure at a dose that produced single-cell necrosis was 12 times the exposure in humans given 400 mg once daily. Serum cholesterol and glucose were minimally to mildly increased in rats but not in mice or dogs.

During in vitro studies, cloned human cardiac potassium channel (hERG), was inhibited by 15% at a concentration (30 μM) of atazanavir corresponding to 30-fold the free drug concentration at Cmax in humans. Similar concentrations of atazanavir increased by 13% the action potential duration (APD90) in rabbit Purkinje fibres study. Electrocardiographic changes (sinus bradycardia, prolongation of PR interval, prolongation of QT interval, and prolongation of QRS complex) were observed only in an initial 2-week oral toxicity study performed in dogs. Subsequent 9-month oral toxicity studies in dogs showed no drug-related electrocardiographic changes. The clinical relevance of these non-clinical data is unknown. Potential cardiac effects of this product in humans cannot be ruled out (see sections 4.4 and 4.8). The potential for PR prolongation should be considered in cases of overdose (see section 4.9).

In a fertility and early embryonic development study in rats, atazanavir altered oestrus cycling with no effects on mating or fertility. No teratogenic effects were observed in rats or rabbits at maternally toxic doses. In pregnant rabbits, gross lesions of the stomach and intestines were observed in dead or moribund does at maternal doses 2 and 4 times the highest dose administered in the definitive embryo-development study. In the pre- and postnatal development assessment in rats, atazanavir produced a transient reduction in body weight in the offspring at a maternally toxic dose. Systemic exposure to atazanavir at doses that resulted in maternal toxicity was at least equal to or slightly greater than that observed in humans given 400 mg once daily.

Atazanavir was negative in an Ames reverse-mutation assay but did induce chromosomal aberrations in vitro in both the absence and presence of metabolic activation. In in vivo studies in rats, atazanavir did not induce micronuclei in bone marrow, DNA damage in duodenum (comet assay), or unscheduled DNA repair in liver at plasma and tissue concentrations exceeding those that were clastogenic in vitro.

In long-term carcinogenicity studies of atazanavir in mice and rats, an increased incidence of benign hepatic adenomas was seen in female mice only. The increased incidence of benign hepatic adenomas in female mice was likely secondary to cytotoxic liver changes manifested by single-cell necrosis and is considered to have no relevance for humans at intended therapeutic exposures. There were no tumorigenic findings in male mice or in rats.

Atazanavir increased opacity of bovine corneas in an in vitro ocular irritation study, indicating it may be an ocular irritant upon direct contact with the eye.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Capsule contents:
Crospovidone
Lactose monohydrate
Magnesium stearate

Capsule shells:
Gelatine
Indigocarmin (E132)
Titanium dioxide (E171)

Blue ink containing:
Shellac
Propylene glycol
Ammonium hydroxide
Indigocarmin (E132)

White ink containing:
Shellac
Titanium dioxide (E171)
Ammonium hydroxide
Propylene glycol
Simethicone

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years

6.4 Special precautions for storage

Do not store above 25°C.

6.5 Nature and contents of container

Each carton contains one high-density polyethylene (HDPE) bottle closed with child-resistant polypropylene closure. Each bottle contains 60 hard capsules.

Each carton contains 60 x 1 capsules; 10 blister cards of 6 x 1 capsules each in Alu/Alu perforated unit dose blisters.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

Any unused product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

BRISTOL-MYERS SQUIBB PHARMA EEIG
Uxbridge Business Park
Sanderson Road
Uxbridge UB8 1DH
United Kingdom

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/03/267/001-002
9.  DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 02 March 2004
Date of latest renewal: 02 March 2009

10.  DATE OF REVISION OF THE TEXT

{month year}

Detailed information on this medicinal product is available on the website of the European Medicines Agency (EMEA) http://www.ema.europa.eu
1. **NAME OF THE MEDICINAL PRODUCT**

REYATAZ 150 mg hard capsules

2. **QUALITATIVE AND QUANTITATIVE COMPOSITION**

Each capsule contains 150 mg of atazanavir (as sulphate)

Excipient: 82.18 mg of lactose per capsule.

For a full list of excipients, see section 6.1.

3. **PHARMACEUTICAL FORM**

Hard capsule

Opaque blue and powder blue capsule printed with white and blue inks, with "BMS 150 mg" on one half and with "3624" on the other half.

4. **CLINICAL PARTICULARS**

4.1 **Therapeutic indications**

REYATAZ capsules, co-administered with low dose ritonavir, are indicated for the treatment of HIV-1 infected adults and paediatric patients 6 years of age and older in combination with other antiretroviral medicinal products.

Based on available virological and clinical data from adult patients, no benefit is expected in patients with strains resistant to multiple protease inhibitors (≥ 4 PI mutations). There are very limited data available from children aged 6 to less than 18 years (see sections 4.4 and 5.1).

The choice of REYATAZ in treatment experienced adult and paediatric patients should be based on individual viral resistance testing and the patient’s treatment history (see sections 4.4 and 5.1).

4.2 **Posology and method of administration**

Therapy should be initiated by a physician experienced in the management of HIV infection.

*Adults*: the recommended dose of REYATAZ capsules is 300 mg once daily taken with ritonavir 100 mg once daily and with food. Ritonavir is used as a booster of atazanavir pharmacokinetics (see sections 4.5 and 5.1).

*Paediatric patients (6 years to less than 18 years of age)*: The dose of REYATAZ capsules for paediatric patients is based on body weight as shown in Table 1 and should not exceed the recommended adult dose. REYATAZ capsules must be taken with ritonavir and have to be taken with food.
Table 1: Dose for Paediatric Patients (6 years to less than 18 years of age) for REYATAZ capsules with ritonavir

<table>
<thead>
<tr>
<th>Body Weight (kg)</th>
<th>REYATAZ dose</th>
<th>ritonavir dose&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>15 to less than 20</td>
<td>150 mg</td>
<td>100 mg&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>20 to less than 40</td>
<td>200 mg</td>
<td>100 mg</td>
</tr>
<tr>
<td>at least 40</td>
<td>300 mg</td>
<td>100 mg</td>
</tr>
</tbody>
</table>

<sup>a</sup> Ritonavir capsules, tablets or oral solution.

<sup>b</sup> Ritonavir oral solution no lower than 80 mg and not more than 100 mg may be used for paediatric patients from 15 kg to less than 20 kg who cannot swallow ritonavir capsules/tablets.

The available data do not support the use of REYATAZ in combination with low dose ritonavir in paediatric patients weighing less than 15 kg.

**Paediatric patients (less than 6 years of age):** REYAYAZ is not recommended in paediatric patients less than 6 years of age due to insufficient data on pharmacokinetics, safety, and efficacy. REYATAZ has not been studied in children less than 3 months of age and is not recommended especially taking into account the potential risk of kernicterus.

**Patients with renal impairment:** no dosage adjustment is needed. REYATAZ with ritonavir is not recommended in patients undergoing haemodialysis (see sections 4.4 and 5.2).

**Patients with hepatic impairment:** REYATAZ with ritonavir has not been studied in patients with hepatic impairment. REYATAZ with ritonavir should be used with caution in patients with mild hepatic impairment. REYATAZ must not be used in patients with moderate to severe hepatic impairment (see sections 4.3, 4.4, and 5.2).

**Method of administration:** for oral administration. The capsules should be swallowed whole. REYATAZ oral powder is available for adult patients who are unable to swallow capsules (see Summary of Product Characteristics for REYATAZ oral powder). REYATAZ oral powder must not be used in paediatric patients unable to swallow capsules due to insufficient data on pharmacokinetics, safety, and efficacy.

### 4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients (see section 6.1).

Patients with moderate to severe hepatic insufficiency (see sections 4.2 and 4.4).

Combination of rifampicin and REYATAZ with concomitant low-dose ritonavir is contraindicated (see section 4.5).

REYATAZ with ritonavir must not be used in combination with medicinal products that are substrates of the CYP3A4 isoform of cytochrome P450 and have narrow therapeutic windows (e.g., astemizole, terfenadine, cisapride, pimozide, quinidine, bepridil, triazolam, midazolam administered orally (for caution on parenterally administered midazolam, see section 4.5), and ergot alkaloids, particularly, ergotamine, dihydroergotamine, ergonovine, methylergonovine) (see section 4.5).

REYATAZ must not be used in combination with products containing St. John’s wort (*Hypericum perforatum*) (see section 4.5).

### 4.4 Special warnings and precautions for use

Patients should be advised that current antiretroviral therapy has not been proven to prevent the risk of transmission of HIV to others through blood or sexual contact. Appropriate precautions should continue to be employed.
Co-administration of REYATAZ with ritonavir at doses greater than 100 mg once daily has not been clinically evaluated. The use of higher ritonavir doses may alter the safety profile of atazanavir (cardiac effects, hyperbilirubinaemia) and therefore is not recommended. Only when atazanavir with ritonavir is co-administered with efavirenz, a dose increase of ritonavir to 200 mg once daily could be considered. In this instance, close clinical monitoring is warranted (see Interaction with other Medicinal Products below).

Patients with coexisting conditions
Atazanavir is primarily hepatically metabolised and increased plasma concentrations were observed in patients with hepatic impairment (see sections 4.2 and 4.3). The safety and efficacy of REYATAZ has not been established in patients with significant underlying liver disorders. Patients with chronic hepatitis B or C and treated with combination antiretroviral therapy are at an increased risk for severe and potentially fatal hepatic adverse reactions. In case of concomitant antiviral therapy for hepatitis B or C, please refer also to the relevant Summary of Product Characteristics for these medicinal products (see section 4.8).

Patients with pre-existing liver dysfunction, including chronic active hepatitis, have an increased frequency of liver function abnormalities during combination antiretroviral therapy and should be monitored according to standard practice. If there is evidence of worsening liver disease in such patients, interruption or discontinuation of treatment must be considered.

No dosage adjustment is needed in patients with renal impairment. However, REYATAZ with ritonavir is not recommended in patients undergoing haemodialysis (see sections 4.2 and 5.2).

Dose related asymptomatic prolongations in PR interval with REYATAZ have been observed in clinical studies. Caution should be used with medicinal products known to induce PR prolongations. In patients with pre-existing conduction problems (second degree or higher atrioventricular or complex bundle-branch block), REYATAZ should be used with caution and only if the benefits exceed the risk (see section 5.1). Particular caution should be used when prescribing REYATAZ in association with medicinal products which have the potential to increase the QT interval and/or in patients with pre-existing risk factors (bradycardia, long congenital QT, electrolyte imbalances (see sections 4.8 and 5.3).

There have been reports of increased bleeding, including spontaneous skin haematomas and haemarthroses, in type A and B haemophiliac patients treated with protease inhibitors. In some patients additional factor VIII was given. In more than half of the reported cases, treatment with protease inhibitors was continued or reintroduced if treatment had been discontinued. A causal relationship has been suggested, although the mechanism of action has not been elucidated. Haemophiliac patients should therefore be made aware of the possibility of increased bleeding.

Fat redistribution and metabolic disorders
Combination antiretroviral therapy has been associated with the redistribution of body fat (lipodystrophy) in HIV patients. The long-term consequences of these events are currently unknown. Knowledge about the mechanism is incomplete. A connection between visceral lipomatosis and protease inhibitors and lipoatrophy and nucleoside reverse transcriptase inhibitors has been hypothesised. A higher risk of lipodystrophy has been associated with individual factors such as older age, and with drug related factors such as longer duration of antiretroviral treatment and associated metabolic disturbances. Clinical examination should include evaluation for physical signs of fat redistribution.

Combination antiretroviral therapy (CART), including REYATAZ (with or without ritonavir)-based CART, is associated with dyslipidaemia. Consideration should be given to the measurement of fasting serum lipids and blood glucose. Lipid disorders should be managed as clinically appropriate (see section 4.8).

In clinical studies, REYATAZ (with or without ritonavir) has been shown to induce dyslipidaemia to a lesser extent than comparators. The clinical impact of such findings has not been demonstrated in the
absence of specific studies on cardiovascular risk. The selection of antiretroviral therapy must be
guided principally by antiviral efficacy. Consultation with standard guidelines for management of
dyslipidaemia is recommended.

**Hyperglycaemia**
New onset diabetes mellitus, hyperglycaemia, and exacerbation of existing diabetes mellitus have been
reported in patients receiving protease inhibitors. In some of these, the hyperglycaemia was severe and
in some cases also associated with ketoacidosis. Many patients had confounding medical conditions,
some of which required therapy with medicinal products that have been associated with development
of diabetes or hyperglycaemia.

**Hyperbilirubinaemia**
Reversible elevations in indirect (unconjugated) bilirubin related to inhibition of UDP-glucuronosyl
transferase (UGT) have occurred in patients receiving REYATAZ (see section 4.8). Hepatic
transaminase elevations that occur with elevated bilirubin in patients receiving REYATAZ should be
evaluated for alternative etiologies. Alternative antiretroviral therapy to REYATAZ may be
considered if jaundice or scleral icterus is unacceptable to a patient. Dose reduction of atazanavir is not
recommended because it may result in a loss of therapeutic effect and development of resistance.

Indinavir is also associated with indirect (unconjugated) hyperbilirubinaemia due to inhibition of
UGT. Combinations of REYATAZ and indinavir have not been studied and co-administration of these
medicinal products is not recommended (see section 4.5).

**Nephrolithiasis**
Nephrolithiasis has been reported in patients receiving REYATAZ (see section 4.8). If signs or
symptoms of nephrolithiasis occur, temporary interruption or discontinuation of treatment may be
considered.

**Immune reactivation syndrome**
In HIV-infected patients with severe immune deficiency at the time of institution of combination
antiretroviral therapy (CART), an inflammatory reaction to asymptomatic or residual opportunistic
pathogens may arise and cause serious clinical conditions, or aggravation of symptoms. Typically,
such reactions have been observed within the first few weeks or months of initiation of CART.
Relevant examples are cytomegalovirus retinitis, generalised and/or focal mycobacterial infections,
and *Pneumocystis carinii* pneumonia. Any inflammatory symptoms should be evaluated and treatment
instituted when necessary.

**Osteonecrosis**
Although the etiology is considered to be multifactorial (including corticosteroid use, alcohol
consumption, severe immunosuppression, higher body mass index), cases of osteonecrosis have been
reported particularly in patients with advanced HIV-disease and/or long-term exposure to combination
antiretroviral therapy (CART). Patients should be advised to seek medical advice if they experience
joint aches and pain, joint stiffness or difficulty in movement.

**Interactions with other medicinal products**
Co-administration of REYATAZ with simvastatin or lovastatin is not recommended (see section 4.5).

Co-administration of REYATAZ with nevirapine or efavirenz is not recommended (see section 4.5).
If the co-administration of REYATAZ with an NNRTI is required, an increase in the dose of both
REYATAZ and ritonavir to 400 mg and 200 mg, respectively, in combination with efavirenz could be
considered with close clinical monitoring.

Atazanavir is metabolised principally by CYP3A4. Co-administration of REYATAZ with ritonavir
and medicinal products that induce CYP3A4 is not recommended (see sections 4.3 and 4.5).

Co-administration of voriconazole and REYATAZ with ritonavir is not recommended unless an
assessment of the benefit/risk justifies the use of voriconazole (see section 4.5).
Concomitant use of REYATAZ/ritonavir and fluticasone or other glucocorticoids that are metabolized by CYP3A4 is not recommended unless the potential benefit of treatment outweighs the risk of systemic corticosteroid effects, including Cushing’s syndrome and adrenal suppression (see section 4.5).

The absorption of atazanavir may be reduced in situations where gastric pH is increased irrespective of cause.

Co-administration of REYATAZ with proton pump inhibitors is not recommended (see section 4.5). If the combination of REYATAZ with a proton pump inhibitor is judged unavoidable, close clinical monitoring is recommended in combination with an increase in the dose of REYATAZ to 400 mg with 100 mg of ritonavir; doses of proton pump inhibitors comparable to omeprazole 20 mg should not be exceeded.

Co-administration of REYATAZ/ritonavir in combination with tenofovir and an H$_2$-receptor antagonist should be avoided (see section 4.5).

**Lactose**
Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

**Paediatric population**

**Safety:**
Asymptomatic PR interval prolongation was more frequent in paediatric patients than adults. Asymptomatic first- and second-degree AV block was reported in paediatric patients (see section 4.8). Caution should be used with medicinal products known to induce PR prolongations. In paediatric patients with pre-existing conduction problems (second degree or higher atrioventricular or complex bundle-branch block), REYATAZ should be used with caution and only if the benefits exceed the risk. Cardiac monitoring is recommended based on the presence of clinical findings (e.g., bradycardia).

**Efficacy**
Atazanavir/ritonavir is not effective in viral strains harbouring multiple mutations of resistance. While in adults no benefit can be expected in patients with $\geq 4$ PI mutations, in treatment experienced children even lower numbers of PI mutations may be predictive of a lack of benefit (see section 5.1).

**4.5 Interaction with other medicinal products and other forms of interaction**

When REYATAZ and ritonavir are co-administered, the metabolic drug interaction profile for ritonavir may predominate because ritonavir is a more potent CYP3A4 inhibitor than atazanavir. The Summary of Product Characteristics for ritonavir must be consulted before initiation of therapy with REYATAZ and ritonavir.

Atazanavir is metabolised in the liver through CYP3A4. It inhibits CYP3A4. Therefore, REYATAZ with ritonavir is contraindicated with medicinal products that are substrates of CYP3A4 and have a narrow therapeutic index: astemizole, terfenadine, cisapride, pimozide, quinidine, bepridil, triazolam, orally administered midazolam, and ergot alkaloids, particularly ergotamine and dihydroergotamine (see section 4.3).

**Other interactions**
Interactions between atazanavir/ritonavir and protease inhibitors, antiretroviral agents other than protease inhibitors, and other non-antiretroviral medicinal products are listed in the tables below (increase is indicated as “$\uparrow$”, decrease as “$\downarrow$”, no change as “$\leftrightarrow$”, twice daily as “BID” and once daily as “QD”). If available, 90% confidence intervals (CI) are shown in parentheses. The studies presented in Table 2 were conducted in healthy subjects unless otherwise noted. Of importance, many studies were conducted with unboosted atazanavir, which is not the approved regimen of atazanavir.
Table 2: Interactions between REYATAZ and other medicinal products

<table>
<thead>
<tr>
<th>Co-administered medicinal products (dose in mg)</th>
<th>Medicinal product assessed</th>
<th>AUC (90% CI)</th>
<th>C&lt;sub&gt;max&lt;/sub&gt; (90% CI)</th>
<th>C&lt;sub&gt;min&lt;/sub&gt; (90% CI)</th>
<th>Recommendations concerning co-administration</th>
</tr>
</thead>
<tbody>
<tr>
<td>ANTI-INFECTIVES</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anti-retrovirals</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Protease inhibitors: The co-administration of REYATAZ/ritonavir and other protease inhibitors has not been studied but would be expected to increase exposure to other protease inhibitors. Therefore, such co-administration is not recommended.</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ritonavir 100 mg QD (atazanavir 300 mg QD)</td>
<td>atazanavir</td>
<td>↑3.50*</td>
<td>↑2.20*</td>
<td>↑8.13*</td>
<td>Ritonavir 100 mg once daily is used as a booster of atazanavir pharmacokinetics.</td>
</tr>
<tr>
<td>studies conducted in HIV-infected patients</td>
<td></td>
<td>(2.44, 5.03)</td>
<td>(1.56, 3.11)</td>
<td>(4.59, 14.39)</td>
<td></td>
</tr>
<tr>
<td>* In a combined analysis, atazanavir 300 mg and ritonavir 100 mg (n=33) was compared to atazanavir 400 mg without ritonavir (n=28). The mechanism of interaction between atazanavir and ritonavir is CYP3A4 inhibition.</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Indinavir</td>
<td>Indinavir</td>
<td></td>
<td></td>
<td></td>
<td>Co-administration of REYATAZ/ritonavir and indinavir is not recommended (see section 4.4).</td>
</tr>
<tr>
<td>Lamivudine 150 mg BID + zidovudine 300 mg BID (atazanavir 400 mg QD)</td>
<td></td>
<td>No significant effect on lamivudine and zidovudine concentrations was observed.</td>
<td></td>
<td>Based on these data and because ritonavir is not expected to have a significant impact on the pharmacokinetics of NRTIs, the co-administration of REYATAZ/ritonavir with these medicinal products is not expected to significantly alter the exposure of the co-administered drugs.</td>
<td></td>
</tr>
<tr>
<td>Didanosine (buffered tablets) 200 mg/stavudine 40 mg, both single dose (atazanavir 400 mg single dose)</td>
<td></td>
<td></td>
<td>Didanosine should be taken at the fasted state 2 hours after REYATAZ/ritonavir taken with food. The co-administration of REYATAZ/ritonavir with stavudine is not expected to significantly alter the exposure of stavudine.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abacavir</td>
<td>The co-administration of REYATAZ/ritonavir with abacavir is not expected to significantly alter the exposure of abacavir.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tenofovir disoproxil fumarate 300 mg QD (atazanavir 300 mg QD with ritonavir 100 mg QD)</td>
<td></td>
<td></td>
<td>No significant effect on atazanavir concentrations was observed when administered with enteric-coated didanosine, but administration with food decreased didanosine concentrations.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Didanosine (enteric coated capsules) 400 mg single dose (atazanavir 300 mg QD with ritonavir 100 mg QD)</td>
<td>Didanosine (with food)</td>
<td>↓0.66</td>
<td>↓0.62</td>
<td>↑1.25</td>
<td>Didanosine should be taken at the fasted state 2 hours after REYATAZ/ritonavir taken with food. The co-administration of REYATAZ/ritonavir with stavudine is not expected to significantly alter the exposure of stavudine.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(0.59, 0.73)</td>
<td>(0.52, 0.74)</td>
<td>(0.92, 1.69)</td>
<td></td>
</tr>
<tr>
<td>Tenoforv disoproxil fumarate 300 mg QD (atazanavir 300 mg QD with ritonavir 100 mg QD) studies conducted in HIV-infected patients</td>
<td></td>
<td>↓0.78*</td>
<td>↓0.84*</td>
<td>↓0.77*</td>
<td>* In a combined analysis from several clinical studies, atazanavir/ritonavir 300/100 mg co-administered with tenofovir</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(0.65, 0.94)</td>
<td>(0.70, 1.00)</td>
<td>(0.57-1.02)</td>
<td></td>
</tr>
</tbody>
</table>

* In a combined analysis from several clinical studies, atazanavir/ritonavir 300/100 mg co-administered with tenofovir.
<table>
<thead>
<tr>
<th>Co-administered medicinal products (dose in mg)</th>
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<th>C&lt;sub&gt;max&lt;/sub&gt; (90% CI)</th>
<th>C&lt;sub&gt;min&lt;/sub&gt; (90% CI)</th>
<th>Recommendations concerning co-administration</th>
</tr>
</thead>
<tbody>
<tr>
<td>disoproxil fumarate 300 mg (n=39) was compared to atazanavir/ritonavir 300/100 mg (n=33). The efficacy of REYATAZ/ritonavir in combination with tenofovir in treatment-experienced patients has been demonstrated in clinical study 045 and in treatment naive patients in clinical study 138 (see sections 4.8 and 5.1). The mechanism of interaction between atazanavir and tenofovir is unknown.</td>
<td>tenofovir disoproxil fumarate</td>
<td>↑1.37 (1.30, 1.45)</td>
<td>↑1.34 (1.20, 1.51)</td>
<td>↑1.29 (1.21, 1.36)</td>
<td>Patients should be closely monitored for tenofovir-associated adverse events, including renal disorders.</td>
</tr>
<tr>
<td>Tenofovir disoproxil fumarate 300 mg QD (atazanavir 300 mg QD with ritonavir 100 mg QD)</td>
<td>atazanavir (pm): all administered with food</td>
<td>↔1.00* (0.91, 1.10)</td>
<td>↑1.17* (1.08, 1.27)</td>
<td>↓0.58* (0.49, 0.69)</td>
<td>Co-administration of efavirenz with REYATAZ/ritonavir is not recommended (see section 4.4)</td>
</tr>
<tr>
<td>Efavirenz 600 mg QD (atazanavir 400 mg QD with ritonavir 100 mg QD)</td>
<td>atazanavir (pm): all administered with food</td>
<td>↔1.06** (0.90, 1.26)</td>
<td>↔1.09** (0.95, 1.26)</td>
<td>↔1.12** (0.84, 1.49)</td>
<td>* When compared to REYATAZ 300 mg/ritonavir 100 mg once daily in the evening without efavirenz. This decrease in atazanavir C&lt;sub&gt;min&lt;/sub&gt;, might negatively impact the efficacy of atazanavir. The mechanism of efavirenz/atazanavir interaction is CYP3A4 induction. ** based on historical comparison.</td>
</tr>
<tr>
<td>Nevirapine 200 mg BID (atazanavir 400 mg QD with ritonavir 100 mg QD) study conducted in HIV infected patients</td>
<td>nevirapine</td>
<td>↑1.26 (1.17, 1.36)</td>
<td>↑1.21 (1.11, 1.32)</td>
<td>↑1.35 (1.25, 1.47)</td>
<td>Co-administration of nevirapine with REYATAZ/ritonavir is not recommended (see section 4.4)</td>
</tr>
<tr>
<td>Antibiotics</td>
<td>clarithromycin (1.75, 2.16)</td>
<td>↑1.50 (1.32, 1.71)</td>
<td>↑2.60 (2.35, 2.88)</td>
<td>No recommendation regarding dose reduction can be made; therefore, caution should be exercised if REYATAZ/ritonavir is co-administered with clarithromycin.</td>
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<tr>
<td></td>
<td>14-OH clarithromycin (0.26, 0.34)</td>
<td>↓0.30 (0.24, 0.33)</td>
<td>↓0.38 (0.34, 0.42)</td>
<td>A dose reduction of clarithromycin may result in subtherapeutic concentrations of 14-OH clarithromycin. The mechanism of the clarithromycin/atazanavir interaction is CYP3A4 inhibition.</td>
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</tr>
<tr>
<td></td>
<td>atazanavir (1.16, 1.43)</td>
<td>↑1.28 (0.93, 1.20)</td>
<td>↑1.06 (1.66, 2.21)</td>
<td>Ketoconazole and itraconazole should be used cautiously with REYATAZ/ritonavir. High doses of ketoconazole and itraconazole (&gt;200 mg/day) are not recommended.</td>
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<tr>
<td></td>
<td>Itraconazole</td>
<td>Itraconazole, like ketoconazole, is a potent inhibitor as well as a substrate of CYP3A4. Based on data obtained with other boosted PIs and ketoconazole, where ketoconazole AUC showed a 3-fold increase, REYATAZ/ritonavir is expected to increase ketoconazole or itraconazole concentrations.</td>
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</tbody>
</table>
| Voriconazole | Co-administration of REYATAZ/ritonavir and voriconazole has not been studied. The effect of co-administration of oral voriconazole and low dose (100 mg) oral ritonavir was investigated in healthy volunteers. Low doses of ritonavir (100 mg BID) decreased the C<sub>max</sub> and AUC of voriconazole | Co-administration of voriconazole and REYATAZ/ritonavir is not recommended unless an assessment of the benefit/risk to
Co-administered medicinal products (dose in mg) & Medicinal product assessed & AUC (90% CI) & C<sub>max</sub> (90% CI) & C<sub>min</sub> (90% CI) & Recommendations concerning co-administration
---
Fluconazole 200 mg QD (atazanavir 300 mg and ritonavir 100 mg QD) & Atazanavir and fluconazole concentrations were not significantly modified when REYATAZ/ritonavir was co-administered with fluconazole. & No dosage adjustments are needed for REYATAZ/ritonavir and fluconazole.

**Antimycobacterial**

| Rifabutin 150 mg twice weekly (atazanavir 300 mg and ritonavir 100 mg QD) | Rifabutin & ↑1.48 **
(1.19, 1.84) & ↑2.49 **
(2.03, 3.06) & ↑1.40 **
(1.05, 1.87) & When given with REYATAZ/ritonavir, the recommended dose of rifabutin is 150 mg 3 times per week on set days (for example Monday-Wednesday-Friday). Increased monitoring for rifabutin-associated adverse reactions including neutropenia and uveitis is warranted due to an expected increase in exposure to rifabutin. Further dosage reduction of rifabutin to 150 mg twice weekly on set days is recommended for patients in whom the 150 mg dose 3 times per week is not tolerated. It should be kept in mind that the twice weekly dosage of 150 mg may not provide an optimal exposure to rifabutin thus leading to a risk of rifamycin resistance and a treatment failure. No dose adjustment is needed for REYATAZ/ritonavir. |
| 25-O-desacetyl-rifabutin & ↑10.90 **
(8.14, 14.61) & ↑7.77 **
(6.13, 9.83) & ↑11.45 **
(8.15, 16.10) & |
** When compared to rifabutin 150 mg QD alone. Total rifabutin and 25-O-desacetyl-rifabutin AUC: ↑2.19 (1.78, 2.69).

In previous studies, the pharmacokinetics of atazanavir was not altered by rifabutin.

Rifampicin & Rifampicin is a strong CYP3A4 inducer and has been shown to cause a 72% decrease in atazanavir AUC which can result in virological failure and resistance development. During attempts to overcome the decreased exposure by increasing the dose of REYATAZ or other protease inhibitors with ritonavir, a high frequency of liver reactions was seen. & The combination of rifampicin and REYATAZ/ritonavir with concomitant low-dose ritonavir is contraindicated (see section 4.3). |

**ACID REDUCING AGENTS**

**H<sub>2</sub>-Receptor antagonists**

<table>
<thead>
<tr>
<th>Without Tenofovir</th>
<th>For patients not taking tenofovir, if REYATAZ 300 mg/ritonavir 100 mg and H&lt;sub&gt;2&lt;/sub&gt;-receptor</th>
</tr>
</thead>
<tbody>
<tr>
<td>In HIV-infected patients with atazanavir/ritonavir at the recommended dose 300/100 mg QD</td>
<td></td>
</tr>
<tr>
<td>- famotidine 20 mg BID</td>
<td></td>
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</tbody>
</table>
Co-administered medicinal products (dose in mg) | Medicinal product assessed | AUC (90% CI) | C\textsubscript{max} (90% CI) | C\textsubscript{min} (90% CI) | Recommendations concerning co-administration
--- | --- | --- | --- | --- | ---
- famotidine 40 mg BID | atazanavir | 10.77 (0.68, 0.86) | 10.77 (0.67, 0.88) | 10.80 (0.69, 0.92) | antagonists are co-administered, a dose equivalent to famotidine 20 mg BID should not be exceeded. If a higher dose of an H\textsubscript{2}-receptor antagonist is required (eg, famotidine 40 mg BID or equivalent) an increase of the REYATAZ/ritonavir dose from 300/100 mg to 400/100 mg can be considered.

In Healthy volunteers with atazanavir/ritonavir at an increased dose of 400/100 mg QD
- famotidine 40 mg BID | atazanavir | ↔1.03 (0.86, 1.22) | ↔1.02 (0.87, 1.18) | ↔0.86 (0.68, 1.08) |

With Tenofovir 300 mg QD
In HIV-infected patients with atazanavir/ritonavir at the recommended dose of 300/100 mg QD
- famotidine 20 mg BID | atazanavir | ↓0.79* (0.66, 0.96) | ↓0.79* (0.64, 0.96) | ↓0.81* (0.63, 1.05) |
- famotidine 40 mg BID | atazanavir | ↓0.76* (0.64, 0.89) | ↓0.77* (0.64, 0.92) | ↓0.75* (0.53, 1.07) |

* When compared to atazanavir 300 mg QD with ritonavir 100 mg QD and tenofovir disoproxil fumarate 300 mg all as a single dose with food. When compared to atazanavir 300 mg with ritonavir 100 mg \textit{without} tenofovir, atazanavir concentrations are expected to be additionally decreased by about 20%.

The mechanism of interaction is decreased solubility of atazanavir as intra-gastric pH increases with H\textsubscript{2} blockers.

Proton pump inhibitors
Omeprazole 40 mg QD (atazanavir 400 mg QD with ritonavir 100 mg QD)
atazanavir (am): 2 hr after omeprazole
\[\text{AUC} \downarrow \text{0.39} (0.35, 0.45) \quad \text{C}_{\text{max}} \downarrow \text{0.44} (0.38, 0.51) \quad \text{C}_{\text{min}} \downarrow \text{0.35} (0.29, 0.41)\]

Omeprazole 20 mg QD (atazanavir 400 mg QD with ritonavir 100 mg QD)
atazanavir (am): 1 hr after omeprazole
\[\text{AUC} \downarrow \text{0.70}^* (0.57, 0.86) \quad \text{C}_{\text{max}} \downarrow \text{0.69}^* (0.58, 0.83) \quad \text{C}_{\text{min}} \downarrow \text{0.69}^* (0.54, 0.88)\]

* When compared to atazanavir 300 mg QD with ritonavir 100 mg QD

The decrease in AUC, C\textsubscript{max}, and C\textsubscript{min} was not mitigated when an increased dose of REYATAZ/ritonavir (400/100 mg once daily) was temporally separated from omeprazole by 12 hours. Although not studied, similar results are expected with other proton pump inhibitors. This decrease in atazanavir exposure might negatively impact the efficacy of atazanavir. The mechanism of interaction is decreased solubility of atazanavir as intra-gastric pH increases with proton pump inhibitors.

Antacids
Antacids and medicinal products containing buffers
Reduced plasma concentrations of atazanavir may be the consequence of increased gastric pH if antacids, including buffered medicinal products, are administered with REYATAZ/ritonavir.

For patients who are taking tenofovir,
Co-administration of REYATAZ/ritonavir in combination with tenofovir and an H\textsubscript{2}-receptor antagonist should be avoided (see section 4.4). If the combination of REYATAZ/ritonavir with both tenofovir and an H\textsubscript{2}-receptor antagonist is judged unavoidable, close clinical monitoring is recommended. A dose increase of REYATAZ to 400 mg with 100 mg of ritonavir may be considered but is still under evaluation.

Antacids
Reduced plasma concentrations of atazanavir may be the consequence of increased gastric pH if antacids, including buffered medicinal products, are administered with REYATAZ/ritonavir.

REYATAZ/ritonavir should be administered 2 hours before or 1 hour after antacids or
<table>
<thead>
<tr>
<th>Co-administered medicinal products (dose in mg)</th>
<th>Medicinal product assessed</th>
<th>AUC (90% CI)</th>
<th>$C_{\text{max}}$ (90% CI)</th>
<th>$C_{\text{min}}$ (90% CI)</th>
<th>Recommendations concerning co-administration</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ANTICOAGULANTS</strong></td>
<td></td>
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<td>buffered medicinal products.</td>
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<tr>
<td>Warfarin</td>
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<td>It is recommended that the INR be monitored</td>
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<td>carefully during treatment with REYATAZ/</td>
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<td></td>
<td></td>
<td>ritonavir, especially when commencing therapy.</td>
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<tr>
<td><strong>ANTINEOPLASTICS AND IMMUNOSUPPRESSANTS</strong></td>
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<tr>
<td>Antineoplastics</td>
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<tr>
<td>Irinotecan</td>
<td>Atazanavir inhibits UGT</td>
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<td></td>
<td></td>
<td>If REYATAZ/ritonavir is co-administered with</td>
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<td></td>
<td>and may interfere with</td>
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<td>irinotecan, patients should be closely</td>
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<td></td>
<td>the metabolism of</td>
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<td>monitored for adverse events related to</td>
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<td></td>
<td>irinotecan, resulting</td>
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<td>irinotecan.</td>
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<td>in increased irinotecan</td>
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<tr>
<td>Immunosuppressants</td>
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<tr>
<td>Cyclosporin</td>
<td>Concentrations of these</td>
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<td></td>
<td>More frequent therapeutic concentration</td>
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<tr>
<td>Tacrolimus</td>
<td>immunosuppressants may</td>
<td></td>
<td></td>
<td></td>
<td>monitoring of these medicinal products is</td>
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<tr>
<td>Sirolimus</td>
<td>be increased when</td>
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<td></td>
<td></td>
<td>recommended until plasma levels have</td>
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<td></td>
<td>co-administered with</td>
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<td>been stabilised.</td>
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<td></td>
<td>REYATAZ/ritonavir due to</td>
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<td></td>
<td>CYP3A4 inhibition.</td>
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<tr>
<td><strong>CARDIOVASCULAR AGENTS</strong></td>
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<tr>
<td>Antiarrhythmics</td>
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<tr>
<td>Amiodarone</td>
<td>Concentrations of these</td>
<td></td>
<td></td>
<td></td>
<td>Caution is warranted and therapeutic</td>
</tr>
<tr>
<td>Systemic lidocaine, Quinidine</td>
<td>antiarrhythmics may be</td>
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<td></td>
<td>concentration monitoring is recommended when</td>
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<td></td>
<td>increased when</td>
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<td>available. The concomitant use of</td>
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<td></td>
<td>co-administered with</td>
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<td></td>
<td>quinidine is contraindicated (see section 4.3).</td>
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<td></td>
<td>REYATAZ/ritonavir. The</td>
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<td></td>
<td>mechanism of amiodarone</td>
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<td>or systemic lidocaine/</td>
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<td></td>
<td>atazanavir interaction is</td>
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<td>CYP3A inhibition. Quinidine</td>
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<td>has a narrow therapeutic</td>
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<td>window and is</td>
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<td>contraindicated due to</td>
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<td></td>
<td>potential inhibition of</td>
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<td></td>
<td>CYP3A by REYATAZ/ritonavir</td>
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<tr>
<td>Calcium channel blockers</td>
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<tr>
<td>Bepridil</td>
<td>REYATAZ/ritonavir should</td>
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<td>Co-administration with bepridil is</td>
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<td></td>
<td>not be used in combination</td>
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<td></td>
<td>contraindicated (see section 4.3).</td>
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<td></td>
<td>with medicinal products</td>
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<td>that are substrates of</td>
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<td></td>
<td>CYP3A4 and have a narrow</td>
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<td></td>
<td>therapeutic index.</td>
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<tr>
<td>Diltiazem 180 mg QD (atazanavir 400 mg QD)</td>
<td>diliazem</td>
<td>12.25</td>
<td>1.98</td>
<td>2.42</td>
<td>An initial dose reduction of diltiazem by</td>
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<tr>
<td></td>
<td>(2.09, 2.41)</td>
<td>(1.78, 2.19)</td>
<td>(2.14, 2.73)</td>
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<td>50% is recommended, with subsequent</td>
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<td>desacetyl-</td>
<td>12.65</td>
<td>7.22</td>
<td>2.21</td>
<td>titration as needed and ECG monitoring.</td>
</tr>
<tr>
<td></td>
<td>diltiazem</td>
<td>(2.45, 2.87)</td>
<td>(2.44, 3.03)</td>
<td>(2.02, 2.42)</td>
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<tr>
<td>Verapamil</td>
<td>Serum concentrations of</td>
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<td>Caution should be exercised when verapamil is</td>
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<td></td>
<td>verapamil may be</td>
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<td></td>
<td>co-administered with REYATAZ/ritonavir.</td>
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<td>increased by REYATAZ/</td>
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<td></td>
<td>ritonavir due to CYP3A4</td>
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<td>inhibition.</td>
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<td>CORTICOSTEROIDS</td>
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<td>Fluticasone propionate intranasal 50 µg 4</td>
<td>The fluticasone propionate</td>
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<td></td>
<td>Co-administration of REYATAZ/ritonavir and</td>
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<td>times daily for 7 days (ritonavir 100 mg</td>
<td>plasma levels increased</td>
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<td>these glucocorticoids is not</td>
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<td>capsules BID)</td>
<td>significantly, whereas</td>
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<td></td>
<td>the intrinsic cortisol</td>
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<td>levels decreased by</td>
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<td></td>
<td>approximately 86%</td>
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<td>(90% confidence interval</td>
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<td>82-89%) Greater effects</td>
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<td>may be expected when</td>
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<td>fluticasone propionate is</td>
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<td>inhaled. Systemic</td>
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<td></td>
<td>corticosteroid effects</td>
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</table>

**Note:** The table provides a summary of the interactions between co-administered medicinal products and REYATAZ/ritonavir, including AUC, $C_{\text{max}}$, and $C_{\text{min}}$ values. Recommendations are provided for each category, highlighting important considerations for patients and healthcare providers.
<table>
<thead>
<tr>
<th>Co-administered medicinal products (dose in mg)</th>
<th>Medicinal product assessed</th>
<th>AUC (90% CI)</th>
<th>C_max (90% CI)</th>
<th>C_min (90% CI)</th>
<th>Recommendations concerning co-administration</th>
</tr>
</thead>
<tbody>
<tr>
<td>including Cushing’s syndrome and adrenal suppression have been reported in patients receiving ritonavir and inhaled or intranasally administered fluticasone propionate; this could also occur with other corticosteroids metabolized via the P450 3A pathway, e.g., budesonide. The effects of high fluticasone systemic exposure on ritonavir plasma levels are yet unknown. The mechanism of interaction is CYP3A4 inhibition.</td>
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<td>recommended unless the potential benefit of treatment outweighs the risk of systemic corticosteroid effects (see section 4.4). A dose reduction of the glucocorticoid should be considered with close monitoring of local and systemic effects or a switch to a glucocorticoid, which is not a substrate for CYP3A4 (e.g., beclomethasone). Moreover, in case of withdrawal of glucocorticoids, progressive dose reduction may have to be performed over a longer period.</td>
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<tr>
<td>ERECTILE DYSFUNCTION</td>
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<td><strong>PDE5 Inhibitors</strong></td>
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<tr>
<td>Sildenafil</td>
<td>Sildenafil is metabolised by CYP3A4. Co-administration with REYATAZ/ritonavir may result in increased concentrations of sildenafil and an increase in sildenafil-associated adverse events, including hypotension, visual changes, and priapism. The mechanism of the sildenafil/atazanavir interaction is CYP3A4 inhibition.</td>
<td></td>
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<td>Patients should be warned about these possible side effects.</td>
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<tr>
<td>HERBAL PRODUCTS</td>
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<tr>
<td>St. John’s wort (Hypericum perforatum):</td>
<td>Concomitant use of St. John's wort with REYATAZ/ritonavir may be expected to result in significant reduction in plasma levels of atazanavir. This effect may be due to an induction of CYP3A4. There is a risk of loss of therapeutic effect and development of resistance (see section 4.3).</td>
<td></td>
<td></td>
<td></td>
<td>Co-administration of REYATAZ/ritonavir with products containing St. John's wort is contraindicated.</td>
</tr>
<tr>
<td>HORMONAL CONTRACEPTIVES</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ethinyloestradiol 25 µg + norgestimate (atazanavir 300 mg QD with ritonavir 100 mg QD)</td>
<td>ethinyloestradiol ▼0.81 (0.75, 0.87) ▼0.84 (0.74, 0.95) ▼0.63 (0.55, 0.71) norgestimate ▼1.85 (1.67, 2.05) ▼1.68 (1.51, 1.88) ▼2.02 (1.77, 2.31)</td>
<td></td>
<td></td>
<td></td>
<td>If an oral contraceptive is administered with REYATAZ/ritonavir, it is recommended that the oral contraceptive contain at least 30 µg of ethinyloestradiol and that the patient be reminded of strict compliance with this contraceptive dosing regimen. Co-administration of REYATAZ/ritonavir with other hormonal contraceptives or oral contraceptives containing progestogens other than norgestimate has not been studied, and therefore should be avoided. An alternate reliable method of contraception is recommended.</td>
</tr>
<tr>
<td></td>
<td>While the concentration of ethinyloestradiol was increased with atazanavir given alone, due to both UGT and CYP3A4 inhibition by atazanavir, the net effect of atazanavir/ritonavir is a decrease in ethinyloestradiol levels because of the inducing effect of ritonavir. The increase in progestin exposure may lead to related side-effects (e.g. insulin resistance, dyslipidemia, acne and spotting), thus possibly affecting the compliance.</td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

36
<table>
<thead>
<tr>
<th>Co-administered medicinal products (dose in mg)</th>
<th>Medicinal product assessed</th>
<th>AUC (90% CI)</th>
<th>C&lt;sub&gt;max&lt;/sub&gt; (90% CI)</th>
<th>C&lt;sub&gt;min&lt;/sub&gt; (90% CI)</th>
<th>Recommendations concerning co-administration</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>LIPID LOWERING AGENTS</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>HMG-CoA reductase inhibitors</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Simvastatin and lovastatin</td>
<td>Simvastatin and lovastatin</td>
<td></td>
<td></td>
<td></td>
<td>Co-administration of simvastatin or lovastatin with REYATAZ/ritonavir is not recommended due to an increased risk of myopathy including rhabdomyolysis. The use of another HMG-CoA reductase inhibitor which does not undergo metabolism by CYP3A such as pravastatin or fluvastatin is recommended.</td>
</tr>
<tr>
<td><strong>Atorvastatin</strong></td>
<td>Atorvastatin</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>OPIOIDS</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Buprenorphine, QD, stable maintenance dose, (atazanavir 300 mg QD with ritonavir 100 mg QD)</td>
<td>buprenorphine ↑1.67 ↑1.37 ↑1.69</td>
<td></td>
<td></td>
<td></td>
<td>Co-administration warrants clinical monitoring for sedation and cognitive effects. A dose reduction of buprenorphine may be considered.</td>
</tr>
<tr>
<td></td>
<td>norbuprenorphine ↑2.05 ↑1.61 ↑2.01</td>
<td>The mechanism of interaction is CYP3A4 and UGT1A1 inhibition. Concentrations of atazanavir were not significantly affected.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Methadone, stable maintenance dose (atazanavir 400 mg QD)</td>
<td>No significant effect on methadone concentrations was observed. Given that low dose ritonavir (100 mg twice daily) has been shown to have no significant effect on methadone concentrations, no interaction is expected if methadone is co-administered with REYATAZ and ritonavir, based on these data.</td>
<td></td>
<td></td>
<td></td>
<td>No dosage adjustment is necessary if methadone is co-administered with REYATAZ and ritonavir.</td>
</tr>
<tr>
<td><strong>SEDATIVES</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Benzodiazepines</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Midazolam</td>
<td>Midazolam and triazolam are extensively metabolized by CYP3A4. Co-administration with REYATAZ/ritonavir may cause a large increase in the concentration of these benzodiazepines. No drug interaction study has been performed for the co-administration of REYATAZ/ritonavir with benzodiazepines. Based on data for other CYP3A4 inhibitors, plasma concentrations of midazolam are expected to be significantly higher when midazolam is given orally. Data from concomitant use of parenteral midazolam with other protease inhibitors suggest a possible 3-4 fold increase in midazolam plasma levels.</td>
<td></td>
<td></td>
<td></td>
<td>REYATAZ/ritonavir should not be co-administered with triazolam or orally administered midazolam (see section 4.3), whereas caution should be used with co-administration of REYATAZ/ritonavir and parenteral midazolam. If REYATAZ is co-administered with parenteral midazolam, it should be done in an intensive care unit (ICU) or similar setting which ensures close clinical monitoring and appropriate medical management in case of respiratory depression and/or prolonged sedation. Dosage adjustment for midazolam should be considered, especially</td>
</tr>
<tr>
<td>Triazolam</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### Co-administered medicinal products (dose in mg)  
<table>
<thead>
<tr>
<th>Medicinal product assessed</th>
<th>AUC (90% CI)</th>
<th>$C_{\text{max}}$ (90% CI)</th>
<th>$C_{\text{min}}$ (90% CI)</th>
<th>Recommendations concerning co-administration</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>if more than a single dose of midazolam is administered.</td>
</tr>
</tbody>
</table>

### 4.6 Pregnancy and lactation

There are no adequate data from the use of atazanavir in pregnant women. Studies in animals have not shown evidence of selective developmental toxicity or effects on reproductive function and fertility (see section 5.3). REYATAZ should be used during pregnancy only if the potential benefit justifies the potential risk.

It is not known whether REYATAZ administered to the mother during pregnancy will exacerbate physiological hyperbilirubinaemia and lead to kernicterus in neonates and infants. In the prepartum period, additional monitoring and alternative therapy to REYATAZ should be considered.

It is not known whether atazanavir is excreted in human milk. Studies in rats have demonstrated that atazanavir is excreted in the milk. It is therefore recommended that mothers being treated with REYATAZ not breast-feed their infants. As a general rule, it is recommended that HIV infected women not breast-feed their infants in order to avoid transmission of HIV.

### 4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed. Patients should be informed that dizziness has been reported during treatment with regimens containing REYATAZ (see section 4.8).

### 4.8 Undesirable effects

REYATAZ has been evaluated for safety in combination therapy with other antiretroviral medicinal products in controlled clinical trials in 1,806 adult patients receiving REYATAZ 400 mg once daily (1,151 patients, 52 weeks median duration and 152 weeks maximum duration) or REYATAZ 300 mg with ritonavir 100 mg once daily (655 patients, 96 weeks median duration and 108 weeks maximum duration).

Adverse reactions were consistent between patients who received REYATAZ 400 mg once daily and patients who received REYATAZ 300 mg with ritonavir 100 mg once daily, except that jaundice and elevated total bilirubin levels were reported more frequently with REYATAZ plus ritonavir.

Among patients who received REYATAZ 400 mg once daily or REYATAZ 300 mg with ritonavir 100 mg once daily, the only adverse reactions of any severity reported very commonly with at least a possible relationship to regimens containing REYATAZ and one or more NRTIs were nausea (20%), diarrhoea (10%), and jaundice (13%). Among patients receiving REYATAZ 300 mg with ritonavir 100 mg, the frequency of jaundice was 19%. In the majority of cases, jaundice was reported within a few days to a few months after the initiation of treatment (see section 4.4).

Combination antiretroviral therapy has been associated with redistribution of body fat (lipodystrophy) in HIV patients, including loss of peripheral and facial subcutaneous fat, increased intra-abdominal and visceral fat, breast hypertrophy, and dorsocervical fat accumulation (buffalo hump).

Combination antiretroviral therapy has been associated with metabolic abnormalities such as hypertriglyceridaemia, hypercholesterolaemia, insulin resistance, hyperglycaemia, and hyperlactataemia (see sections 4.4 and 5.1).
Adult patients
The following adverse reactions of moderate intensity or greater with at least a possible relationship to regimens containing REYATAZ and one or more NRTIs have also been reported. The frequency of adverse reactions listed below is defined using the following convention: very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1,000 to < 1/100), rare (≥ 1/10,000 to < 1/1,000), or very rare (< 1/10,000). Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Cardiac disorders: rare: oedema, palpitation

Nervous system disorders: common: headache;
uncommon: peripheral neuropathy, syncope, amnesia, dizziness, somnolence, dysgeusia

Eye disorders: common: ocular icterus

Respiratory, thoracic and mediastinal disorders: uncommon: dyspnoea

Gastrointestinal disorders: common: vomiting, diarrhoea, abdominal pain, nausea, dyspepsia;
uncommon: pancreatitis, gastritis, abdominal distension, stomatitis aphthous, flatulence, dry mouth

Renal and urinary disorders: uncommon: nephrolithiasis, hematuria, proteinuria, pollakiuria;
rare: kidney pain

Skin and subcutaneous tissue disorders: common: rash;
uncommon: urticaria, alopecia, pruritus;
rare: vesiculobullous rash, eczema, vasodilatation

Musculoskeletal and connective tissue disorders: uncommon: muscle atrophy, arthralgia, myalgia;
rare: myopathy

Metabolism and nutrition disorders: uncommon: weight decreased, weight gain, anorexia, appetite increased

Vascular disorders: uncommon: hypertension

General disorders and administration site conditions: common: lipodystrophy syndrome, fatigue;
uncommon: chest pain, malaise, pyrexia, asthenia;
rare: gait disturbance

Immune system disorders: uncommon: hypersensitivity

Hepatobiliary disorders: common: jaundice;
uncommon: hepatitis;
rare: hepatosplenomegaly

Reproductive system and breast disorders: uncommon: gynaecomastia

Psychiatric disorders: uncommon: depression, disorientation, anxiety, insomnia, sleep disorder, abnormal dream
In HIV-infected patients with severe immune deficiency at the time of initiation of combination antiretroviral therapy (CART), an inflammatory reaction to asymptomatic or residual opportunistic infections may arise (see section 4.4).

Cases of osteonecrosis have been reported, particularly in patients with generally acknowledged risk factors, advanced HIV disease or long-term exposure to combination antiretroviral therapy (CART). The frequency of this is unknown (see section 4.4).

**Laboratory abnormalities**
The most frequently reported laboratory abnormality in patients receiving regimens containing REYATAZ and one or more NRTIs was elevated total bilirubin reported predominantly as elevated indirect [unconjugated] bilirubin (87% Grade 1, 2, 3, or 4). Grade 3 or 4 elevation of total bilirubin was noted in 37% (6% Grade 4). Among experienced patients treated with REYATAZ 300 mg once daily with 100 mg ritonavir once daily for a median duration of 95 weeks, 53% had Grade 3-4 total bilirubin elevations. Among naive patients treated with REYATAZ 300 mg once daily with 100 mg ritonavir once daily for a median duration of 96 weeks, 48% had Grade 3-4 total bilirubin elevations (see section 4.4).

Other marked clinical laboratory abnormalities (Grade 3 or 4) reported in $\geq 2\%$ of patients receiving regimens containing REYATAZ and one or more NRTIs included: elevated creatine kinase (7%), elevated alanine aminotransferase/serum glutamic-pyruvic transaminase (ALT/SGPT) (5%), low neutrophils (5%), elevated aspartate aminotransferase/serum glutamic-oxaloacetic transaminase (AST/SGOT) (3%), and elevated lipase (3%).

Two percent of patients treated with REYATAZ experienced concurrent Grade 3-4 ALT/AST and Grade 3-4 total bilirubin elevations.

Patients co-infected with hepatitis B and/or hepatitis C virus
Among 1,151 patients receiving atazanavir 400 mg once daily, 177 patients were co-infected with chronic hepatitis B or C, and among 655 patients receiving atazanavir 300 mg once daily with ritonavir 100 mg once daily, 97 patients were co-infected with chronic hepatitis B or C. Co-infected patients were more likely to have baseline hepatic transaminase elevations than those without chronic viral hepatitis. No differences in frequency of bilirubin elevations were observed between these patients and those without viral hepatitis. The frequency of treatment emergent hepatitis or transaminase elevations in co-infected patients was comparable between REYATAZ and comparator regimens (see section 4.4).

**Paediatric population**
In clinical studies, paediatric patients 3 months to less than 18 years of age had a mean duration of treatment with REYATAZ of 115 weeks. The safety profile in these studies was overall comparable to that seen in adults. Both asymptomatic first-degree (23%) and second-degree (1%) atrioventricular block were reported in paediatric patients. The most frequently reported laboratory abnormality in paediatric patients receiving REYATAZ was elevation of total bilirubin ($\geq 2.6$ times ULN, Grade 3-4) which occurred in 45% of patients.

**Postmarketing experience**
There have been postmarketing reports of unknown frequency for torsades de pointes, QTc prolongation, diabetes mellitus, hyperglycaemia, nephrolithiasis, and gallbladder disorders including cholelithiasis, cholecystitis, and cholestasis.

**4.9 Overdose**
Human experience of acute overdose with REYATAZ is limited. Single doses up to 1,200 mg have been taken by healthy volunteers without symptomatic untoward effects. At high doses that lead to high drug exposures, jaundice due to indirect (unconjugated) hyperbilirubinaemia (without associated liver function test changes) or PR interval prolongations may be observed (see sections 4.4 and 4.8).
Treatment of overdose with REYATAZ should consist of general supportive measures, including monitoring of vital signs and electrocardiogram (ECG), and observations of the patient's clinical status. If indicated, elimination of unabsorbed atazanavir should be achieved by emesis or gastric lavage. Administration of activated charcoal may also be used to aid removal of unabsorbed drug. There is no specific antidote for overdose with REYATAZ. Since atazanavir is extensively metabolised by the liver and is highly protein bound, dialysis is unlikely to be beneficial in significant removal of this medicinal product.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: protease inhibitor, ATC code: J05AE08

Mechanism of action: atazanavir is an azapeptide HIV-1 protease inhibitor (PI). The compound selectively inhibits the virus-specific processing of viral Gag-Pol proteins in HIV-1 infected cells, thus preventing formation of mature virions and infection of other cells.

Antiviral activity in vitro: atazanavir exhibits anti-HIV-1 (including all clades tested) and anti-HIV-2 activity in cell culture.

Resistance

Antiretroviral treatment naive adult patients
In clinical trials of antiretroviral treatment naive patients treated with unboosted atazanavir, the I50L substitution, sometimes in combination with an A71V change, is the signature resistance substitution for atazanavir. Resistance levels to atazanavir ranged from 3.5- to 29-fold without evidence of phenotypic cross resistance to other PIs. In clinical trials of antiretroviral treatment naive patients treated with boosted atazanavir, the I50L substitution did not emerge in any patient without baseline PI substitutions. The N88S substitution has been rarely observed in patients with virologic failure on atazanavir (with or without ritonavir). While it may contribute to decreased susceptibility to atazanavir when it occurs with other protease substitutions, in clinical studies N88S by itself does not always lead to phenotypic resistance to atazanavir or have a consistent impact on clinical efficacy.

Table 3. De novo substitutions in treatment naive patients failing therapy with atazanavir + ritonavir (Study 138, 96 weeks)

<table>
<thead>
<tr>
<th>Frequency</th>
<th>de novo PI substitution (n=26)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;20%</td>
<td>none</td>
</tr>
<tr>
<td>10-20%</td>
<td>none</td>
</tr>
</tbody>
</table>

*a Number of patients with paired genotypes classified as virological failures (HIV RNA ≥ 400 copies/ml).

The M184I/V substitution emerged in 5/26 REYATAZ/ritonavir and 7/26 lopinavir/ritonavir virologic failure patients, respectively.

Antiretroviral treatment experienced adult patients
In antiretroviral treatment experienced patients from Studies 009, 043, and 045, 100 isolates from patients designated as virological failures on therapy that included either atazanavir, atazanavir + ritonavir, or atazanavir + saquinavir were determined to have developed resistance to atazanavir. Of the 60 isolates from patients treated with either atazanavir or atazanavir + ritonavir, 18 (30%) displayed the I50L phenotype previously described in naive patients.

Table 4. De novo substitutions in treatment experienced patients failing therapy with atazanavir + ritonavir (Study 045, 48 weeks)

<table>
<thead>
<tr>
<th>Frequency</th>
<th>de novo PI substitution (n=35)*a,b</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;20%</td>
<td>M36, M46, I54, A71, V82</td>
</tr>
<tr>
<td>10-20%</td>
<td>L10, I15, K20, V32, E35, S37, F53, I62, G73, I84, L90</td>
</tr>
</tbody>
</table>

*a Number of patients with paired genotypes classified as virological failures (HIV RNA ≥ 400 copies/ml).
Ten patients had baseline phenotypic resistance to atazanavir + ritonavir (fold change [FC] > 5.2). FC susceptibility in cell culture relative to the wild-type reference was assayed using PhenoSense™ (Monogram Biosciences, South San Francisco, California, USA).

None of the de novo substitutions (see Table 4) are specific to atazanavir and may reflect re-emergence of archived resistance on atazanavir + ritonavir in Study 045 treatment-experienced population.

The resistance in antiretroviral treatment experienced patients mainly occurs by accumulation of the major and minor resistance substitutions described previously to be involved in protease inhibitor resistance.

**Clinical results**

*In antiretroviral naïve adult patients*  
*Study 138* is an international randomised, open-label, multicenter, prospective trial of treatment naïve patients comparing REYATAZ/ritonavir (300 mg/100 mg once daily) to lopinavir/ritonavir (400 mg/100 mg twice daily), each in combination with fixed dose tenofovir/emtricitabine (300 mg/200 mg tablets once daily). The REYATAZ/ritonavir arm showed similar (non-inferior) antiviral efficacy compared to the lopinavir/ritonavir arm, as assessed by the proportion of patients with HIV RNA < 50 copies/ml at week 48 (Table 5). Analyses of data through 96 weeks of treatment demonstrated durability of antiviral activity (Table 5).
Table 5:  Efficacy Outcomes in Study 138

<table>
<thead>
<tr>
<th>Parameter</th>
<th>REYATAZ/ritonavir(^b) (300 mg/100 mg once daily)</th>
<th>Lopinavir/ritonavir(^c) (400 mg/100 mg twice daily)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Week 48</td>
<td>Week 96</td>
</tr>
<tr>
<td>HIV RNA &lt;50 copies/ml, %</td>
<td></td>
<td></td>
</tr>
<tr>
<td>All patients(^d)</td>
<td>78</td>
<td>74</td>
</tr>
<tr>
<td>Difference estimate [95% CI](^d)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Per protocol analysis(^e)</td>
<td>86</td>
<td>91</td>
</tr>
<tr>
<td>(n=392(^f))</td>
<td>(n=352)</td>
<td>(n=372)</td>
</tr>
<tr>
<td>Difference estimate [95% CI]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HIV RNA &lt;50 copies/ml, % by Baseline Characteristic(^d)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HIV RNA &lt;100,000 copies/ml</td>
<td>82 (n=217)</td>
<td>75 (n=217)</td>
</tr>
<tr>
<td>HIV RNA ≥100,000 copies/ml</td>
<td>74 (n=223(^f))</td>
<td>74 (n=223)</td>
</tr>
<tr>
<td>CD4 count &lt;50 cells/mm(^3)</td>
<td>78 (n=58)</td>
<td>78 (n=58)</td>
</tr>
<tr>
<td>50 to &lt;100 cells/mm(^3)</td>
<td>76 (n=45)</td>
<td>71 (n=45)</td>
</tr>
<tr>
<td>100 to &lt;200 cells/mm(^3)</td>
<td>75 (n=106)</td>
<td>71 (n=106)</td>
</tr>
<tr>
<td>≥200 cells/mm(^3)</td>
<td>80 (n=222)</td>
<td>76 (n=222)</td>
</tr>
<tr>
<td>HIV RNA Mean Change from Baseline, log10 copies/ml</td>
<td></td>
<td></td>
</tr>
<tr>
<td>All patients</td>
<td>-3.09 (n=397)</td>
<td>-3.21 (n=360)</td>
</tr>
<tr>
<td>CD4 Mean Change from Baseline, cells/mm(^3)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>All patients</td>
<td>203 (n=370)</td>
<td>268 (n=336)</td>
</tr>
<tr>
<td>CD4 Mean Change from Baseline, cells/mm(^3) by Baseline Characteristic</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HIV RNA &lt;100,000 copies/ml</td>
<td>179 (n=183)</td>
<td>243 (n=163)</td>
</tr>
<tr>
<td>HIV RNA ≥100,000 copies/ml</td>
<td>227 (n=187)</td>
<td>291 (n=173)</td>
</tr>
</tbody>
</table>

\(^a\) Mean baseline CD4 cell count was 214 cells/mm\(^3\) (range 2 to 810 cells/mm\(^3\)) and mean baseline plasma HIV-1 RNA was 4.94 log10 copies/ml (range 2.6 to 5.88 log10 copies/ml)

\(^b\) REYATAZ/RTV with tenofovir/emtricitabine (fixed dose 300 mg/200 mg tablets once daily).

\(^c\) Lopinavir/RTV with tenofovir/emtricitabine (fixed dose 300 mg/200 mg tablets once daily).

\(^d\) Intent-to-treat analysis, with missing values considered as failures.

\(^e\) Per protocol analysis: Excluding non-completers and patients with major protocol deviations.

\(^f\) Number of patients evaluable.

In antiretroviral experienced adult patients

Study 045 is a randomised, multicenter trial comparing REYATAZ/ritonavir (300/100 mg once daily) and REYATAZ/saquinavir (400/1,200 mg once daily), to lopinavir + ritonavir (400/100 mg fixed dose combination twice daily), each in combination with tenofovir (see sections 4.5 and 4.8) and one NRTI, in patients with virologic failure on two or more prior regimens containing at least one PI, NRTI, and NNRTI. For randomised patients, the mean time of prior antiretroviral exposure was 138 weeks for PIs, 281 weeks for NRTIs, and 85 weeks for NNRTIs. At baseline, 34\% of patients were receiving a PI and 60\% were receiving an NNRTI. Fifteen of 120 (13\%) patients in the REYATAZ + ritonavir treatment arm and 17 of 123 (14\%) patients in the lopinavir + ritonavir arm had four or more of the PI substitutions L10, M46, I54, V82, I84, and L90. Thirty-two percent of patients in the study had a viral strain with fewer than two NRTI substitutions.

The primary endpoint was the time-averaged difference in change from baseline in HIV RNA through 48 weeks (Table 6).
Table 6: Efficacy Outcomes at Week 48 and at Week 96 (Study 045)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>ATV/RTVb (300 mg/100 mg once daily) n=120</th>
<th>LPV/RTVc (400 mg/100 mg twice daily) n=123</th>
<th>Time-averaged difference ATV/RTV-LPV/RTV</th>
<th>97.5% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV RNA Mean Change from Baseline, log10 copies/ml</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All patients</td>
<td>-1.93 (n=90e)</td>
<td>-2.29 (n=64)</td>
<td>-1.87 (n=99)</td>
<td>-2.08 (n=65)</td>
</tr>
<tr>
<td>HIV RNA &lt;50 copies/ml, %f (responder/evaluable)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All patients</td>
<td>36 (43/120)</td>
<td>32 (38/120)</td>
<td>42 (52/123)</td>
<td>35 (41/118)</td>
</tr>
<tr>
<td>HIV RNA &lt;50 copies/ml by select baseline PI substitutions, g % (responder/evaluable)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0-2</td>
<td>44 (28/63)</td>
<td>41 (26/63)</td>
<td>56 (32/57)</td>
<td>48 (26/54)</td>
</tr>
<tr>
<td>3</td>
<td>18 (2/11)</td>
<td>9 (1/11)</td>
<td>38 (6/16)</td>
<td>33 (5/15)</td>
</tr>
<tr>
<td>≥4</td>
<td>27 (12/45)</td>
<td>24 (11/45)</td>
<td>28 (14/50)</td>
<td>20 (10/49)</td>
</tr>
</tbody>
</table>

CD4 Mean Change from Baseline, cells/mm³ | | | | |
| All patients | 110 (n=83) | 122 (n=60) | 121 (n=94) | 154 (n=60) | NA | NA |

*The mean baseline CD4 cell count was 337 cells/mm³ (range: 14 to 1,543 cells/mm³) and the mean baseline plasma HIV-1 RNA level was 4.4 log₁₀ copies/ml (range: 2.6 to 5.88 log₁₀ copies/ml).

b ATV/RTV with tenofovir/emtricitabine (fixed dose 300 mg/200 mg tablets once daily).

c LPV/RTV with tenofovir/emtricitabine (fixed dose 300 mg/200 mg tablets once daily).

d Confidence interval.

e Number of patients evaluable.

f Intent-to-treat analysis, with missing values considered as failures. Responders on LPV/RTV who completed treatment before Week 96 are excluded from Week 96 analysis. The proportion of patients with HIV RNA < 400 copies/ml were 53% and 43% for ATV/RTV and LPV/RTV at weeks 48 and 96 respectively.

g Select substitutions include any change at positions L10, K20, L24, V32, L33, M36, M46, G48, I50, I54, L63, A71, G73, V82, I84, and L90 (0-2, 3, 4 or more) at baseline.

NA = not applicable.

Through 48 weeks of treatment, the mean changes from baseline in HIV RNA levels for REYATAZ + ritonavir and lopinavir + ritonavir were similar (non-inferior). Consistent results were obtained with the last observation carried forward method of analysis (time-averaged difference of 0.11, 97.5% confidence interval [-0.15, 0.36]). By as-treated analysis, excluding missing values, the proportions of patients with HIV RNA < 400 copies/ml (< 50 copies/ml) in the REYATAZ + ritonavir arm and the lopinavir + ritonavir arm were 55% (40%) and 56% (46%), respectively.

Through 96 weeks of treatment, mean HIV RNA changes from baseline for REYATAZ + ritonavir and lopinavir + ritonavir met criteria for non-inferiority based on observed cases. Consistent results were obtained with the last observation carried forward method of analysis. By as-treated analysis, excluding missing values, the proportions of patients with HIV RNA <400 copies/ml (<50 copies/ml) for REYATAZ + ritonavir were 84% (72%) and for lopinavir + ritonavir were 82% (72%). It is important to note that at time of the 96-week analysis, 48 % of patients overall remained on study.

REYATAZ + saquinavir was shown to be inferior to lopinavir + ritonavir.

Paediatric population

Assessment of the pharmacokinetics, safety, tolerability, and efficacy of REYATAZ is based on data from the open-label, multicenter clinical trial PACTG 1020A conducted in patients from 3 months to 21 years of age. Overall in this study, 182 paediatric patients (81 antiretroviral-naive and 101 antiretroviral-experienced) received once daily REYATAZ (capsule or powder formulation), with or without ritonavir, in combination with two NRTIs.

The clinical data derived from this study are inadequate to support the use of atazanavir (with or without ritonavir) in children below 6 years of age.

Efficacy data observed in the 41 paediatric patients aged 6 years to less than 18 years that received REYATAZ capsules with ritonavir are presented in Table 7. For treatment-naive paediatric patients, the mean baseline CD4 cell count was 344 cells/mm³ (range: 2 to 800 cells/mm³) and mean baseline...
plasma HIV 1 RNA was 4.67 log_{10} copies/ml (range: 3.70 to 5.00 log_{10} copies/ml). For treatment-experienced paediatric patients, the mean baseline CD4 cell count was 522 cells/mm^3 (range: 100 to 1157 cells/ mm^3) and mean baseline plasma HIV 1 RNA was 4.09 log_{10} copies/ml (range: 3.28 to 5.00 log_{10} copies/ml).

Table 7: Efficacy Outcomes (paediatric patients 6 years to less than 18 years of age) at Week 48 (Study PACTG 1020A)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Treatment-Naive REYATAZ Capsules/ritonavir (300 mg/100 mg once daily) n=16</th>
<th>Treatment-Experienced REYATAZ Capsules/ritonavir (300 mg/100 mg once daily) n=25</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV RNA &lt;50 copies/ml, % a</td>
<td>All patients 81 (13/16)</td>
<td>24 (6/25)</td>
</tr>
<tr>
<td>HIV RNA &lt;400 copies/ml, % a</td>
<td>All patients 88 (14/16)</td>
<td>32 (8/25)</td>
</tr>
<tr>
<td>CD4 Mean Change from Baseline, cells/mm^3</td>
<td>All patients 293 (n=14^b)</td>
<td>229 (n=14^b)</td>
</tr>
<tr>
<td>HIV RNA &lt;50 copies/ml by select baseline PI substitutions, % (responder/evaluable^d)</td>
<td>0-2 NA</td>
<td>27 (4/15)</td>
</tr>
<tr>
<td></td>
<td>3 NA</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>≥4 NA</td>
<td>0 (0/3)</td>
</tr>
</tbody>
</table>

a Intent-to-treat analysis, with missing values considered as failures.
^b Number of patients evaluable.
^c PI major L24I, D30N, V32I, L33F, M46IL, 147AV, G48V, 150LV, F53LY, I54ALMSTV, L76V, V82AFLST, I84V, N88DS, L90M; PI minor: L10CFIRV, V11I, E35G, K43T, Q58E, A71ILTV, G73ACST, T74P, N83D, L89V.
^d Includes patients with baseline resistance data.
NA = not applicable.

Data in the paediatric population are very limited. Available data do suggest that atazanavir in combination with ritonavir may not be effective in treatment experienced children even with very few (<3) PI mutations.

5.2 Pharmacokinetic properties

The pharmacokinetics of atazanavir were evaluated in healthy adult volunteers and in HIV-infected patients; significant differences were observed between the two groups. The pharmacokinetics of atazanavir exhibit a non-linear disposition. In healthy subjects, the AUC of atazanavir from the capsules and oral powder were similar.

Absorption: in HIV-infected patients (n=33, combined studies), multiple dosing of REYATAZ 300 mg once daily with ritonavir 100 mg once daily with food produced a geometric mean (CV%) for atazanavir, C_{max} of 4466 (42%) ng/ml, with time to C_{max} of approximately 2.5 hours. The geometric mean (CV%) for atazanavir C_{min} and AUC was 654 (76%) ng/ml and 44185 (51%) ng•h/ml, respectively.

Food effect: co-administration of REYATAZ and ritonavir with food optimises the bioavailability of atazanavir. Co-administration of a single 300-mg dose of REYATAZ and 100-mg dose of ritonavir with a light meal resulted in a 33% increase in the AUC and a 40% increase in both the C_{max} and the 24-hour concentration of atazanavir relative to the fasting state. Co-administration with a high-fat meal did not affect the AUC of atazanavir relative to fasting conditions and the C_{max} was within 11% of fasting values. The 24-hour concentration following a high fat meal was increased by approximately 33% due to delayed absorption; the median T_{max} increased from 2.0 to 5.0 hours. Administration of REYATAZ with ritonavir with either a light or a high-fat meal decreased the coefficient of variation.
of AUC and C\text{max} by approximately 25% compared to the fasting state. To enhance bioavailability and minimise variability, REYATAZ is to be taken with food.

\textit{Distribution}: atazanavir was approximately 86% bound to human serum proteins over a concentration range of 100 to 10,000 ng/ml. Atazanavir binds to both alpha-1-acid glycoprotein (AAG) and albumin to a similar extent (89% and 86%, respectively, at 1,000 ng/ml). In a multiple-dose study in HIV-infected patients dosed with 400 mg of atazanavir once daily with a light meal for 12 weeks, atazanavir was detected in the cerebrospinal fluid and semen.

\textit{Metabolism}: studies in humans and \textit{in vitro} studies using human liver microsomes have demonstrated that atazanavir is principally metabolised by CYP3A4 isozyme to oxygenated metabolites. Metabolites are then excreted in the bile as either free or glucuronidated metabolites. Additional minor metabolic pathways consist of N-dealkylation and hydrolysis. Two minor metabolites of atazanavir in plasma have been characterised. Neither metabolite demonstrated \textit{in vitro} antiviral activity.

\textit{Elimination}: following a single 400-mg dose of $^{14}$C-atazanavir, 79% and 13% of the total radioactivity was recovered in the faeces and urine, respectively. Unchanged drug accounted for approximately 20% and 7% of the administered dose in the faeces and urine, respectively. Mean urinary excretion of unchanged drug was 7% following 2 weeks of dosing at 800 mg once daily. In HIV-infected adult patients (n=33, combined studies) the mean half-life within a dosing interval for atazanavir was 12 hours at steady state following a dose of 300 mg daily with ritonavir 100 mg once daily with a light meal.

\textbf{Special populations}

\textbf{Paediatric patients}: The pharmacokinetics of atazanavir in paediatric patients exhibit an increased absorption rate compared to adults. There is a slight trend toward a higher clearance in younger children when normalised for body weight. As a result, greater peak to trough ratios are observed. The geometric mean AUC values in paediatric patients at recommended doses are expected to be similar to those observed in adults, with higher geometric mean C\text{max} (13-17%) and lower geometric mean C\text{min} (up to 30%) values compared to those in adults. The variability of pharmacokinetic parameters in younger children is higher.

\textbf{Impaired renal function}: in healthy subjects, the renal elimination of unchanged atazanavir was approximately 7% of the administered dose. There are no pharmacokinetic data available for REYATAZ with ritonavir in patients with renal insufficiency. REYATAZ (without ritonavir) has been studied in adult patients with severe renal impairment (n=20), including those on haemodialysis, at multiple doses of 400 mg once daily. Although this study presented some limitations (i.e., unbound drug concentrations not studied), results suggested that the atazanavir pharmacokinetic parameters were decreased by 30% to 50% in patients undergoing haemodialysis compared to patients with normal renal function. The mechanism of this decrease is unknown. (See sections 4.2 and 4.4.)

\textbf{Impaired hepatic function}: atazanavir is metabolised and eliminated primarily by the liver. The effects of hepatic impairment on the pharmacokinetics of atazanavir after a 300 mg dose with ritonavir have not been studied. Concentrations of atazanavir with or without ritonavir are expected to be increased in patients with moderately or severely impaired hepatic function (see sections 4.2, 4.3, and 4.4).

\textbf{Age/Gender}: a study of the pharmacokinetics of atazanavir was performed in 59 healthy male and female subjects (29 young, 30 elderly). There were no clinically important pharmacokinetic differences based on age or gender.

\textbf{Race}: a population pharmacokinetic analysis of samples from Phase II clinical trials indicated no effect of race on the pharmacokinetics of atazanavir.
5.3 Preclinical safety data

In repeat-dose toxicity studies, conducted in mice, rats, and dogs, atazanavir-related findings were generally confined to the liver and included generally minimal to mild increases in serum bilirubin and liver enzymes, hepatocellular vacuolation and hypertrophy, and, in female mice only, hepatic single-cell necrosis. Systemic exposures of atazanavir in mice (males), rats, and dogs at doses associated with hepatic changes were at least equal to that observed in humans given 400 mg once daily. In female mice, atazanavir exposure at a dose that produced single-cell necrosis was 12 times the exposure in humans given 400 mg once daily. Serum cholesterol and glucose were minimally to mildly increased in rats but not in mice or dogs.

During in vitro studies, cloned human cardiac potassium channel (hERG), was inhibited by 15% at a concentration (30 μM) of atazanavir corresponding to 30-fold the free drug concentration at Cmax in humans. Similar concentrations of atazanavir increased by 13% the action potential duration (APD90) in rabbit Purkinje fibres study. Electrocardiographic changes (sinus bradycardia, prolongation of PR interval, prolongation of QT interval, and prolongation of QRS complex) were observed only in an initial 2-week oral toxicity study performed in dogs. Subsequent 9-month oral toxicity studies in dogs showed no drug-related electrocardiographic changes. The clinical relevance of these non-clinical data is unknown. Potential cardiac effects of this product in humans cannot be ruled out (see sections 4.4 and 4.8). The potential for PR prolongation should be considered in cases of overdose (see section4.9).

In a fertility and early embryonic development study in rats, atazanavir altered oestrus cycling with no effects on mating or fertility. No teratogenic effects were observed in rats or rabbits at maternally toxic doses. In pregnant rabbits, gross lesions of the stomach and intestines were observed in dead or moribund does at maternal doses 2 and 4 times the highest dose administered in the definitive embryo-development study. In the pre- and postnatal development assessment in rats, atazanavir produced a transient reduction in body weight in the offspring at a maternally toxic dose. Systemic exposure to atazanavir at doses that resulted in maternal toxicity was at least equal to or slightly greater than that observed in humans given 400 mg once daily.

Atazanavir was negative in an Ames reverse-mutation assay but did induce chromosomal aberrations in vitro in both the absence and presence of metabolic activation. In in vivo studies in rats, atazanavir did not induce micronuclei in bone marrow, DNA damage in duodenum (comet assay), or unscheduled DNA repair in liver at plasma and tissue concentrations exceeding those that were clastogenic in vitro.

In long-term carcinogenicity studies of atazanavir in mice and rats, an increased incidence of benign hepatic adenomas was seen in female mice only. The increased incidence of benign hepatic adenomas in female mice was likely secondary to cytotoxic liver changes manifested by single-cell necrosis and is considered to have no relevance for humans at intended therapeutic exposures. There were no tumorigenic findings in male mice or in rats.

Atazanavir increased opacity of bovine corneas in an in vitro ocular irritation study, indicating it may be an ocular irritant upon direct contact with the eye.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Capsule contents:
Crospovidone
Lactose monohydrate
Magnesium stearate

Capsule shells:
Gelatine
Indigocarmin (E132)
Titanium dioxide (E171)

Blue ink containing:
Shellac
Propylene glycol
Ammonium hydroxide
Indigocarmin (E132)

White ink containing:
Shellac
Titanium dioxide (E171)
Ammonium hydroxide
Propylene glycol
Simethicone

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years

6.4 Special precautions for storage

Do not store above 25°C.

6.5 Nature and contents of container

Each carton contains one high-density polyethylene (HDPE) bottle closed with child-resistant polypropylene closure. Each bottle contains 60 hard capsules.

Each carton contains 60 x 1 capsules; 10 blister cards of 6 x 1 capsules each in Alu/Alu perforated unit dose blisters.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

Any unused product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

BRISTOL-MYERS SQUIBB PHARMA EEIG
Uxbridge Business Park
Sanderson Road
Uxbridge UB8 1DH
United Kingdom

8. MARKETING AUTHORIZATION NUMBER(S)

EU/1/03/267/003-004
9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 02 March 2004
Date of latest renewal: 02 March 2009

10. DATE OF REVISION OF THE TEXT

{month year}

Detailed information on this medicinal product is available on the website of the European Medicines Agency (EMEA) http://www.emea.europa.eu
1. **NAME OF THE MEDICINAL PRODUCT**

REYATAZ 200 mg hard capsules

2. **QUALITATIVE AND QUANTITATIVE COMPOSITION**

Each capsule contains 200 mg of atazanavir (as sulphate)

Excipient: 109.57 mg of lactose per capsule.

For a full list of excipients, see section 6.1.

3. **PHARMACEUTICAL FORM**

Hard capsule

Opaque blue capsule printed with white ink, with "BMS 200 mg" on one half and with "3631" on the other half.

4. **CLINICAL PARTICULARS**

4.1 **Therapeutic indications**

REYATAZ capsules, co-administered with low dose ritonavir, are indicated for the treatment of HIV-1 infected adults and paediatric patients 6 years of age and older in combination with other antiretroviral medicinal products.

Based on available virological and clinical data from adult patients, no benefit is expected in patients with strains resistant to multiple protease inhibitors (≥ 4 PI mutations). There are very limited data available from children aged 6 to less than 18 years (see sections 4.4 and 5.1).

The choice of REYATAZ in treatment experienced adult and paediatric patients should be based on individual viral resistance testing and the patient’s treatment history (see sections 4.4 and 5.1).

4.2 **Posology and method of administration**

Therapy should be initiated by a physician experienced in the management of HIV infection.

*Adults*: the recommended dose of REYATAZ capsules is 300 mg once daily taken with ritonavir 100 mg once daily and with food. Ritonavir is used as a booster of atazanavir pharmacokinetics (see sections 4.5 and 5.1).

*Paediatric patients (6 years to less than 18 years of age)*: The dose of REYATAZ capsules for paediatric patients is based on body weight as shown in Table 1 and should not exceed the recommended adult dose. REYATAZ capsules must be taken with ritonavir and have to be taken with food.
Table 1: Dose for Paediatric Patients (6 years to less than 18 years of age) for REYATAZ capsules with ritonavir

<table>
<thead>
<tr>
<th>Body Weight (kg)</th>
<th>REYATAZ dose</th>
<th>ritonavir dose&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>15 to less than 20</td>
<td>150 mg</td>
<td>100 mg&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>20 to less than 40</td>
<td>200 mg</td>
<td>100 mg</td>
</tr>
<tr>
<td>at least 40</td>
<td>300 mg</td>
<td>100 mg</td>
</tr>
</tbody>
</table>

<sup>a</sup> Ritonavir capsules, tablets or oral solution.

<sup>b</sup> Ritonavir oral solution no lower than 80 mg and not more than 100 mg may be used for paediatric patients from 15 kg to less than 20 kg who cannot swallow ritonavir capsules/tablets.

The available data do not support the use of REYATAZ in combination with low dose ritonavir in paediatric patients weighing less than 15 kg.

**Paediatric patients (less than 6 years of age):** REYAYAZ is not recommended in paediatric patients less than 6 years of age due to insufficient data on pharmacokinetics, safety, and efficacy. REYATAZ has not been studied in children less than 3 months of age and is not recommended especially taking into account the potential risk of kernicterus.

**Patients with renal impairment:** no dosage adjustment is needed. REYATAZ with ritonavir is not recommended in patients undergoing haemodialysis (see sections 4.4 and 5.2).

**Patients with hepatic impairment:** REYATAZ with ritonavir has not been studied in patients with hepatic impairment. REYATAZ with ritonavir should be used with caution in patients with mild hepatic impairment. REYATAZ must not be used in patients with moderate to severe hepatic impairment (see sections 4.3, 4.4, and 5.2).

**Method of administration:** for oral administration. The capsules should be swallowed whole. REYATAZ oral powder is available for adult patients who are unable to swallow capsules (see Summary of Product Characteristics for REYATAZ oral powder). REYATAZ oral powder must not be used in paediatric patients unable to swallow capsules due to insufficient data on pharmacokinetics, safety, and efficacy.

### 4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients (see section 6.1).

Patients with moderate to severe hepatic insufficiency (see sections 4.2 and 4.4).

Combination of rifampicin and REYATAZ with concomitant low-dose ritonavir is contraindicated (see section 4.5).

REYATAZ with ritonavir must not be used in combination with medicinal products that are substrates of the CYP3A4 isoform of cytochrome P450 and have narrow therapeutic windows (e.g., astemizole, terfenadine, cisapride, pimozide, quinidine, bepridil, triazolam, midazolam administered orally (for caution on parenterally administered midazolam, see section 4.5), and ergot alkaloids, particularly, ergotamine, dihydroergotamine, ergonovine, methylergonovine) (see section 4.5).

REYATAZ must not be used in combination with products containing St. John’s wort (*Hypericum perforatum*) (see section 4.5).

### 4.4 Special warnings and precautions for use

Patients should be advised that current antiretroviral therapy has not been proven to prevent the risk of transmission of HIV to others through blood or sexual contact. Appropriate precautions should continue to be employed.
Co-administration of REYATAZ with ritonavir at doses greater than 100 mg once daily has not been clinically evaluated. The use of higher ritonavir doses may alter the safety profile of atazanavir (cardiac effects, hyperbilirubinaemia) and therefore is not recommended. Only when atazanavir with ritonavir is co-administered with efavirenz, a dose increase of ritonavir to 200 mg once daily could be considered. In this instance, close clinical monitoring is warranted (see Interaction with other Medicinal Products below).

Patients with coexisting conditions
Atazanavir is primarily hepatically metabolised and increased plasma concentrations were observed in patients with hepatic impairment (see sections 4.2 and 4.3). The safety and efficacy of REYATAZ has not been established in patients with significant underlying liver disorders. Patients with chronic hepatitis B or C and treated with combination antiretroviral therapy are at an increased risk for severe and potentially fatal hepatic adverse reactions. In case of concomitant antiviral therapy for hepatitis B or C, please refer also to the relevant Summary of Product Characteristics for these medicinal products (see section 4.8).

Patients with pre-existing liver dysfunction, including chronic active hepatitis, have an increased frequency of liver function abnormalities during combination antiretroviral therapy and should be monitored according to standard practice. If there is evidence of worsening liver disease in such patients, interruption or discontinuation of treatment must be considered.

No dosage adjustment is needed in patients with renal impairment. However, REYATAZ with ritonavir is not recommended in patients undergoing haemodialysis (see sections 4.2 and 5.2).

Dose related asymptomatic prolongations in PR interval with REYATAZ have been observed in clinical studies. Caution should be used with medicinal products known to induce PR prolongations. In patients with pre-existing conduction problems (second degree or higher atioventricular or complex bundle-branch block), REYATAZ should be used with caution and only if the benefits exceed the risk (see section 5.1). Particular caution should be used when prescribing REYATAZ in association with medicinal products which have the potential to increase the QT interval and/or in patients with pre-existing risk factors (bradycardia, long congenital QT, electrolyte imbalances (see sections 4.8 and 5.3).

There have been reports of increased bleeding, including spontaneous skin haematomas and haemarthroses, in type A and B haemophiliac patients treated with protease inhibitors. In some patients additional factor VIII was given. In more than half of the reported cases, treatment with protease inhibitors was continued or reintroduced if treatment had been discontinued. A causal relationship has been suggested, although the mechanism of action has not been elucidated. Haemophiliac patients should therefore be made aware of the possibility of increased bleeding.

Fat redistribution and metabolic disorders
Combination antiretroviral therapy has been associated with the redistribution of body fat (lipodystrophy) in HIV patients. The long-term consequences of these events are currently unknown. Knowledge about the mechanism is incomplete. A connection between visceral lipomatosis and protease inhibitors and lipoatrophy and nucleoside reverse transcriptase inhibitors has been hypothesised. A higher risk of lipodystrophy has been associated with individual factors such as older age, and with drug related factors such as longer duration of antiretroviral treatment and associated metabolic disturbances. Clinical examination should include evaluation for physical signs of fat redistribution.

Combination antiretroviral therapy (CART), including REYATAZ (with or without ritonavir)-based CART, is associated with dyslipidaemia. Consideration should be given to the measurement of fasting serum lipids and blood glucose. Lipid disorders should be managed as clinically appropriate (see section 4.8).

In clinical studies, REYATAZ (with or without ritonavir) has been shown to induce dyslipidaemia to a lesser extent than comparators. The clinical impact of such findings has not been demonstrated in the
absence of specific studies on cardiovascular risk. The selection of antiretroviral therapy must be
guided principally by antiviral efficacy. Consultation with standard guidelines for management of
dyslipidaemia is recommended.

**Hyperglycaemia**
New onset diabetes mellitus, hyperglycaemia, and exacerbation of existing diabetes mellitus have been
reported in patients receiving protease inhibitors. In some of these, the hyperglycaemia was severe and
in some cases also associated with ketoacidosis. Many patients had confounding medical conditions,
some of which required therapy with medicinal products that have been associated with development
of diabetes or hyperglycaemia.

**Hyperbilirubinaemia**
Reversible elevations in indirect (unconjugated) bilirubin related to inhibition of UDP-glucuronosyl
transferase (UGT) have occurred in patients receiving REYATAZ (see section 4.8). Hepatic
transaminase elevations that occur with elevated bilirubin in patients receiving REYATAZ should be
evaluated for alternative etiologies. Alternative antiretroviral therapy to REYATAZ may be
considered if jaundice or scleral icterus is unacceptable to a patient. Dose reduction of atazanavir is not
recommended because it may result in a loss of therapeutic effect and development of resistance.

Indinavir is also associated with indirect (unconjugated) hyperbilirubinaemia due to inhibition of
UGT. Combinations of REYATAZ and indinavir have not been studied and co-administration of these
medicinal products is not recommended (see section 4.5).

**Nephrolithiasis**
Nephrolithiasis has been reported in patients receiving REYATAZ (see section 4.8). If signs or
symptoms of nephrolithiasis occur, temporary interruption or discontinuation of treatment may be
considered.

**Immune reactivation syndrome**
In HIV-infected patients with severe immune deficiency at the time of institution of combination
antiretroviral therapy (CART), an inflammatory reaction to asymptomatic or residual opportunistic
pathogens may arise and cause serious clinical conditions, or aggravation of symptoms. Typically,
such reactions have been observed within the first few weeks or months of initiation of CART.
Relevant examples are cytomegalovirus retinitis, generalised and/or focal mycobacterial infections,
and *Pneumocystis carinii* pneumonia. Any inflammatory symptoms should be evaluated and treatment
instituted when necessary.

**Osteonecrosis**
Although the etiology is considered to be multifactorial (including corticosteroid use, alcohol
consumption, severe immunosuppression, higher body mass index), cases of osteonecrosis have been
reported particularly in patients with advanced HIV-disease and/or long-term exposure to combination
antiretroviral therapy (CART). Patients should be advised to seek medical advice if they experience
joint aches and pain, joint stiffness or difficulty in movement.

**Interactions with other medicinal products**
Co-administration of REYATAZ with simvastatin or lovastatin is not recommended (see section 4.5).

Co-administration of REYATAZ with nevirapine or efavirenz is not recommended (see section 4.5).
If the co-administration of REYATAZ with an NNRTI is required, an increase in the dose of both
REYATAZ and ritonavir to 400 mg and 200 mg, respectively, in combination with efavirenz could be
considered with close clinical monitoring.

Atazanavir is metabolised principally by CYP3A4. Co-administration of REYATAZ with ritonavir
and medicinal products that induce CYP3A4 is not recommended (see sections 4.3 and 4.5).

Co-administration of voriconazole and REYATAZ with ritonavir is not recommended unless an
assessment of the benefit/risk justifies the use of voriconazole (see section 4.5).
Concomitant use of REYATAZ/ritonavir and fluticasone or other glucocorticoids that are metabolized by CYP3A4 is not recommended unless the potential benefit of treatment outweighs the risk of systemic corticosteroid effects, including Cushing's syndrome and adrenal suppression (see section 4.5).

The absorption of atazanavir may be reduced in situations where gastric pH is increased irrespective of cause.

Co-administration of REYATAZ with proton pump inhibitors is not recommended (see section 4.5). If the combination of REYATAZ with a proton pump inhibitor is judged unavoidable, close clinical monitoring is recommended in combination with an increase in the dose of REYATAZ to 400 mg with 100 mg of ritonavir; doses of proton pump inhibitors comparable to omeprazole 20 mg should not be exceeded.

Co-administration of REYATAZ/ritonavir in combination with tenofovir and an H₂-receptor antagonist should be avoided (see section 4.5).

Lactose
Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

Paediatric population
Safety:
Asymptomatic PR interval prolongation was more frequent in paediatric patients than adults. Asymptomatic first- and second-degree AV block was reported in paediatric patients (see section 4.8). Caution should be used with medicinal products known to induce PR prolongations. In paediatric patients with pre-existing conduction problems (second degree or higher atioventricular or complex bundle-branch block), REYATAZ should be used with caution and only if the benefits exceed the risk. Cardiac monitoring is recommended based on the presence of clinical findings (e.g., bradycardia).

Efficacy
Atazanavir/ritonavir is not effective in viral strains harbouring multiple mutations of resistance. While in adults no benefit can be expected in patients with ≥4 PI mutations, in treatment experienced children even lower numbers of PI mutations may be predictive of a lack of benefit (see section 5.1).

4.5 Interaction with other medicinal products and other forms of interaction

When REYATAZ and ritonavir are co-administered, the metabolic drug interaction profile for ritonavir may predominate because ritonavir is a more potent CYP3A4 inhibitor than atazanavir. The Summary of Product Characteristics for ritonavir must be consulted before initiation of therapy with REYATAZ and ritonavir.

Atazanavir is metabolised in the liver through CYP3A4. It inhibits CYP3A4. Therefore, REYATAZ with ritonavir is contraindicated with medicinal products that are substrates of CYP3A4 and have a narrow therapeutic index: astemizole, terfenadine, cisapride, pimozide, quinidine, bepridil, triazolam, orally administered midazolam, and ergot alkaloids, particularly ergotamine and dihydroergotamine (see section 4.3).

Other interactions
Interactions between atazanavir/ritonavir and protease inhibitors, antiretroviral agents other than protease inhibitors, and other non-antiretroviral medicinal products are listed in the tables below (increase is indicated as “↑”, decrease as “↓”, no change as “↔”, twice daily as “BID” and once daily as “QD”). If available, 90% confidence intervals (CI) are shown in parentheses. The studies presented in Table 2 were conducted in healthy subjects unless otherwise noted. Of importance, many studies were conducted with unboosted atazanavir, which is not the approved regimen of atazanavir.
Table 2: Interactions between REYATAZ and other medicinal products

<table>
<thead>
<tr>
<th>Co-administered medicinal products (dose in mg)</th>
<th>Medicinal product assessed</th>
<th>AUC (90% CI)</th>
<th>C&lt;sub&gt;max&lt;/sub&gt; (90% CI)</th>
<th>C&lt;sub&gt;min&lt;/sub&gt; (90% CI)</th>
<th>Recommendations concerning co-administration</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ANTI-INFECTION</strong></td>
<td><strong>Co-administered medicinal products (dose in mg)</strong></td>
<td><strong>Medicinal product assessed</strong></td>
<td><strong>AUC</strong> <em>(90% CI)</em></td>
<td><strong>C&lt;sub&gt;max&lt;/sub&gt;</strong> <em>(90% CI)</em></td>
<td><strong>C&lt;sub&gt;min&lt;/sub&gt;</strong> <em>(90% CI)</em></td>
</tr>
<tr>
<td><strong>Antiretrovirals</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Protease inhibitors</strong>: The co-administration of REYATAZ/ritonavir and other protease inhibitors has not been studied but would be expected to increase exposure to other protease inhibitors. Therefore, such co-administration is not recommended.</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>Ritonavir 100 mg once daily</strong></td>
<td>atazanavir</td>
<td>↑3.50*</td>
<td>↑2.20*</td>
<td>↑8.13*</td>
</tr>
<tr>
<td></td>
<td>(atazanavir 300 mg QD)</td>
<td>studies conducted in HIV-infected patients</td>
<td>(2.44, 5.03)</td>
<td>(1.56, 3.11)</td>
<td>(4.59, 14.39)</td>
</tr>
<tr>
<td></td>
<td>* In a combined analysis, atazanavir 300 mg and ritonavir 100 mg (n=33) was compared to atazanavir 400 mg without ritonavir (n=28). The mechanism of interaction between atazanavir and ritonavir is CYP3A4 inhibition.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Indinavir</td>
<td>Indinavir is associated with indirect unconjugated hyperbilirubinaemia due to inhibition of UGT.</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Lamivudine 150 mg BID + zidovudine 300 mg BID (atazanavir 400 mg QD)</td>
<td>No significant effect on lamivudine and zidovudine concentrations was observed.</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Abacavir</td>
<td>The co-administration of REYATAZ/ritonavir with abacavir is not expected to significantly alter the exposure of abacavir.</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Didanosine (buffered tablets)</td>
<td>atazanavir, simultaneous administration with ddI+d4T (fasted)</td>
<td>↓0.13</td>
<td>↓0.11</td>
<td>↓0.16</td>
</tr>
<tr>
<td></td>
<td>200 mg/stavudine 40 mg, both single dose (atazanavir 400 mg single dose)</td>
<td>(0.08, 0.21)</td>
<td>(0.06, 0.18)</td>
<td>(0.10, 0.27)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>atazanavir, dosed 1 hr after ddI+d4T (fasted)</td>
<td>↔1.03</td>
<td>↑1.12</td>
<td>↔1.03</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(0.64, 1.67)</td>
<td>(0.67, 1.18)</td>
<td>(0.61, 1.73)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Atazanavir concentrations were greatly decreased when co-administered with didanosine (buffered tablets) and stavudine. The mechanism of interaction is a reduced solubility of atazanavir with increasing pH related to the presence of anti-acid agent in didanosine buffered tablets. No significant effect on didanosine and stavudine concentrations was observed.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Didanosine (enteric coated capsules) 400 mg single dose (atazanavir 300 mg QD with ritonavir 100 mg QD)</td>
<td>Didanosine (with food)</td>
<td>↓0.66</td>
<td>↓0.62</td>
<td>↑1.25</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(0.59, 0.73)</td>
<td>(0.52, 0.74)</td>
<td>(0.92, 1.69)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>No significant effect on atazanavir concentrations was observed when administered with enteric-coated didanosine, but administration with food decreased didanosine concentrations.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Tenofovir disoproxil fumarate 300 mg QD (atazanavir 300 mg QD with ritonavir 100 mg QD) studies conducted in HIV-infected patients</td>
<td>atazanavir</td>
<td>↓0.78*</td>
<td>↓0.84*</td>
<td>↓0.77*</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(0.65, 0.94)</td>
<td>(0.70, 1.00)</td>
<td>(0.57-1.02)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>* In a combined analysis from several clinical studies, atazanavir/ritonavir 300/100 mg co-administered with tenofovir</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
The efficacy of REYATAZ/ritonavir in combination with tenofovir in treatment-experienced patients has been demonstrated in clinical study 045 and in treatment naive patients in clinical study 138 (see sections 4.8 and 5.1). The mechanism of interaction between atazanavir and tenofovir is unknown.

### Tenofovir disoproxil fumarate

300 mg QD (atazanavir 300 mg QD with ritonavir 100 mg QD)

<table>
<thead>
<tr>
<th>Medicinal product assessed</th>
<th>AUC (90% CI)</th>
<th>C_{max} (90% CI)</th>
<th>C_{min} (90% CI)</th>
<th>Recommendations concerning co-administration</th>
</tr>
</thead>
<tbody>
<tr>
<td>tenofovir disoproxil fumarate</td>
<td>↑1.37 (1.30, 1.45)</td>
<td>↑1.34 (1.20, 1.51)</td>
<td>↑1.29 (1.21, 1.36)</td>
<td>Patients should be closely monitored for tenofovir-associated adverse events, including renal disorders.</td>
</tr>
</tbody>
</table>

### Non-nucleoside reverse transcriptase inhibitors (NNRTIs)

**Efavirenz 600 mg QD**

(atazanavir 400 mg QD with ritonavir 100 mg QD)

| atazanavir (pm): all administered with food | ↔️1.00* (0.91, 1.10) | ↑1.17* (1.08, 1.27) | ↓0.58* (0.49, 0.69) | Co-administration of efavirenz with REYATAZ/ritonavir is not recommended (see section 4.4) |

* When compared to REYATAZ 300 mg/ritonavir 100 mg once daily in the evening without efavirenz. This decrease in atazanavir C_{min}, might negatively impact the efficacy of atazanavir. The mechanism of efavirenz/atazanavir interaction is CYP3A4 induction.

** based on historical comparison.

**Nevirapine 200 mg BID**

(atazanavir 400 mg QD with ritonavir 100 mg QD) study conducted in HIV infected patients

| nevirapine | ↑1.26 (1.17, 1.36) | ↑1.21 (1.11, 1.32) | ↑1.35 (1.25, 1.47) | Co-administration of nevirapine with REYATAZ/ritonavir is not recommended (see section 4.4) |

* When compared to REYATAZ 300 mg and ritonavir 100 mg without nevirapine. This decrease in atazanavir C_{min}, might negatively impact the efficacy of atazanavir. The mechanism of nevirapine/atazanavir interaction is CYP3A4 induction.

** Antibiotics **

**Clarithromycin 500 mg BID**

(atazanavir 400 mg QD)

| clarithromycin | ↑1.94 (1.75, 2.16) | ↑1.50 (1.32, 1.71) | ↑2.60 (2.35, 2.88) | No recommendation regarding dose reduction can be made; therefore, caution should be exercised if REYATAZ/ritonavir is co-administered with clarithromycin. |

14-OH clarithromycin

| ↓0.30 (0.26, 0.34) | ↓0.28 (0.24, 0.33) | ↓0.38 (0.34, 0.42) | |

A dose reduction of clarithromycin may result in subtherapeutic concentrations of 14-OH clarithromycin. The mechanism of the clarithromycin/atazanavir interaction is CYP3A4 inhibition.

**Antifungals**

**Ketoconazole 200 mg QD**

(atazanavir 400 mg QD)

| No significant effect on atazanavir concentrations was observed. |

**Itraconazole**

Itraconazole, like ketoconazole, is a potent inhibitor as well as a substrate of CYP3A4.

Based on data obtained with other boosted PIs and ketoconazole, where ketoconazole AUC showed a 3-fold increase, REYATAZ/ritonavir is expected to increase ketoconazole or itraconazole concentrations.

| ketoconazole and itraconazole should be used cautiously with REYATAZ/ritonavir. High doses of ketoconazole and itraconazole (>200 mg/day) are not recommended. |

**Voriconazole**

Co-administration of REYATAZ/ritonavir and voriconazole has not been studied.

The effect of co-administration of oral voriconazole and low dose (100 mg) oral ritonavir was investigated in healthy volunteers. Low doses of ritonavir (100 mg BID) decreased the C_{max} and AUC of voriconazole

| Co-administration of voriconazole and REYATAZ/ritonavir is not recommended unless an assessment of the benefit/risk to... |
Co-administered medicinal products (dose in mg) | Medicinal product assessed | AUC (90% CI) | C_{max} (90% CI) | C_{min} (90% CI) | Recommendations concerning co-administration
---|---|---|---|---|---
Voriconazole | | | | | (90% CI) by an average of 24% (19% to 36%) and 39% (22% to 52%), respectively. Administration of voriconazole resulted in a minor decrease in steady state C_{max} and AUC of ritonavir (90% CI) with an average of 24% (16% to 39%) and 14% (26% to 1%), respectively. the patient justifies the use of voriconazole (see section 4.4). Patients should be carefully monitored for adverse events and/or loss of efficacy during the co-administration of voriconazole and REYATAZ/ritonavir.

Fluconazole 200 mg QD (atazanavir 300 mg and ritonavir 100 mg QD) | Atazanavir and fluconazole concentrations were not significantly modified when REYATAZ/ritonavir was co-administered with fluconazole. No dosage adjustments are needed for REYATAZ/ritonavir and fluconazole.

Antimycobacterial

<table>
<thead>
<tr>
<th>Rifabutin 150 mg twice weekly (atazanavir 300 mg and ritonavir 100 mg QD)</th>
<th>rifabutin</th>
<th>↑1.48 **</th>
<th>↑2.49 **</th>
<th>↑1.40 **</th>
</tr>
</thead>
<tbody>
<tr>
<td>25-O-desacetyl-rifabutin</td>
<td>(1.19, 1.84)</td>
<td>(2.03, 3.06)</td>
<td>(1.05, 1.87)</td>
<td>(8.14, 14.61)</td>
</tr>
</tbody>
</table>

** When compared to rifabutin 150 mg QD alone. Total rifabutin and 25-O-desacetyl-rifabutin AUC: ↑2.19 (1.78, 2.69).

In previous studies, the pharmacokinetics of atazanavir was not altered by rifabutin.

Rifampicin | Rifampicin is a strong CYP3A4 inducer and has been shown to cause a 72% decrease in atazanavir AUC which can result in virological failure and resistance development. During attempts to overcome the decreased exposure by increasing the dose of REYATAZ or other protease inhibitors with ritonavir, a high frequency of liver reactions was seen. The combination of rifampicin and REYATAZ with concomitant low-dose ritonavir is contraindicated (see section 4.3).

ACID REDUCING AGENTS

H2-Receptor antagonists

| Without Tenofovir | | | | | For patients not taking tenofovir, if REYATAZ 300 mg/ritonavir 100 mg and H2-receptor |
|---|---|---|---|---|
| In HIV-infected patients with atazanavir/ritonavir at the recommended dose 300/100 mg QD | atazanavir | ↓0.82 | ↓0.80 | ↔-0.99 |
| - famotidine 20 mg BID | (0.75, 1.01) | (0.68, 0.93) | (0.84, 1.18) |
Co-administered medicinal products (dose in mg) | Medicinal product assessed | AUC (90% CI) | C<sub>max</sub> (90% CI) | C<sub>min</sub> (90% CI) | Recommendations concerning co-administration
--- | --- | --- | --- | --- | ---
- famotidine 40 mg BID | atazanavir | ↓0.77 (0.68, 0.86) | ↓0.77 (0.67, 0.88) | ↓0.80 (0.69, 0.92) | antagonists are co-administered, a dose equivalent to famotidine 20 mg BID should not be exceeded. If a higher dose of an H<sub>2</sub>-receptor antagonist is required (eg, famotidine 40 mg BID or equivalent) an increase of the REYATAZ/ritonavir dose from 300/100 mg to 400/100 mg can be considered.

In Healthy volunteers with atazanavir/ritonavir at an increased dose of 400/100 mg QD
- famotidine 40 mg BID | atazanavir | ↔1.03 (0.86, 1.22) | ↔1.02 (0.87, 1.18) | ↓0.86 (0.68, 1.08) | antagonists are co-administered, a dose equivalent to famotidine 20 mg BID should not be exceeded. If a higher dose of an H<sub>2</sub>-receptor antagonist is required (eg, famotidine 40 mg BID or equivalent) an increase of the REYATAZ/ritonavir dose from 300/100 mg to 400/100 mg can be considered.

With Tenofovir 300 mg QD
In HIV-infected patients with atazanavir/ritonavir at the recommended dose of 300/100 mg QD
- famotidine 20 mg BID | atazanavir | ↓0.79* (0.66, 0.96) | ↓0.79* (0.64, 0.96) | ↓0.81* (0.63, 1.05) | For patients who are taking tenofovir, Co-administration of REYATAZ/ritonavir in combination with tenofovir and an H<sub>2</sub>-receptor antagonist should be avoided (see section 4.4). If the combination of REYATAZ/ritonavir with both tenofovir and an H<sub>2</sub>-receptor antagonist is judged unavoidable, close clinical monitoring is recommended. A dose increase of REYATAZ to 400 mg with 100 mg of ritonavir may be considered but is still under evaluation.
- famotidine 40 mg BID | atazanavir | ↓0.76* (0.64, 0.89) | ↓0.77* (0.64, 0.92) | ↓0.75* (0.53, 1.07) | When compared to atazanavir 300 mg QD with ritonavir 100 mg QD and tenofovir disoproxil fumarate 300 mg all as a single dose with food. When compared to atazanavir 300 mg with ritonavir 100 mg <i>without</i> tenofovir, atazanavir concentrations are expected to be additionally decreased by about 20%. If a higher dose of an H<sub>2</sub>-receptor antagonist is required (eg, famotidine 40 mg BID or equivalent) an increase of the REYATAZ/ritonavir dose from 300/100 mg to 400/100 mg can be considered.

Proton pump inhibitors
Omeprazole 40 mg QD (atazanavir 400 mg QD with ritonavir 100 mg QD) | atazanavir (am): 2 hr after omeprazole | ↓0.39 (0.35, 0.45) | ↓0.44 (0.38, 0.51) | ↓0.35 (0.29, 0.41) | Co-administration of REYATAZ/ritonavir with proton pump inhibitors is not recommended. If the combination of REYATAZ/ritonavir with a proton pump inhibitor is judged unavoidable, close clinical monitoring is recommended in combination with an increase in the dose of REYATAZ to 400 mg with 100 mg of ritonavir; doses of proton pump inhibitors comparable to omeprazole 20 mg should not be exceeded (see section 4.4).
- Omeprazole 20 mg QD (atazanavir 400 mg QD with ritonavir 100 mg QD) | atazanavir (am): 1 hr after omeprazole | ↓0.70* (0.57, 0.86) | ↓0.69* (0.58, 0.83) | ↓0.69* (0.54, 0.88) | When compared to atazanavir 300 mg QD with ritonavir 100 mg QD and tenofovir disoproxil fumarate 300 mg all as a single dose with food. When compared to atazanavir 300 mg with ritonavir 100 mg <i>without</i> tenofovir, atazanavir concentrations are expected to be additionally decreased by about 20%. If a higher dose of an H<sub>2</sub>-receptor antagonist is required (eg, famotidine 40 mg BID or equivalent) an increase of the REYATAZ/ritonavir dose from 300/100 mg to 400/100 mg can be considered.

Antacids
Antacids and medicinal products containing buffers | | | | | Reduced plasma concentrations of atazanavir may be the consequence of increased gastric pH if antacids, including buffered medicinal products, are administered with REYATAZ/ritonavir.

* When compared to atazanavir 300 mg QD with ritonavir 100 mg QD and tenofovir disoproxil fumarate 300 mg all as a single dose with food. When compared to atazanavir 300 mg with ritonavir 100 mg <i>without</i> tenofovir, atazanavir concentrations are expected to be additionally decreased by about 20%.

The mechanism of interaction is decreased solubility of atazanavir as intra-gastric pH increases with H<sub>2</sub> blockers.
The decrease in AUC, C<sub>max</sub>, and C<sub>min</sub> was not mitigated when an increased dose of REYATAZ/ritonavir (400/100 mg once daily) was temporally separated from omeprazole by 12 hours. Although not studied, similar results are expected with other proton pump inhibitors. This decrease in atazanavir exposure might negatively impact the efficacy of atazanavir. The mechanism of interaction is decreased solubility of atazanavir as intra-gastric pH increases with proton pump inhibitors.

REYATAZ/ritonavir should be administered 2 hours before or 1 hour after antacids or

58
### Co-administered medicinal products (dose in mg)

<table>
<thead>
<tr>
<th>Medicinal product assessed</th>
<th>AUC (90% CI)</th>
<th>C(_{\text{max}}) (90% CI)</th>
<th>C(_{\text{min}}) (90% CI)</th>
<th>Recommendations concerning co-administration</th>
</tr>
</thead>
</table>

#### ANTICOAGULANTS

Warfarin

Co-administration with REYATAZ/ritonavir has the potential to produce a decrease or, less often, an increase in INR (International Normalised Ratio).

It is recommended that the INR be monitored carefully during treatment with REYATAZ/ritonavir, especially when commencing therapy.

#### ANTINEOPLASTICS AND IMMUNOSUPPRESSANTS

**Antineoplastics**

Irinotecan

Atazanavir inhibits UGT and may interfere with the metabolism of irinotecan, resulting in increased irinotecan toxicities.

If REYATAZ/ritonavir is co-administered with irinotecan, patients should be closely monitored for adverse events related to irinotecan.

**Immunosuppressants**

Cyclosporin

Concentrations of these immunosuppressants may be increased when co-administered with REYATAZ/ritonavir due to CYP3A4 inhibition.

More frequent therapeutic concentration monitoring of these medicinal products is recommended until plasma levels have been stabilised.

#### CARDIOVASCULAR AGENTS

**Antiarrhythmics**

Amiodarone, Systemic lidocaine, Quinidine

Concentrations of these antiarrhythmics may be increased when co-administered with REYATAZ/ritonavir. The mechanism of amiodarone or systemic lidocaine/atazanavir interaction is CYP3A inhibition. Quinidine has a narrow therapeutic window and is contraindicated due to potential inhibition of CYP3A by REYATAZ/ritonavir.

Caution is warranted and therapeutic concentration monitoring is recommended when available. The concomitant use of quinidine is contraindicated (see section 4.3).

**Calcium channel blockers**

Bepridil

REYATAZ/ritonavir should not be used in combination with medicinal products that are substrates of CYP3A4 and have a narrow therapeutic index.

Co-administration with bepridil is contraindicated (see section 4.3)

Diltiazem 180 mg QD (atazanavir 400 mg QD)

No significant effect on atazanavir concentrations was observed. There was an increase in the maximum PR interval compared to atazanavir alone. Co-administration of diltiazem and REYATAZ/ritonavir has not been studied. The mechanism of diltiazem/atazanavir interaction is CYP3A4 inhibition.

An initial dose reduction of diltiazem by 50% is recommended, with subsequent titration as needed and ECG monitoring.

Verapamil

Serum concentrations of verapamil may be increased by REYATAZ/ritonavir due to CYP3A4 inhibition.

Caution should be exercised when verapamil is co-administered with REYATAZ/ritonavir.

#### CORTICOSTEROIDS

Fluticasone propionate intranasal 50 µg 4 times daily for 7 days (ritonavir 100 mg capsules BID)

The fluticasone propionate plasma levels increased significantly, whereas the intrinsic cortisol levels decreased by approximately 86% (90% confidence interval 82-89%). Greater effects may be expected when fluticasone propionate is inhaled. Systemic corticosteroid effects

Co-administration of REYATAZ/ritonavir and these glucocorticoids is not
including Cushing’s syndrome and adrenal suppression have been reported in patients receiving ritonavir and inhaled or intranasally administered fluticasone propionate; this could also occur with other corticosteroids metabolized via the P450 3A pathway, e.g., budesonide. The effects of high fluticasone systemic exposure on ritonavir plasma levels are yet unknown. The mechanism of interaction is CYP3A4 inhibition.

**ERECTILE DYSFUNCTION**

**PDE5 Inhibitors**

<table>
<thead>
<tr>
<th>Medicinal product assessed</th>
<th>AUC (90% CI)</th>
<th>Cmax (90% CI)</th>
<th>Cmin (90% CI)</th>
<th>Recommendations concerning co-administration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sildenafil</td>
<td>↓ 0.81 (0.75, 0.87)</td>
<td>↑ 1.85 (1.67, 2.05)</td>
<td>↓ 1.68 (1.51, 1.88)</td>
<td>Patients should be warned about these possible side effects.</td>
</tr>
</tbody>
</table>

**HERBAL PRODUCTS**

<table>
<thead>
<tr>
<th>Medicinal product assessed</th>
<th>AUC (90% CI)</th>
<th>Cmax (90% CI)</th>
<th>Cmin (90% CI)</th>
<th>Recommendations concerning co-administration</th>
</tr>
</thead>
<tbody>
<tr>
<td>ethinyloestradiol 25 μg + norgestimate (atazanavir 300 mg QD with ritonavir 100 mg QD)</td>
<td>↓ 0.63 (0.55, 0.71)</td>
<td>↑ 2.02 (1.77, 2.31)</td>
<td>↓ 1.08 (0.74, 0.95)</td>
<td>If an oral contraceptive is administered with REYATAZ/ritonavir, it is recommended that the oral contraceptive contain at least 30 μg of ethinyloestradiol and that the patient be reminded of strict compliance with this contraceptive dosing regimen. Co-administration of REYATAZ/ritonavir with other hormonal contraceptives or oral contraceptives containing progestogens other than norgestimate has not been studied, and therefore should be avoided. An alternate reliable method of contraception is recommended.</td>
</tr>
</tbody>
</table>

**HORMONAL CONTRACEPTIVES**

Patients should be warned about these possible side effects.

**St. John’s wort (Hypericum perforatum):**

Concomitant use of St. John’s wort with REYATAZ/ritonavir may be expected to result in significant reduction in plasma levels of atazanavir. This effect may be due to an induction of CYP3A4. There is a risk of loss of therapeutic effect and development of resistance (see section 4.3). Co-administration of REYATAZ/ritonavir with products containing St. John’s wort is contraindicated.
<table>
<thead>
<tr>
<th>Co-administered medicinal products (dose in mg)</th>
<th>Medicinal product assessed</th>
<th>AUC (90% CI)</th>
<th>C&lt;sub&gt;max&lt;/sub&gt; (90% CI)</th>
<th>C&lt;sub&gt;min&lt;/sub&gt; (90% CI)</th>
<th>Recommendations concerning co-administration</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>LIPID LOWERING AGENTS</strong></td>
<td></td>
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</tr>
<tr>
<td><strong>HMG-CoA reductase inhibitors</strong></td>
<td></td>
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<tr>
<td>Simvastatin</td>
<td>Simvastatin and lovastatin are highly dependent on CYP3A4 for their metabolism and co-administration with REYATAZ/ritonavir may result in increased concentrations.</td>
<td></td>
<td></td>
<td></td>
<td>Co-administration of simvastatin or lovastatin with <strong>REYATAZ/ritonavir</strong> is not recommended due to an increased risk of myopathy including rhabdomyolysis. The use of another HMG-CoA reductase inhibitor which does not undergo metabolism by CYP3A such as pravastatin or fluvastatin is recommended.</td>
</tr>
<tr>
<td>Lovastatin</td>
<td></td>
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<td></td>
</tr>
<tr>
<td><strong>Atorvastatin</strong></td>
<td>The risk of myopathy including rhabdomyolysis may also be increased with atorvastatin, which is also metabolised by CYP3A4.</td>
<td></td>
<td></td>
<td></td>
<td>Caution should be exercised.</td>
</tr>
<tr>
<td><strong>OPIOIDS</strong></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Buprenorphine, QD, stable maintenance dose, (atazanavir 300 mg QD with ritonavir 100 mg QD)</td>
<td>buprenorphine  ↑1.67 ↑1.37 ↑1.69</td>
<td></td>
<td></td>
<td></td>
<td>Co-administration warrants clinical monitoring for sedation and cognitive effects. A dose reduction of buprenorphine may be considered.</td>
</tr>
<tr>
<td></td>
<td>norbuprenorphine ↑2.05 ↑1.61 ↑2.01</td>
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<td></td>
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</tr>
<tr>
<td></td>
<td>The mechanism of interaction is CYP3A4 and UGT1A1 inhibition. Concentrations of atazanavir were not significantly affected.</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Methadone, stable maintenance dose (atazanavir 400 mg QD)</td>
<td>No significant effect on methadone concentrations was observed. Given that low dose ritonavir (100 mg twice daily) has been shown to have no significant effect on methadone concentrations, no interaction is expected if methadone is co-administered with <strong>REYATAZ</strong> and ritonavir, based on these data.</td>
<td></td>
<td></td>
<td></td>
<td>No dosage adjustment is necessary if methadone is co-administered with <strong>REYATAZ</strong> and ritonavir.</td>
</tr>
<tr>
<td><strong>SEDATIVES</strong></td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td><strong>Benzodiazepines</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Midazolam</td>
<td>Midazolam and triazolam are extensively metabolized by CYP3A4. Co-administration with <strong>REYATAZ/ritonavir</strong> may cause a large increase in the concentration of these benzodiazepines. No drug interaction study has been performed for the co-administration of <strong>REYATAZ/ritonavir</strong> with benzodiazepines. Based on data for other CYP3A4 inhibitors, plasma concentrations of midazolam are expected to be significantly higher when midazolam is given orally. Data from concomitant use of parenteral midazolam with other protease inhibitors suggest a possible 3-4 fold increase in midazolam plasma levels.</td>
<td></td>
<td></td>
<td></td>
<td><strong>REYATAZ/ritonavir</strong> should not be co-administered with triazolam or orally administered midazolam (see section 4.3), whereas caution should be used with co-administration of <strong>REYATAZ/ritonavir</strong> and parenteral midazolam. If <strong>REYATAZ</strong> is co-administered with parenteral midazolam, it should be done in an intensive care unit (ICU) or similar setting which ensures close clinical monitoring and appropriate medical management in case of respiratory depression and/or prolonged sedation. Dosage adjustment for midazolam should be considered, especially</td>
</tr>
<tr>
<td>Triazolam</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
4.6 Pregnancy and lactation

There are no adequate data from the use of atazanavir in pregnant women. Studies in animals have not shown evidence of selective developmental toxicity or effects on reproductive function and fertility (see section 5.3). REYATAZ should be used during pregnancy only if the potential benefit justifies the potential risk.

It is not known whether REYATAZ administered to the mother during pregnancy will exacerbate physiological hyperbilirubinaemia and lead to kernicterus in neonates and infants. In the prepartum period, additional monitoring and alternative therapy to REYATAZ should be considered.

It is not known whether atazanavir is excreted in human milk. Studies in rats have demonstrated that atazanavir is excreted in the milk. It is therefore recommended that mothers being treated with REYATAZ not breast-feed their infants. As a general rule, it is recommended that HIV infected women not breast-feed their infants in order to avoid transmission of HIV.

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed. Patients should be informed that dizziness has been reported during treatment with regimens containing REYATAZ (see section 4.8).

4.8 Undesirable effects

REYATAZ has been evaluated for safety in combination therapy with other antiretroviral medicinal products in controlled clinical trials in 1,806 adult patients receiving REYATAZ 400 mg once daily (1,151 patients, 52 weeks median duration and 152 weeks maximum duration) or REYATAZ 300 mg with ritonavir 100 mg once daily (655 patients, 96 weeks median duration and 108 weeks maximum duration).

Adverse reactions were consistent between patients who received REYATAZ 400 mg once daily and patients who received REYATAZ 300 mg with ritonavir 100 mg once daily, except that jaundice and elevated total bilirubin levels were reported more frequently with REYATAZ plus ritonavir.

Among patients who received REYATAZ 400 mg once daily or REYATAZ 300 mg with ritonavir 100 mg once daily, the only adverse reactions of any severity reported very commonly with at least a possible relationship to regimens containing REYATAZ and one or more NRTIs were nausea (20%), diarrhoea (10%), and jaundice (13%). Among patients receiving REYATAZ 300 mg with ritonavir 100 mg, the frequency of jaundice was 19%. In the majority of cases, jaundice was reported within a few days to a few months after the initiation of treatment (see section 4.4).

Combination antiretroviral therapy has been associated with redistribution of body fat (lipodystrophy) in HIV patients, including loss of peripheral and facial subcutaneous fat, increased intra-abdominal and visceral fat, breast hypertrophy, and dorsocervical fat accumulation (buffalo hump).

Combination antiretroviral therapy has been associated with metabolic abnormalities such as hypertriglyceridaemia, hypercholesterolaemia, insulin resistance, hyperglycaemia, and hyperlactataemia (see sections 4.4 and 5.1).
Adult patients
The following adverse reactions of moderate intensity or greater with at least a possible relationship to regimens containing REYATAZ and one or more NRTIs have also been reported. The frequency of adverse reactions listed below is defined using the following convention: very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1,000 to < 1/100), rare (≥ 1/10,000 to < 1/1,000), or very rare (< 1/10,000). Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Cardiac disorders: rare: oedema, palpitation

Nervous system disorders: common: headache;
uncommon: peripheral neuropathy, syncope, amnesia, dizziness, somnolence, dysgeusia

Eye disorders: common: ocular icterus

Respiratory, thoracic and mediastinal disorders: uncommon: dyspnoea

Gastrointestinal disorders: common: vomiting, diarrhoea, abdominal pain, nausea, dyspepsia;
uncommon: pancreatitis, gastritis, abdominal distension, stomatitis aphthous, flatulence, dry mouth

Renal and urinary disorders: uncommon: nephrolithiasis, hematuria, proteinuria, pollakiuria;
rare: kidney pain

Skin and subcutaneous tissue disorders: common: rash;
uncommon: urticaria, alopecia, pruritus;
rare: vesiculobullous rash, eczema, vasodilatation

Musculoskeletal and connective tissue disorders: uncommon: muscle atrophy, arthralgia, myalgia;
rare: myopathy

Metabolism and nutrition disorders: uncommon: weight decreased, weight gain, anorexia, appetite increased

Vascular disorders: uncommon: hypertension

General disorders and administration site conditions: common: lipodystrophy syndrome, fatigue;
uncommon: chest pain, malaise, pyrexia, asthenia;
rare: gait disturbance

Immune system disorders: uncommon: hypersensitivity

Hepatobiliary disorders: common: jaundice;
uncommon: hepatitis;
rare: hepatosplenomegaly

Reproductive system and breast disorders: uncommon: gynaecomastia

Psychiatric disorders: uncommon: depression, disorientation, anxiety, insomnia, sleep disorder, abnormal dream
In HIV-infected patients with severe immune deficiency at the time of initiation of combination antiretroviral therapy (CART), an inflammatory reaction to asymptomatic or residual opportunistic infections may arise (see section 4.4).

Cases of osteonecrosis have been reported, particularly in patients with generally acknowledged risk factors, advanced HIV disease or long-term exposure to combination antiretroviral therapy (CART). The frequency of this is unknown (see section 4.4).

**Laboratory abnormalities**
The most frequently reported laboratory abnormality in patients receiving regimens containing REYATAZ and one or more NRTIs was elevated total bilirubin reported predominantly as elevated indirect [unconjugated] bilirubin (87% Grade 1, 2, 3, or 4). Grade 3 or 4 elevation of total bilirubin was noted in 37% (6% Grade 4). Among experienced patients treated with REYATAZ 300 mg once daily with 100 mg ritonavir once daily for a median duration of 95 weeks, 53% had Grade 3-4 total bilirubin elevations. Among naive patients treated with REYATAZ 300 mg once daily with 100 mg ritonavir once daily for a median duration of 96 weeks, 48% had Grade 3-4 total bilirubin elevations (see section 4.4).

Other marked clinical laboratory abnormalities (Grade 3 or 4) reported in ≥ 2% of patients receiving regimens containing REYATAZ and one or more NRTIs included: elevated creatine kinase (7%), elevated alanine aminotransferase/serum glutamic-pyruvic transaminase (ALT/SGPT) (5%), low neutrophils (5%), elevated aspartate aminotransferase/serum glutamic-oxaloacetic transaminase (AST/SGOT) (3%), and elevated lipase (3%).

Two percent of patients treated with REYATAZ experienced concurrent Grade 3-4 ALT/AST and Grade 3-4 total bilirubin elevations.

**Patients co-infected with hepatitis B and/or hepatitis C virus**

Among 1,151 patients receiving atazanavir 400 mg once daily, 177 patients were co-infected with chronic hepatitis B or C, and among 655 patients receiving atazanavir 300 mg once daily with ritonavir 100 mg once daily, 97 patients were co-infected with chronic hepatitis B or C. Co-infected patients were more likely to have baseline hepatic transaminase elevations than those without chronic viral hepatitis. No differences in frequency of bilirubin elevations were observed between these patients and those without viral hepatitis. The frequency of treatment emergent hepatitis or transaminase elevations in co-infected patients was comparable between REYATAZ and comparator regimens (see section 4.4).

**Paediatric population**

In clinical studies, paediatric patients 3 months to less than 18 years of age had a mean duration of treatment with REYATAZ of 115 weeks. The safety profile in these studies was overall comparable to that seen in adults. Both asymptomatic first-degree (23%) and second-degree (1%) atrioventricular block were reported in paediatric patients. The most frequently reported laboratory abnormality in paediatric patients receiving REYATAZ was elevation of total bilirubin (≥ 2.6 times ULN, Grade 3-4) which occurred in 45% of patients.

**Postmarketing experience**

There have been postmarketing reports of unknown frequency for torsades de pointes, QTc prolongation, diabetes mellitus, hyperglycaemia, nephrolithiasis, and gallbladder disorders including cholelithiasis, cholecystitis, and cholestasis.

**4.9 Overdose**

Human experience of acute overdose with REYATAZ is limited. Single doses up to 1,200 mg have been taken by healthy volunteers without symptomatic untoward effects. At high doses that lead to high drug exposures, jaundice due to indirect (unconjugated) hyperbilirubinaemia (without associated liver function test changes) or PR interval prolongations may be observed (see sections 4.4 and 4.8).
Treatment of overdose with REYATAZ should consist of general supportive measures, including monitoring of vital signs and electrocardiogram (ECG), and observations of the patient's clinical status. If indicated, elimination of unabsorbed atazanavir should be achieved by emesis or gastric lavage. Administration of activated charcoal may also be used to aid removal of unabsorbed drug. There is no specific antidote for overdose with REYATAZ. Since atazanavir is extensively metabolised by the liver and is highly protein bound, dialysis is unlikely to be beneficial in significant removal of this medicinal product.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: protease inhibitor, ATC code: J05AE08

**Mechanism of action:** atazanavir is an azapeptide HIV-1 protease inhibitor (PI). The compound selectively inhibits the virus-specific processing of viral Gag-Pol proteins in HIV-1 infected cells, thus preventing formation of mature virions and infection of other cells.

**Antiviral activity in vitro:** atazanavir exhibits anti-HIV-1 (including all clades tested) and anti-HIV-2 activity in cell culture.

**Resistance**

*Antiretroviral treatment naive adult patients*

In clinical trials of antiretroviral treatment naive patients treated with unboosted atazanavir, the I50L substitution, sometimes in combination with an A71V change, is the signature resistance substitution for atazanavir. Resistance levels to atazanavir ranged from 3.5- to 29-fold without evidence of phenotypic cross resistance to other PIs. In clinical trials of antiretroviral treatment naive patients treated with boosted atazanavir, the I50L substitution did not emerge in any patient without baseline PI substitutions. The N88S substitution has been rarely observed in patients with virologic failure on atazanavir (with or without ritonavir). While it may contribute to decreased susceptibility to atazanavir when it occurs with other protease substitutions, in clinical studies N88S by itself does not always lead to phenotypic resistance to atazanavir or have a consistent impact on clinical efficacy.

<table>
<thead>
<tr>
<th>Table 3. De novo substitutions in treatment naive patients failing therapy with atazanavir + ritonavir (Study 138, 96 weeks)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Frequency</td>
</tr>
<tr>
<td>&gt;20%</td>
</tr>
<tr>
<td>10-20%</td>
</tr>
</tbody>
</table>

* Number of patients with paired genotypes classified as virological failures (HIV RNA ≥ 400 copies/ml).

The M184I/V substitution emerged in 5/26 REYATAZ/ritonavir and 7/26 lopinavir/ritonavir virologic failure patients, respectively.

*Antiretroviral treatment experienced adult patients*

In antiretroviral treatment experienced patients from Studies 009, 043, and 045, 100 isolates from patients designated as virological failures on therapy that included either atazanavir, atazanavir + ritonavir, or atazanavir + saquinavir were determined to have developed resistance to atazanavir. Of the 60 isolates from patients treated with either atazanavir or atazanavir + ritonavir, 18 (30%) displayed the I50L phenotype previously described in naive patients.

<table>
<thead>
<tr>
<th>Table 4. De novo substitutions in treatment experienced patients failing therapy with atazanavir + ritonavir (Study 045, 48 weeks)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Frequency</td>
</tr>
<tr>
<td>&gt;20%</td>
</tr>
<tr>
<td>10-20%</td>
</tr>
</tbody>
</table>

* Number of patients with paired genotypes classified as virological failures (HIV RNA ≥ 400 copies/ml).
Ten patients had baseline phenotypic resistance to atazanavir + ritonavir (fold change [FC]>5.2). FC susceptibility in cell culture relative to the wild-type reference was assayed using PhenoSense™ (Monogram Biosciences, South San Francisco, California, USA).

None of the de novo substitutions (see Table 4) are specific to atazanavir and may reflect re-emergence of archived resistance on atazanavir + ritonavir in Study 045 treatment-experienced population.

The resistance in antiretroviral treatment experienced patients mainly occurs by accumulation of the major and minor resistance substitutions described previously to be involved in protease inhibitor resistance.

**Clinical results**

*In antiretroviral naïve adult patients*

Study 138 is an international randomised, open-label, multicenter, prospective trial of treatment naïve patients comparing REYATAZ/ritonavir (300 mg/100 mg once daily) to lopinavir/ritonavir (400 mg/100 mg twice daily), each in combination with fixed dose tenofovir/emtricitabine (300 mg/200 mg tablets once daily). The REYATAZ/ritonavir arm showed similar (non-inferior) antiviral efficacy compared to the lopinavir/ritonavir arm, as assessed by the proportion of patients with HIV RNA < 50 copies/ml at week 48 (Table 5). Analyses of data through 96 weeks of treatment demonstrated durability of antiviral activity (Table 5).
### Table 5: Efficacy Outcomes in Study 138

<table>
<thead>
<tr>
<th>Parameter</th>
<th>REYATAZ/ritonavir&lt;sup&gt;b&lt;/sup&gt; (300 mg/100 mg once daily)</th>
<th>Lopinavir/ritonavir&lt;sup&gt;c&lt;/sup&gt; (400 mg/100 mg twice daily)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Week 48</td>
<td>Week 96</td>
</tr>
<tr>
<td><strong>HIV RNA &lt;50 copies/ml, %</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All patients&lt;sup&gt;d&lt;/sup&gt;</td>
<td>78 (n=440)</td>
<td>74 (n=440)</td>
</tr>
<tr>
<td>Difference estimate</td>
<td></td>
<td></td>
</tr>
<tr>
<td>[95% CI]&lt;sup&gt;d&lt;/sup&gt;</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Per protocol analysis&lt;sup&gt;e&lt;/sup&gt;</td>
<td>86 (n=392&lt;sup&gt;f&lt;/sup&gt;)</td>
<td>91 (n=352&lt;sup&gt;f&lt;/sup&gt;)</td>
</tr>
<tr>
<td>Difference estimate&lt;sup&gt;e&lt;/sup&gt;</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>HIV RNA &lt;50 copies/ml, % by Baseline Characteristic&lt;sup&gt;d&lt;/sup&gt;</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HIV RNA &lt;100,000 copies/ml</td>
<td>82 (n=217&lt;sup&gt;g&lt;/sup&gt;)</td>
<td>75 (n=217&lt;sup&gt;g&lt;/sup&gt;)</td>
</tr>
<tr>
<td>&gt;100,000 copies/ml</td>
<td>74 (n=223&lt;sup&gt;g&lt;/sup&gt;)</td>
<td>74 (n=223&lt;sup&gt;g&lt;/sup&gt;)</td>
</tr>
<tr>
<td>CD4 count &lt;50 cells/mm&lt;sup&gt;3&lt;/sup&gt;</td>
<td>78 (n=58)</td>
<td>78 (n=58)</td>
</tr>
<tr>
<td>50 to &lt;100 cells/mm&lt;sup&gt;3&lt;/sup&gt;</td>
<td>76 (n=45)</td>
<td>71 (n=45)</td>
</tr>
<tr>
<td>100 to &lt;200 cells/mm&lt;sup&gt;3&lt;/sup&gt;</td>
<td>75 (n=106)</td>
<td>71 (n=106)</td>
</tr>
<tr>
<td>&gt;200 cells/mm&lt;sup&gt;3&lt;/sup&gt;</td>
<td>80 (n=222)</td>
<td>76 (n=222)</td>
</tr>
<tr>
<td><strong>HIV RNA Mean Change from Baseline, log&lt;sub&gt;10&lt;/sub&gt; copies/ml</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All patients</td>
<td>-3.09 (n=397)</td>
<td>-3.21 (n=360)</td>
</tr>
<tr>
<td>CD4 Mean Change from Baseline, cells/mm&lt;sup&gt;3&lt;/sup&gt;</td>
<td></td>
<td></td>
</tr>
<tr>
<td>All patients</td>
<td>203 (n=370)</td>
<td>268 (n=336)</td>
</tr>
<tr>
<td>CD4 Mean Change from Baseline, cells/mm&lt;sup&gt;3&lt;/sup&gt; by Baseline Characteristic</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HIV RNA &lt;100,000 copies/ml</td>
<td>179 (n=183)</td>
<td>243 (n=163)</td>
</tr>
<tr>
<td>&gt;100,000 copies/ml</td>
<td>227 (n=187)</td>
<td>291 (n=173)</td>
</tr>
</tbody>
</table>

<sup>a</sup> Mean baseline CD4 cell count was 214 cells/mm<sup>3</sup> (range 2 to 810 cells/mm<sup>3</sup>) and mean baseline plasma HIV-1 RNA was 4.94 log<sub>10</sub> copies/ml (range 2.6 to 5.88 log<sub>10</sub> copies/ml)

<sup>b</sup> REYATAZ/RTV with tenofovir/emtricitabine (fixed dose 300 mg/200 mg tablets once daily).

<sup>c</sup> Lopinavir/RTV with tenofovir/emtricitabine (fixed dose 300 mg/200 mg tablets twice daily).

<sup>d</sup> Intent-to-treat analysis, with missing values considered as failures.

<sup>e</sup> Per protocol analysis: Excluding non-completers and patients with major protocol deviations.

<sup>f</sup> Number of patients evaluable.

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**In antiretroviral experienced adult patients**

*Study 045* is a randomised, multicenter trial comparing REYATAZ/ritonavir (300/100 mg once daily) and REYATAZ/saquinavir (400/1,200 mg once daily), to lopinavir + ritonavir (400/100 mg fixed dose combination twice daily), each in combination with tenofovir (see sections 4.5 and 4.8) and one NRTI, in patients with virologic failure on two or more prior regimens containing at least one PI, NRTI, and NNRTI. For randomised patients, the mean time of prior antiretroviral exposure was 138 weeks for PIs, 281 weeks for NRTIs, and 85 weeks for NNRTIs. At baseline, 34% of patients were receiving a PI and 60% were receiving an NNRTI. Fifteen of 120 (13%) patients in the REYATAZ + ritonavir treatment arm and 17 of 123 (14%) patients in the lopinavir + ritonavir arm had four or more of the PI substitutions L10, M46, I54, V82, I84, and L90. Thirty-two percent of patients in the study had a viral strain with fewer than two NRTI substitutions.

The primary endpoint was the time-averaged difference in change from baseline in HIV RNA through 48 weeks (Table 6).
Table 6: Efficacy Outcomes at Week 48 and at Week 96 (Study 045)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>ATV/RTVb (300 mg/100 mg once daily) n=120</th>
<th>LPV/RTVc (400 mg/100 mg twice daily) n=123</th>
<th>Time-averaged difference ATV/RTV-LPV/RTV [97.5% CId]</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Week 48</td>
<td>Week 96</td>
<td>Week 48 Week 96</td>
</tr>
<tr>
<td>HIV RNA Mean Change from Baseline, log10 copies/ml</td>
<td>-1.93 (n=90e)</td>
<td>-2.29 (n=64)</td>
<td>-1.87 (n=99)</td>
</tr>
<tr>
<td>HIV RNA &lt;50 copies/ml, % (responder/evaluable)</td>
<td>36 (43/120)</td>
<td>32 (38/120)</td>
<td>42 (52/123)</td>
</tr>
<tr>
<td>HIV RNA &lt;50 copies/ml by select baseline PI substitutions, % (responder/evaluable)</td>
<td>0-2 44 (28/63)</td>
<td>41 (26/63)</td>
<td>56 (32/57)</td>
</tr>
<tr>
<td>3 18 (2/11)</td>
<td>9 (1/11)</td>
<td>38 (6/16)</td>
<td>33 (5/15)</td>
</tr>
<tr>
<td>≥4 27 (12/45)</td>
<td>24 (11/45)</td>
<td>28 (14/50)</td>
<td>20 (10/49)</td>
</tr>
<tr>
<td>CD4 Mean Change from Baseline, cells/mm³</td>
<td>All patients 110 (n=83)</td>
<td>122 (n=60)</td>
<td>121 (n=94)</td>
</tr>
</tbody>
</table>

The mean baseline CD4 cell count was 337 cells/mm³ (range: 14 to 1,543 cells/mm³) and the mean baseline plasma HIV-1 RNA level was 4.4 log₁₀ copies/ml (range: 2.6 to 5.88 log₁₀ copies/ml).

b ATV/RTV with tenofovir/emtricitabine (fixed dose 300 mg/200 mg tablets once daily).

c LPV/RTV with tenofovir/emtricitabine (fixed dose 300 mg/200 mg tablets once daily).

d Confidence interval.
e Number of patients evaluable.
f Intent-to-treat analysis, with missing values considered as failures. Responders on LPV/RTV who completed treatment before Week 96 are excluded from Week 96 analysis. The proportion of patients with HIV RNA < 400 copies/ml were 53% and 43% for ATV/RTV and 54% and 46% for LPV/RTV at weeks 48 and 96 respectively.
g Select substitutions include any change at positions L10, K20, L24, V32, L33, M36, M46, G48, I50, I54, L63, A71, G73, V82, I84, and L90 (0-2, 3, 4 or more) at baseline.

NA = not applicable.

Through 48 weeks of treatment, the mean changes from baseline in HIV RNA levels for REYATAZ + ritonavir and lopinavir + ritonavir were similar (non-inferior). Consistent results were obtained with the last observation carried forward method of analysis (time-averaged difference of 0.11, 97.5% confidence interval [-0.15, 0.36]). By as-treated analysis, excluding missing values, the proportions of patients with HIV RNA < 400 copies/ml (< 50 copies/ml) in the REYATAZ + ritonavir arm and the lopinavir + ritonavir arm were 55% (40%) and 56% (46%), respectively.

Through 96 weeks of treatment, mean HIV RNA changes from baseline for REYATAZ + ritonavir and lopinavir + ritonavir met criteria for non-inferiority based on observed cases. Consistent results were obtained with the last observation carried forward method of analysis. By as-treated analysis, excluding missing values, the proportions of patients with HIV RNA <400 copies/ml (<50 copies/ml) for REYATAZ + ritonavir were 84% (72%) and for lopinavir + ritonavir were 82% (72%). It is important to note that at time of the 96-week analysis, 48 % of patients overall remained on study.

REYATAZ + saquinavir was shown to be inferior to lopinavir + ritonavir.

**Paediatric population**

Assessment of the pharmacokinetics, safety, tolerability, and efficacy of REYATAZ is based on data from the open-label, multicenter clinical trial PACTG 1020A conducted in patients from 3 months to 21 years of age. Overall in this study, 182 paediatric patients (81 antiretroviral-naive and 101 antiretroviral-experienced) received once daily REYATAZ (capsule or powder formulation), with or without ritonavir, in combination with two NRTIs.

The clinical data derived from this study are inadequate to support the use of atazanavir (with or without ritonavir) in children below 6 years of age.

Efficacy data observed in the 41 paediatric patients aged 6 years to less than 18 years that received REYATAZ capsules with ritonavir are presented in Table 7. For treatment-naive paediatric patients, the mean baseline CD4 cell count was 344 cells/mm³ (range: 2 to 800 cells/ mm³) and mean baseline
plasma HIV 1 RNA was 4.67 log_{10} copies/ml (range: 3.70 to 5.00 log_{10} copies/ml). For treatment-
experience paediatric patients, the mean baseline CD4 cell count was 522 cells/mm^3 (range: 100 to
1157 cells/ mm^3) and mean baseline plasma HIV 1 RNA was 4.09 log_{10} copies/ml (range: 3.28 to
5.00 log_{10} copies/ml).

Table 7: Efficacy Outcomes (paediatric patients 6 years to less than 18 years of age) at Week
48 (Study PACTG 1020A)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Treatment-Naive REYATAZ Capsules/ritonavir (300 mg/100 mg once daily) n=16</th>
<th>Treatment-Experienced REYATAZ Capsules/ritonavir (300 mg/100 mg once daily) n=25</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV RNA &lt;50 copies/ml, % a</td>
<td>All patients 81 (13/16)</td>
<td>24 (6/25)</td>
</tr>
<tr>
<td>HIV RNA &lt;400 copies/ml, % a</td>
<td>All patients 88 (14/16)</td>
<td>32 (8/25)</td>
</tr>
<tr>
<td>CD4 Mean Change from Baseline, cells/mm^3</td>
<td>All patients 293 (n=14b)</td>
<td>229 (n=14b)</td>
</tr>
<tr>
<td>HIV RNA &lt;50 copies/ml by select baseline PI substitutions, % (responder/evaluable)</td>
<td>0-2</td>
<td>NA</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>NA</td>
</tr>
<tr>
<td></td>
<td>≥4</td>
<td>0 (0/3)</td>
</tr>
</tbody>
</table>

a Intent-to-treat analysis, with missing values considered as failures.
b Number of patients evaluable.
d Includes patients with baseline resistance data.
NA = not applicable.

Data in the paediatric population are very limited. Available data do suggest that atazanavir in
combination with ritonavir may not be effective in treatment experienced children even with very few
(<3) PI mutations.

5.2 Pharmacokinetic properties

The pharmacokinetics of atazanavir were evaluated in healthy adult volunteers and in HIV-infected
patients; significant differences were observed between the two groups. The pharmacokinetics of
atazanavir exhibit a non-linear disposition. In healthy subjects, the AUC of atazanavir from the capsules
and oral powder were similar.

Absorption: in HIV-infected patients (n=33, combined studies), multiple dosing of REYATAZ 300 mg
once daily with ritonavir 100 mg once daily with food produced a geometric mean (CV%) for
atazanavir, C_max of 4466 (42%) ng/ml, with time to C_max of approximately 2.5 hours. The geometric
mean (CV%) for atazanavir C_min and AUC was 654 (76%) ng/ml and 44185 (51%) ng•h/ml,
respectively.

Food effect: co-administration of REYATAZ and ritonavir with food optimises the bioavailability of
atazanavir. Co-administration of a single 300-mg dose of REYATAZ and 100-mg dose of ritonavir
with a light meal resulted in a 33% increase in the AUC and a 40% increase in both the C_max and the
24-hour concentration of atazanavir relative to the fasting state. Co-administration with a high-fat meal
did not affect the AUC of atazanavir relative to fasting conditions and the C_max was within 11% of
fasting values. The 24-hour concentration following a high fat meal was increased by approximately
33% due to delayed absorption; the median T_max increased from 2.0 to 5.0 hours. Administration of
REYATAZ with ritonavir with either a light or a high-fat meal decreased the coefficient of variation
of AUC and $C_{\text{max}}$ by approximately 25% compared to the fasting state. To enhance bioavailability and minimise variability, REYATAZ is to be taken with food.

**Distribution:** atazanavir was approximately 86% bound to human serum proteins over a concentration range of 100 to 10,000 ng/ml. Atazanavir binds to both alpha-1-acid glycoprotein (AAG) and albumin to a similar extent (89% and 86%, respectively, at 1,000 ng/ml). In a multiple-dose study in HIV-infected patients dosed with 400 mg of atazanavir once daily with a light meal for 12 weeks, atazanavir was detected in the cerebrospinal fluid and semen.

**Metabolism:** studies in humans and *in vitro* studies using human liver microsomes have demonstrated that atazanavir is principally metabolised by CYP3A4 isozyme to oxygenated metabolites. Metabolites are then excreted in the bile as either free or glucuronidated metabolites. Additional minor metabolic pathways consist of N-dealkylation and hydrolysis. Two minor metabolites of atazanavir in plasma have been characterised. Neither metabolite demonstrated *in vitro* antiviral activity.

**Elimination:** following a single 400-mg dose of $^{14}$C-atazanavir, 79% and 13% of the total radioactivity was recovered in the faeces and urine, respectively. Unchanged drug accounted for approximately 20% and 7% of the administered dose in the faeces and urine, respectively. Mean urinary excretion of unchanged drug was 7% following 2 weeks of dosing at 800 mg once daily. In HIV-infected adult patients ($n=33$, combined studies) the mean half-life within a dosing interval for atazanavir was 12 hours at steady state following a dose of 300 mg daily with ritonavir 100 mg once daily with a light meal.

**Special populations**

**Paediatric patients:** The pharmacokinetics of atazanavir in paediatric patients exhibit an increased absorption rate compared to adults. There is a slight trend toward a higher clearance in younger children when normalised for body weight. As a result, greater peak to trough ratios are observed. The geometric mean AUC values in paediatric patients at recommended doses are expected to be similar to those observed in adults, with higher geometric mean $C_{\text{max}}$ (13-17%) and lower geometric mean $C_{\text{min}}$ (up to 30%) values compared to those in adults. The variability of pharmacokinetic parameters in younger children is higher.

**Impaired renal function:** in healthy subjects, the renal elimination of unchanged atazanavir was approximately 7% of the administered dose. There are no pharmacokinetic data available for REYATAZ with ritonavir in patients with renal insufficiency. REYATAZ (without ritonavir) has been studied in adult patients with severe renal impairment ($n=20$), including those on haemodialysis, at multiple doses of 400 mg once daily. Although this study presented some limitations (i.e., unbound drug concentrations not studied), results suggested that the atazanavir pharmacokinetic parameters were decreased by 30% to 50% in patients undergoing haemodialysis compared to patients with normal renal function. The mechanism of this decrease is unknown. (See sections 4.2 and 4.4.)

**Impaired hepatic function:** atazanavir is metabolised and eliminated primarily by the liver. The effects of hepatic impairment on the pharmacokinetics of atazanavir after a 300 mg dose with ritonavir have not been studied. Concentrations of atazanavir with or without ritonavir are expected to be increased in patients with moderately or severely impaired hepatic function (see sections 4.2, 4.3, and 4.4).

**Age/Gender:** a study of the pharmacokinetics of atazanavir was performed in 59 healthy male and female subjects (29 young, 30 elderly). There were no clinically important pharmacokinetic differences based on age or gender.

**Race:** a population pharmacokinetic analysis of samples from Phase II clinical trials indicated no effect of race on the pharmacokinetics of atazanavir.
5.3 Preclinical safety data

In repeat-dose toxicity studies, conducted in mice, rats, and dogs, atazanavir-related findings were generally confined to the liver and included generally minimal to mild increases in serum bilirubin and liver enzymes, hepatocellular vacuolation and hypertrophy, and, in female mice only, hepatic single-cell necrosis. Systemic exposures of atazanavir in mice (males), rats, and dogs at doses associated with hepatic changes were at least equal to that observed in humans given 400 mg once daily. In female mice, atazanavir exposure at a dose that produced single-cell necrosis was 12 times the exposure in humans given 400 mg once daily. Serum cholesterol and glucose were minimally to mildly increased in rats but not in mice or dogs.

During in vitro studies, cloned human cardiac potassium channel (hERG), was inhibited by 15% at a concentration (30 μM) of atazanavir corresponding to 30-fold the free drug concentration at Cmax in humans. Similar concentrations of atazanavir increased by 13% the action potential duration (APD90) in rabbit Purkinje fibres study. Electrocardiographic changes (sinus bradycardia, prolongation of PR interval, prolongation of QT interval, and prolongation of QRS complex) were observed only in an initial 2-week oral toxicity study performed in dogs. Subsequent 9-month oral toxicity studies in dogs showed no drug-related electrocardiographic changes. The clinical relevance of these non-clinical data is unknown. Potential cardiac effects of this product in humans cannot be ruled out (see sections 4.4 and 4.8). The potential for PR prolongation should be considered in cases of overdose (see section 4.9).

In a fertility and early embryonic development study in rats, atazanavir altered oestrus cycling with no effects on mating or fertility. No teratogenic effects were observed in rats or rabbits at maternally toxic doses. In pregnant rabbits, gross lesions of the stomach and intestines were observed in dead or moribund does at maternal doses 2 and 4 times the highest dose administered in the definitive embryo-development study. In the pre- and postnatal development assessment in rats, atazanavir produced a transient reduction in body weight in the offspring at a maternally toxic dose. Systemic exposure to atazanavir at doses that resulted in maternal toxicity was at least equal to or slightly greater than that observed in humans given 400 mg once daily.

Atazanavir was negative in an Ames reverse-mutation assay but did induce chromosomal aberrations in vitro in both the absence and presence of metabolic activation. In in vivo studies in rats, atazanavir did not induce micronuclei in bone marrow, DNA damage in duodenum (comet assay), or unscheduled DNA repair in liver at plasma and tissue concentrations exceeding those that were clastogenic in vitro.

In long-term carcinogenicity studies of atazanavir in mice and rats, an increased incidence of benign hepatic adenomas was seen in female mice only. The increased incidence of benign hepatic adenomas in female mice was likely secondary to cyotoxic liver changes manifested by single-cell necrosis and is considered to have no relevance for humans at intended therapeutic exposures. There were no tumorigenic findings in male mice or in rats.

Atazanavir increased opacity of bovine corneas in an in vitro ocular irritation study, indicating it may be an ocular irritant upon direct contact with the eye.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Capsule contents:
Crospovidone
Lactose monohydrate
Magnesium stearate

Capsule shells:
Gelatine
Indigocarmin (E132)
Titanium dioxide (E171)

White ink containing:
Shellac
Titanium dioxide (E171)
Ammonium hydroxide
Propylene glycol
Simethicone

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years

6.4 Special precautions for storage

Do not store above 25°C.

6.5 Nature and contents of container

Each carton contains one high-density polyethylene (HDPE) bottle closed with child-resistant polypropylene closure. Each bottle contains 60 hard capsules.

Each carton contains 60 x 1 capsules; 10 blister cards of 6 x 1 capsules each in Alu/Alu perforated unit dose blisters.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

Any unused product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

BRISTOL-MYERS SQUIBB PHARMA EEIG
Uxbridge Business Park
Sanderson Road
Uxbridge UB8 1DH
United Kingdom

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/03/267/005-006

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 02 March 2004
Date of latest renewal: 02 March 2009
10. DATE OF REVISION OF THE TEXT

{month year}

Detailed information on this medicinal product is available on the website of the European Medicines Agency (EMEA) http://www.emea.europa.eu
1. NAME OF THE MEDICINAL PRODUCT
REYATAZ 300 mg hard capsules

2. QUALITATIVE AND QUANTITATIVE COMPOSITION
Each capsule contains 300 mg of atazanavir (as sulphate)
Excipient: 164.36 mg of lactose per capsule.
For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM
Hard capsule
Opaque red and blue capsule printed with white ink, with "BMS 300 mg" on one half and with "3622" on the other half.

4. CLINICAL PARTICULARS
4.1 Therapeutic indications
REYATAZ capsules, co-administered with low dose ritonavir, are indicated for the treatment of HIV-1 infected adults and paediatric patients 6 years of age and older in combination with other antiretroviral medicinal products.

Based on available virological and clinical data from adult patients, no benefit is expected in patients with strains resistant to multiple protease inhibitors (≥ 4 PI mutations). There are very limited data available from children aged 6 to less than 18 years (see sections 4.4 and 5.1).

The choice of REYATAZ in treatment experienced adult and paediatric patients should be based on individual viral resistance testing and the patient’s treatment history (see sections 4.4 and 5.1).

4.2 Posology and method of administration
Therapy should be initiated by a physician experienced in the management of HIV infection.

Adults: the recommended dose of REYATAZ capsules is 300 mg once daily taken with ritonavir 100 mg once daily and with food. Ritonavir is used as a booster of atazanavir pharmacokinetics (see sections 4.5 and 5.1).

Paediatric patients (6 years to less than 18 years of age): The dose of REYATAZ capsules for paediatric patients is based on body weight as shown in Table 1 and should not exceed the recommended adult dose. REYATAZ capsules must be taken with ritonavir and have to be taken with food.
Table 1: Dose for Paediatric Patients (6 years to less than 18 years of age) for REYATAZ capsules with ritonavir

<table>
<thead>
<tr>
<th>Body Weight (kg)</th>
<th>REYATAZ dose</th>
<th>ritonavir dose&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>15 to less than 20</td>
<td>150 mg</td>
<td>100 mg&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>20 to less than 40</td>
<td>200 mg</td>
<td>100 mg</td>
</tr>
<tr>
<td>at least 40</td>
<td>300 mg</td>
<td>100 mg</td>
</tr>
</tbody>
</table>

<sup>a</sup> Ritonavir capsules, tablets or oral solution.

<sup>b</sup> Ritonavir oral solution no lower than 80 mg and not more than 100 mg may be used for paediatric patients from 15 kg to less than 20 kg who cannot swallow ritonavir capsules/tablets.

The available data do not support the use of REYATAZ in combination with low dose ritonavir in paediatric patients weighing less than 15 kg.

*Paediatric patients (less than 6 years of age):* REYAYAZ is not recommended in paediatric patients less than 6 years of age due to insufficient data on pharmacokinetics, safety, and efficacy. REYATAZ has not been studied in children less than 3 months of age and is not recommended especially taking into account the potential risk of kernicterus.

*Patients with renal impairment:* no dosage adjustment is needed. REYATAZ with ritonavir is not recommended in patients undergoing haemodialysis (see sections 4.4 and 5.2).

*Patients with hepatic impairment:* REYATAZ with ritonavir has not been studied in patients with hepatic impairment. REYATAZ with ritonavir should be used with caution in patients with mild hepatic impairment. REYATAZ must not be used in patients with moderate to severe hepatic impairment (see sections 4.3, 4.4, and 5.2).

*Method of administration:* for oral administration. The capsules should be swallowed whole. REYATAZ oral powder is available for adult patients who are unable to swallow capsules (see Summary of Product Characteristics for REYATAZ oral powder). REYATAZ oral powder must not be used in paediatric patients unable to swallow capsules due to insufficient data on pharmacokinetics, safety, and efficacy.

### 4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients (see section 6.1).

Patients with moderate to severe hepatic insufficiency (see sections 4.2 and 4.4).

Combination of rifampicin and REYATAZ with concomitant low-dose ritonavir is contraindicated (see section 4.5).

REYATAZ with ritonavir must not be used in combination with medicinal products that are substrates of the CYP3A4 isoform of cytochrome P450 and have narrow therapeutic windows (e.g., astemizole, terfenadine, cisapride, pimozone, quinidine, bepridil, triazolam, midazolam administered orally (for caution on parenterally administered midazolam, see section 4.5), and ergot alkaloids, particularly, ergotamine, dihydroergotamine, ergonovine, methylergonovine) (see section 4.5).

REYATAZ must not be used in combination with products containing St. John’s wort (*Hypericum perforatum*) (see section 4.5).

### 4.4 Special warnings and precautions for use

Patients should be advised that current antiretroviral therapy has not been proven to prevent the risk of transmission of HIV to others through blood or sexual contact. Appropriate precautions should continue to be employed.
Co-administration of REYATAZ with ritonavir at doses greater than 100 mg once daily has not been clinically evaluated. The use of higher ritonavir doses may alter the safety profile of atazanavir (cardiac effects, hyperbilirubinaemia) and therefore is not recommended. Only when atazanavir with ritonavir is co-administered with efavirenz, a dose increase of ritonavir to 200 mg once daily could be considered. In this instance, close clinical monitoring is warranted (see Interaction with other Medicinal Products below).

Patients with coexisting conditions
Atazanavir is primarily hepatically metabolised and increased plasma concentrations were observed in patients with hepatic impairment (see sections 4.2 and 4.3). The safety and efficacy of REYATAZ has not been established in patients with significant underlying liver disorders. Patients with chronic hepatitis B or C and treated with combination antiretroviral therapy are at an increased risk for severe and potentially fatal hepatic adverse reactions. In case of concomitant antiviral therapy for hepatitis B or C, please refer also to the relevant Summary of Product Characteristics for these medicinal products (see section 4.8).

Patients with pre-existing liver dysfunction, including chronic active hepatitis, have an increased frequency of liver function abnormalities during combination antiretroviral therapy and should be monitored according to standard practice. If there is evidence of worsening liver disease in such patients, interruption or discontinuation of treatment must be considered.

No dosage adjustment is needed in patients with renal impairment. However, REYATAZ with ritonavir is not recommended in patients undergoing haemodialysis (see sections 4.2 and 5.2).

Dose related asymptomatic prolongations in PR interval with REYATAZ have been observed in clinical studies. Caution should be used with medicinal products known to induce PR prolongations. In patients with pre-existing conduction problems (second degree or higher atrioventricular or complex bundle-branch block), REYATAZ should be used with caution and only if the benefits exceed the risk (see section 5.1). Particular caution should be used when prescribing REYATAZ in association with medicinal products which have the potential to increase the QT interval and/or in patients with pre-existing risk factors (bradycardia, long congenital QT, electrolyte imbalances (see sections 4.8 and 5.3).

There have been reports of increased bleeding, including spontaneous skin haematomas and haemarthroses, in type A and B haemophiliac patients treated with protease inhibitors. In some patients additional factor VIII was given. In more than half of the reported cases, treatment with protease inhibitors was continued or reintroduced if treatment had been discontinued. A causal relationship has been suggested, although the mechanism of action has not been elucidated. Haemophiliac patients should therefore be made aware of the possibility of increased bleeding.

Fat redistribution and metabolic disorders
Combination antiretroviral therapy has been associated with the redistribution of body fat (lipodystrophy) in HIV patients. The long-term consequences of these events are currently unknown. Knowledge about the mechanism is incomplete. A connection between visceral lipomatosis and protease inhibitors and lipoatrophy and nucleoside reverse transcriptase inhibitors has been hypothesised. A higher risk of lipodystrophy has been associated with individual factors such as older age, and with drug related factors such as longer duration of antiretroviral treatment and associated metabolic disturbances. Clinical examination should include evaluation for physical signs of fat redistribution.

Combination antiretroviral therapy (CART), including REYATAZ (with or without ritonavir)-based CART, is associated with dyslipidaemia. Consideration should be given to the measurement of fasting serum lipids and blood glucose. Lipid disorders should be managed as clinically appropriate (see section 4.8).

In clinical studies, REYATAZ (with or without ritonavir) has been shown to induce dyslipidaemia to a lesser extent than comparators. The clinical impact of such findings has not been demonstrated in the
absence of specific studies on cardiovascular risk. The selection of antiretroviral therapy must be
guided principally by antiviral efficacy. Consultation with standard guidelines for management of
dyslipidaemia is recommended.

**Hyperglycaemia**
New onset diabetes mellitus, hyperglycaemia, and exacerbation of existing diabetes mellitus have been
reported in patients receiving protease inhibitors. In some of these, the hyperglycaemia was severe and
in some cases also associated with ketoacidosis. Many patients had confounding medical conditions,
some of which required therapy with medicinal products that have been associated with development
of diabetes or hyperglycaemia.

**Hyperbilirubinaemia**
Reversible elevations in indirect (unconjugated) bilirubin related to inhibition of UDP-glucuronosyl
transferase (UGT) have occurred in patients receiving REYATAZ (see section 4.8). Hepatic
transaminase elevations that occur with elevated bilirubin in patients receiving REYATAZ should be
evaluated for alternative etiologies. Alternative antiretroviral therapy to REYATAZ may be
considered if jaundice or scleral icterus is unacceptable to a patient. Dose reduction of atazanavir is not
recommended because it may result in a loss of therapeutic effect and development of resistance.

Indinavir is also associated with indirect (unconjugated) hyperbilirubinaemia due to inhibition of
UGT. Combinations of REYATAZ and indinavir have not been studied and co-administration of these
medicinal products is not recommended (see section 4.5).

**Nephrolithiasis**
Nephrolithiasis has been reported in patients receiving REYATAZ (see section 4.8). If signs or
symptoms of nephrolithiasis occur, temporary interruption or discontinuation of treatment may be
considered.

**Immune reactivation syndrome**
In HIV-infected patients with severe immune deficiency at the time of institution of combination
antiretroviral therapy (CART), an inflammatory reaction to asymptomatic or residual opportunistic
pathogens may arise and cause serious clinical conditions, or aggravation of symptoms. Typically,
such reactions have been observed within the first few weeks or months of initiation of CART.
Relevant examples are cytomegalovirus retinitis, generalised and/or focal mycobacterial infections,
and *Pneumocystis carinii* pneumonia. Any inflammatory symptoms should be evaluated and treatment
instituted when necessary.

**Osteonecrosis**
Although the etiology is considered to be multifactorial (including corticosteroid use, alcohol
consumption, severe immunosuppression, higher body mass index), cases of osteonecrosis have been
reported particularly in patients with advanced HIV-disease and/or long-term exposure to combination
antiretroviral therapy (CART). Patients should be advised to seek medical advice if they experience
joint aches and pain, joint stiffness or difficulty in movement.

**Interactions with other medicinal products**
Co-administration of REYATAZ with simvastatin or lovastatin is not recommended (see section 4.5).

Co-administration of REYATAZ with nevirapine or efavirenz is not recommended (see section 4.5).
If the co-administration of REYATAZ with an NNRTI is required, an increase in the dose of both
REYATAZ and ritonavir to 400 mg and 200 mg, respectively, in combination with efavirenz could be
considered with close clinical monitoring.

Atazanavir is metabolised principally by CYP3A4. Co-administration of REYATAZ with ritonavir
and medicinal products that induce CYP3A4 is not recommended (see sections 4.3 and 4.5).

Co-administration of voriconazole and REYATAZ with ritonavir is not recommended unless an
assessment of the benefit/risk justifies the use of voriconazole (see section 4.5).
Concomitant use of REYATAZ/ritonavir and fluticasone or other glucocorticoids that are metabolized by CYP3A4 is not recommended unless the potential benefit of treatment outweighs the risk of systemic corticosteroid effects, including Cushing's syndrome and adrenal suppression (see section 4.5).

The absorption of atazanavir may be reduced in situations where gastric pH is increased irrespective of cause.

Co-administration of REYATAZ with proton pump inhibitors is not recommended (see section 4.5). If the combination of REYATAZ with a proton pump inhibitor is judged unavoidable, close clinical monitoring is recommended in combination with an increase in the dose of REYATAZ to 400 mg with 100 mg of ritonavir; doses of proton pump inhibitors comparable to omeprazole 20 mg should not be exceeded.

Co-administration of REYATAZ/ritonavir in combination with tenofovir and an H₂-receptor antagonist should be avoided (see section 4.5).

Lactose
Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

Paediatric population
Safety:
Asymptomatic PR interval prolongation was more frequent in paediatric patients than adults. Asymptomatic first- and second-degree AV block was reported in paediatric patients (see section 4.8). Caution should be used with medicinal products known to induce PR prolongations. In paediatric patients with pre-existing conduction problems (second degree or higher atrioventricular or complex bundle-branch block), REYATAZ should be used with caution and only if the benefits exceed the risk. Cardiac monitoring is recommended based on the presence of clinical findings (e.g., bradycardia).

Efficacy
Atazanavir/ritonavir is not effective in viral strains harbouring multiple mutations of resistance. While in adults no benefit can be expected in patients with ≥4 PI mutations, in treatment experienced children even lower numbers of PI mutations may be predictive of a lack of benefit (see section 5.1).

4.5 Interaction with other medicinal products and other forms of interaction

When REYATAZ and ritonavir are co-administered, the metabolic drug interaction profile for ritonavir may predominate because ritonavir is a more potent CYP3A4 inhibitor than atazanavir. The Summary of Product Characteristics for ritonavir must be consulted before initiation of therapy with REYATAZ and ritonavir.

Atazanavir is metabolised in the liver through CYP3A4. It inhibits CYP3A4. Therefore, REYATAZ with ritonavir is contraindicated with medicinal products that are substrates of CYP3A4 and have a narrow therapeutic index: astemizole, terfenadine, cisapride, pimozide, quinidine, bepridil, triazolam, orally administered midazolam, and ergot alkaloids, particularly ergotamine and dihydroergotamine (see section 4.3).

Other interactions
Interactions between atazanavir/ritonavir and protease inhibitors, antiretroviral agents other than protease inhibitors, and other non-antiretroviral medicinal products are listed in the tables below (increase is indicated as “↑”, decrease as “↓”, no change as “↔”, twice daily as “BID” and once daily as “QD”). If available, 90% confidence intervals (CI) are shown in parentheses. The studies presented in Table 2 were conducted in healthy subjects unless otherwise noted. Of importance, many studies were conducted with unboosted atazanavir, which is not the approved regimen of atazanavir.
Table 2: Interactions between REYATAZ and other medicinal products

<table>
<thead>
<tr>
<th>Co-administered medicinal products (dose in mg)</th>
<th>Medicinal product assessed</th>
<th>AUC (90% CI)</th>
<th>C&lt;sub&gt;max&lt;/sub&gt; (90% CI)</th>
<th>C&lt;sub&gt;min&lt;/sub&gt; (90% CI)</th>
<th>Recommendations concerning co-administration</th>
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<tr>
<td><strong>ANTI-INFECTIVES</strong></td>
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<td><strong>Antiretrovirals</strong></td>
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<tr>
<td><strong>Protease inhibitors:</strong> The co-administration of REYATAZ/ritonavir and other protease inhibitors has not been studied but would be expected to increase exposure to other protease inhibitors. Therefore, such co-administration is not recommended.</td>
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<tr>
<td>Ritonavir 100 mg QD (atazanavir 300 mg QD) studies conducted in HIV-infected patients</td>
<td>atazanavir</td>
<td>↑3.50* (2.44, 5.03)</td>
<td>↑2.20* (1.56, 3.11)</td>
<td>↑8.13* (4.59, 14.39)</td>
<td>Ritonavir 100 mg once daily is used as a booster of atazanavir pharmacokinetics.</td>
</tr>
<tr>
<td>* In a combined analysis, atazanavir 300 mg and ritonavir 100 mg (n=33) was compared to atazanavir 400 mg without ritonavir (n=28). The mechanism of interaction between atazanavir and ritonavir is CYP3A4 inhibition.</td>
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<tr>
<td>Indinavir</td>
<td>Indinavir is associated with indirect unconjugated hyperbilirubinaemia due to inhibition of UGT.</td>
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<tr>
<td><strong>Nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs)</strong></td>
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<tr>
<td>Lamivudine 150 mg BID + zidovudine 300 mg BID (atazanavir 400 mg QD)</td>
<td>No significant effect on lamivudine and zidovudine concentrations was observed.</td>
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<tr>
<td>Based on these data and because ritonavir is not expected to have a significant impact on the pharmacokinetics of NRTIs, the co-administration of REYATAZ/ritonavir with these medicinal products is not expected to significantly alter the exposure of the co-administered drugs.</td>
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<tr>
<td>Abacavir</td>
<td>The co-administration of REYATAZ/ritonavir with abacavir is not expected to significantly alter the exposure of abacavir.</td>
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<tr>
<td>Didanosine (buffered tablets) 200 mg/stavudine 40 mg, both single dose (atazanavir 400 mg single dose)</td>
<td>atazanavir, simultaneous administration with ddI+d4T (fasted)</td>
<td>↓0.13 (0.08, 0.21)</td>
<td>↓0.11 (0.06, 0.18)</td>
<td>↓0.16 (0.10, 0.27)</td>
<td>Didanosine should be taken at the fasted state 2 hours after REYATAZ/ritonavir taken with food. The co-administration of REYATAZ/ritonavir with stavudine is not expected to significantly alter the exposure of stavudine.</td>
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<tr>
<td></td>
<td>atazanavir, dosed 1 hr after ddI+d4T (fasted)</td>
<td>↔1.03 (0.64, 1.67)</td>
<td>↑1.12 (0.67, 1.18)</td>
<td>↔1.03 (0.61, 1.73)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Atazanavir concentrations were greatly decreased when co-administered with didanosine (buffered tablets) and stavudine. The mechanism of interaction is a reduced solubility of atazanavir with increasing pH related to the presence of anti-acid agent in didanosine buffered tablets. No significant effect on didanosine and stavudine concentrations was observed.</td>
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<tr>
<td>Didanosine (enteric coated capsules) 400 mg single dose (atazanavir 300 mg QD with ritonavir 100 mg QD)</td>
<td>Didanosine (with food)</td>
<td>↓0.66 (0.59, 0.73)</td>
<td>↓0.62 (0.52, 0.74)</td>
<td>↑1.25 (0.92, 1.69)</td>
<td>No significant effect on atazanavir concentrations was observed when administered with enteric-coated didanosine, but administration with food decreased didanosine concentrations.</td>
</tr>
<tr>
<td></td>
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<td></td>
</tr>
<tr>
<td>Tenofovir disoproxil fumarate 300 mg QD (atazanavir 300 mg QD with ritonavir 100 mg QD) studies conducted in HIV-infected patients</td>
<td>atazanavir</td>
<td>↓0.78* (0.65, 0.94)</td>
<td>↓0.84* (0.70, 1.00)</td>
<td>↓0.77* (0.57-1.02)</td>
<td>* In a combined analysis from several clinical studies, atazanavir/ritonavir 300/100 mg co-administered with tenofovir</td>
</tr>
</tbody>
</table>
disoproxil fumarate 300 mg (n=39) was compared to atazanavir/ritonavir 300/100 mg (n=33).

The efficacy of REYATAZ/ritonavir in combination with tenofovir in treatment-experienced patients has been demonstrated in clinical study 045 and in treatment naive patients in clinical study 138 (see sections 4.8 and 5.1). The mechanism of interaction between atazanavir and tenofovir is unknown.

<table>
<thead>
<tr>
<th>Co-administered medicinal products (dose in mg)</th>
<th>Medicinal product assessed</th>
<th>AUC (90% CI)</th>
<th>C_{max} (90% CI)</th>
<th>C_{min} (90% CI)</th>
<th>Recommendations concerning co-administration</th>
</tr>
</thead>
<tbody>
<tr>
<td>disoproxil fumarate 300 mg QD (atazanavir 300 mg QD with ritonavir 100 mg QD)</td>
<td>tenofovir disoproxil fumarate</td>
<td>↑1.37 (1.30, 1.45)</td>
<td>↑1.34 (1.20, 1.51)</td>
<td>↑1.29 (1.21, 1.36)</td>
<td>Patients should be closely monitored for tenofovir-associated adverse events, including renal disorders.</td>
</tr>
</tbody>
</table>

### Non-nucleoside reverse transcriptase inhibitors (NNRTIs)

<table>
<thead>
<tr>
<th>Non-nucleoside reverse transcriptase inhibitors (NNRTIs)</th>
<th>atazanavir (pm): all administered with food</th>
<th>Recommendations concerning co-administration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Efavirenz 600 mg QD (atazanavir 400 mg QD with ritonavir 100 mg QD)</td>
<td>↔1.00* (0.91, 1.00)天然</td>
<td>Co-administration of efavirenz with REYATAZ/ritonavir is not recommended (see section 4.4)</td>
</tr>
</tbody>
</table>

* When compared to REYATAZ 300 mg/ritonavir 100 mg once daily in the evening without efavirenz. This decrease in atazanavir C_{min}, might negatively impact the efficacy of atazanavir. The mechanism of efavirenz/atazanavir interaction is CYP3A4 induction.

** based on historical comparison.

<table>
<thead>
<tr>
<th>Nevirapine 200 mg BID (atazanavir 400 mg QD with ritonavir 100 mg QD) study conducted in HIV infected patients</th>
<th>nevirapine</th>
<th>Co-administration of nevirapine with REYATAZ/ritonavir is not recommended (see section 4.4)</th>
</tr>
</thead>
<tbody>
<tr>
<td>all administered with food</td>
<td>↑1.26 (1.17, 1.36)</td>
<td>↓1.08* (0.85, 1.24)</td>
</tr>
<tr>
<td>all administered with food</td>
<td>↑1.21 (1.11, 1.32)</td>
<td>↓1.02* (0.84, 1.49)</td>
</tr>
<tr>
<td>atazanavir</td>
<td>↑1.35 (1.25, 1.47)</td>
<td>↑1.12* (1.02, 1.24)</td>
</tr>
</tbody>
</table>

* When compared to REYATAZ 300 mg and ritonavir 100 mg without nevirapine. This decrease in atazanavir C_{min}, might negatively impact the efficacy of atazanavir. The mechanism of nevirapine/atazanavir interaction is CYP3A4 induction.

### Antibiotics

<table>
<thead>
<tr>
<th>Antibiotics</th>
<th>clarithromycin (1.75, 2.16)</th>
<th>↑1.50 (1.32, 1.71)</th>
<th>↑2.60 (2.35, 2.88)</th>
<th>No recommendation regarding dose reduction can be made; therefore, caution should be exercised if REYATAZ/ritonavir is co-administered with clarithromycin.</th>
</tr>
</thead>
<tbody>
<tr>
<td>clarithromycin 500 mg BID (atazanavir 400 mg QD)</td>
<td>↑1.94 (1.75, 2.16)</td>
<td>↑1.50 (1.32, 1.71)</td>
<td>↑2.60 (2.35, 2.88)</td>
<td>No recommendation regarding dose reduction can be made; therefore, caution should be exercised if REYATAZ/ritonavir is co-administered with clarithromycin.</td>
</tr>
<tr>
<td>14-OH clarithromycin</td>
<td>↑0.30 (0.26, 0.34)</td>
<td>↓0.28 (0.24, 0.33)</td>
<td>↓0.38 (0.34, 0.42)</td>
<td>No recommendation regarding dose reduction can be made; therefore, caution should be exercised if REYATAZ/ritonavir is co-administered with clarithromycin.</td>
</tr>
<tr>
<td>atazanavir</td>
<td>↑1.28 (1.16, 1.43)</td>
<td>↔1.06 (0.93, 1.20)</td>
<td>↑1.91 (1.66, 2.21)</td>
<td>No recommendation regarding dose reduction can be made; therefore, caution should be exercised if REYATAZ/ritonavir is co-administered with clarithromycin.</td>
</tr>
</tbody>
</table>

A dose reduction of clarithromycin may result in subtherapeutic concentrations of 14-OH clarithromycin. The mechanism of the clarithromycin/atazanavir interaction is CYP3A4 inhibition.

### Antifungals

<table>
<thead>
<tr>
<th>Antifungals</th>
<th>No significant effect on atazanavir concentrations was observed.</th>
<th>Ketoconazole anditraconazole should be used cautiously with REYATAZ/ritonavir. High doses of ketoconazole anditraconazole (&gt;200 mg/day) are not recommended.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ketoconazole 200 mg QD (atazanavir 400 mg QD)</td>
<td>Itraconazole, like ketoconazole, is a potent inhibitor as well as a substrate of CYP3A4.</td>
<td>Based on data obtained with other boosted PIs and ketoconazole, where ketoconazole AUC showed a 3-fold increase, REYATAZ/ritonavir is expected to increase ketoconazole oritraconazole concentrations.</td>
</tr>
</tbody>
</table>

<p>| Itraconazole | Co-administration of REYATAZ/ritonavir and voriconazole has not been studied. | Co-administration of voriconazole and REYATAZ/ritonavir is not recommended unless an assessment of the benefit/risk to |</p>
<table>
<thead>
<tr>
<th>Co-administered medicinal products (dose in mg)</th>
<th>Medicinal product assessed</th>
<th>AUC (90% CI)</th>
<th>C&lt;sub&gt;max&lt;/sub&gt; (90% CI)</th>
<th>C&lt;sub&gt;min&lt;/sub&gt; (90% CI)</th>
<th>Recommendations concerning co-administration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fluconazole 200 mg QD (atazanavir 300 mg and ritonavir 100 mg QD)</td>
<td>Atazanavir and fluconazole concentrations were not significantly modified when REYATAZ/ritonavir was co-administered with fluconazole.</td>
<td></td>
<td></td>
<td></td>
<td>No dosage adjustments are needed for REYATAZ/ritonavir and fluconazole.</td>
</tr>
<tr>
<td>Rifabutin 150 mg twice weekly (atazanavir 300 mg and ritonavir 100 mg QD)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>When given with REYATAZ/ritonavir, the recommended dose of rifabutin is 150 mg 3 times per week on set days (for example Monday-Wednesday-Friday). Increased monitoring for rifabutin-associated adverse reactions including neutropenia and uveitis is warranted due to an expected increase in exposure to rifabutin. Further dosage reduction of rifabutin to 150 mg twice weekly on set days is recommended for patients in whom the 150 mg dose 3 times per week is not tolerated. It should be kept in mind that the twice weekly dosage of 150 mg may not provide an optimal exposure to rifabutin thus leading to a risk of rifamycin resistance and a treatment failure. No dose adjustment is needed for REYATAZ/ritonavir.</td>
</tr>
<tr>
<td>Rifampicin</td>
<td>Rifampicin is a strong CYP3A4 inducer and has been shown to cause a 72% decrease in atazanavir AUC which can result in virological failure and resistance development. During attempts to overcome the decreased exposure by increasing the dose of REYATAZ or other protease inhibitors with ritonavir, a high frequency of liver reactions was seen.</td>
<td></td>
<td></td>
<td></td>
<td>The combination of rifampicin and REYATAZ with concomitant low-dose ritonavir is contraindicated (see section 4.3).</td>
</tr>
</tbody>
</table>

**ACID REDUCING AGENTS**

**H<sub>2</sub>-Receptor antagonists**

<table>
<thead>
<tr>
<th>Without Tenofovir</th>
<th></th>
<th>For patients not taking tenofovir, if REYATAZ 300 mg/ritonavir 100 mg and H&lt;sub&gt;2&lt;/sub&gt;-receptor</th>
</tr>
</thead>
<tbody>
<tr>
<td>In HIV-infected patients with atazanavir/ritonavir at the recommended dose 300/100 mg QD</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- famotidine 20 mg BID</td>
<td>atazanavir</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.82</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(0.75, 1.01)</td>
</tr>
</tbody>
</table>
### Co-administered medicinal products (dose in mg)

<table>
<thead>
<tr>
<th>Medicinal product assessed</th>
<th>AUC (90% CI)</th>
<th>C&lt;sub&gt;max&lt;/sub&gt; (90% CI)</th>
<th>C&lt;sub&gt;min&lt;/sub&gt; (90% CI)</th>
<th>Recommendations concerning co-administration</th>
</tr>
</thead>
<tbody>
<tr>
<td>famotidine 40 mg BID</td>
<td>atazanavir</td>
<td>↓0.77 (0.68, 0.86)</td>
<td>↓0.77 (0.67, 0.88)</td>
<td>↓0.80 (0.69, 0.92)</td>
</tr>
</tbody>
</table>

**In Healthy volunteers with atazanavir/ritonavir at an increased dose of 400/100 mg QD**

<table>
<thead>
<tr>
<th>Medicinal product assessed</th>
<th>AUC (90% CI)</th>
<th>C&lt;sub&gt;max&lt;/sub&gt; (90% CI)</th>
<th>C&lt;sub&gt;min&lt;/sub&gt; (90% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>famotidine 40 mg BID</td>
<td>atazanavir</td>
<td>↔1.03 (0.86, 1.22)</td>
<td>↔1.02 (0.87, 1.18)</td>
</tr>
</tbody>
</table>

### With Tenofovir 300 mg QD

**In HIV-infected patients with atazanavir/ritonavir at the recommended dose of 300/100 mg QD**

<table>
<thead>
<tr>
<th>Medicinal product assessed</th>
<th>AUC (90% CI)</th>
<th>C&lt;sub&gt;max&lt;/sub&gt; (90% CI)</th>
<th>C&lt;sub&gt;min&lt;/sub&gt; (90% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>famotidine 20 mg BID</td>
<td>atazanavir</td>
<td>↓0.79* (0.66, 0.96)</td>
<td>↓0.79* (0.64, 0.96)</td>
</tr>
<tr>
<td>famotidine 40 mg BID</td>
<td>atazanavir</td>
<td>↓0.76* (0.64, 0.89)</td>
<td>↓0.77* (0.64, 0.92)</td>
</tr>
</tbody>
</table>

* When compared to atazanavir 300 mg QD with ritonavir 100 mg QD and tenofovir disoproxil fumarate 300 mg all as a single dose with food. When compared to atazanavir 300 mg with ritonavir 100 mg *without* tenofovir, atazanavir concentrations are expected to be additionally decreased by about 20%.

The mechanism of interaction is decreased solubility of atazanavir as intra-gastric pH increases with H<sub>2</sub> blockers.

### Proton pump inhibitors

**Omeprazole 40 mg QD**

<table>
<thead>
<tr>
<th>Medicinal product assessed</th>
<th>AUC (90% CI)</th>
<th>C&lt;sub&gt;max&lt;/sub&gt; (90% CI)</th>
<th>C&lt;sub&gt;min&lt;/sub&gt; (90% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>atazanavir (am): 2 hr after omeprazole</td>
<td>↓0.39 (0.35, 0.45)</td>
<td>↓0.44 (0.38, 0.51)</td>
<td>↓0.35 (0.29, 0.41)</td>
</tr>
</tbody>
</table>

**Omeprazole 20 mg QD**

<table>
<thead>
<tr>
<th>Medicinal product assessed</th>
<th>AUC (90% CI)</th>
<th>C&lt;sub&gt;max&lt;/sub&gt; (90% CI)</th>
<th>C&lt;sub&gt;min&lt;/sub&gt; (90% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>atazanavir (am): 1 hr after omeprazole</td>
<td>↓0.70* (0.57, 0.86)</td>
<td>↓0.69* (0.58, 0.83)</td>
<td>↓0.69* (0.54, 0.88)</td>
</tr>
</tbody>
</table>

* When compared to atazanavir 300 mg QD with ritonavir 100 mg QD

The decrease in AUC, C<sub>max</sub>, and C<sub>min</sub> was not mitigated when an increased dose of REYATAZ/ritonavir (400/100 mg once daily) was temporally separated from omeprazole by 12 hours. Although not studied, similar results are expected with other proton pump inhibitors. This decrease in atazanavir exposure might negatively impact the efficacy of atazanavir. The mechanism of interaction is decreased solubility of atazanavir as intra-gastric pH increases with proton pump inhibitors.

### Antacids

**Antacids and medicinal products containing buffers**

Reduced plasma concentrations of atazanavir may be the consequence of increased gastric pH if antacids, including buffered medicinal products, are administered with REYATAZ/ritonavir.

For patients who are taking tenofovir,

Co-administration of REYATAZ/ritonavir in combination with tenofovir and an H<sub>2</sub>-receptor antagonist should be avoided (see section 4.4). If the combination of REYATAZ/ritonavir with both tenofovir and an H<sub>2</sub>-receptor antagonist is judged unavoidable, close clinical monitoring is recommended. A dose increase of REYATAZ to 400 mg with 100 mg of ritonavir may be considered but is still under evaluation.

**Antacids**

REYATAZ/ritonavir should be administered 2 hours before or 1 hour after antacids or...
<table>
<thead>
<tr>
<th>Co-administered medicinal products (dose in mg)</th>
<th>Medicinal product assessed</th>
<th>AUC (90% CI)</th>
<th>$C_{\text{max}}$ (90% CI)</th>
<th>$C_{\text{min}}$ (90% CI)</th>
<th>Recommendations concerning co-administration</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>buffered medicinal products.</td>
</tr>
<tr>
<td><strong>ANTICOAGULANTS</strong></td>
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<tr>
<td>Warfarin</td>
<td>Co-administration with REYATAZ/ritonavir has the potential to produce a decrease or, less often, an increase in INR (International Normalised Ratio).</td>
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<tr>
<td></td>
<td>It is recommended that the INR be monitored carefully during treatment with REYATAZ/ritonavir, especially when commencing therapy.</td>
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</tr>
<tr>
<td><strong>ANTINEOPLASTICS AND IMMUNOSUPPRESSANTS</strong></td>
<td></td>
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<tr>
<td>Antineoplastics</td>
<td></td>
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</tr>
<tr>
<td>Irinotecan</td>
<td>Atazanavir inhibits UGT and may interfere with the metabolism of irinotecan, resulting in increased irinotecan toxicities.</td>
<td></td>
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<tr>
<td>Immunosuppressants</td>
<td></td>
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</tr>
<tr>
<td>Cyclosporin</td>
<td>Concentrations of these immunosuppressants may be increased when co-administered with REYATAZ/ritonavir due to CYP3A4 inhibition.</td>
<td></td>
<td></td>
<td></td>
<td>More frequent therapeutic concentration monitoring of these medicinal products is recommended until plasma levels have been stabilised.</td>
</tr>
<tr>
<td>Tacrolimus</td>
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<tr>
<td>Sirolimus</td>
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</tr>
<tr>
<td><strong>CARDIOVASCULAR AGENTS</strong></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Antiarrhythmics</td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Amiodarone, Systemic lidocaine, Quinidine</td>
<td>Concentrations of these antiarrhythmics may be increased when co-administered with REYATAZ/ritonavir. The mechanism of amiodarone or systemic lidocaine/atazanavir interaction is CYP3A inhibition. Quinidine has a narrow therapeutic window and is contraindicated due to potential inhibition of CYP3A by REYATAZ/ritonavir.</td>
<td></td>
<td></td>
<td></td>
<td>Caution is warranted and therapeutic concentration monitoring is recommended when available. The concomitant use of quinidine is contraindicated (see section 4.3).</td>
</tr>
<tr>
<td>Calcium channel blockers</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Bepridil</td>
<td>REYATAZ/ritonavir should not be used in combination with medicinal products that are substrates of CYP3A4 and have a narrow therapeutic index.</td>
<td></td>
<td></td>
<td></td>
<td>Co-administration with bepridil is contraindicated (see section 4.3)</td>
</tr>
<tr>
<td>Diltiazem 180 mg QD (atazanavir 400 mg QD)</td>
<td>diltiazem 12.25 (2.09, 2.41) $\uparrow$ 1.98 (1.78, 2.19) $\uparrow$ 2.42 (2.14, 2.73)</td>
<td></td>
<td></td>
<td></td>
<td>An initial dose reduction of diltiazem by 50% is recommended, with subsequent titration as needed and ECG monitoring.</td>
</tr>
<tr>
<td></td>
<td>desacytel-diltiazem 2.65 (2.45, 2.87) $\uparrow$ 2.72 (2.44, 3.03) $\uparrow$ 2.21 (2.02, 2.42)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>No significant effect on atazanavir concentrations was observed. There was an increase in the maximum PR interval compared to atazanavir alone. Co-administration of diltiazem and REYATAZ/ritonavir has not been studied. The mechanism of diltiazem/atazanavir interaction is CYP3A4 inhibition.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Verapamil</td>
<td>Serum concentrations of verapamil may be increased by REYATAZ/ritonavir due to CYP3A4 inhibition.</td>
<td></td>
<td></td>
<td></td>
<td>Caution should be exercised when verapamil is co-administered with REYATAZ/ritonavir.</td>
</tr>
<tr>
<td><strong>CORTICOSTEROIDS</strong></td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Fluticasone propionate intranasal 50 µg 4 times daily for 7 days (ritonavir 100 mg capsules BID)</td>
<td>The fluticasone propionate plasma levels increased significantly, whereas the intrinsic cortisol levels decreased by approximately 86% (90% confidence interval 82-89%). Greater effects may be expected when fluticasone propionate is inhaled. Systemic corticosteroid effects</td>
<td></td>
<td></td>
<td></td>
<td>Co-administration of REYATAZ/ritonavir and these glucocorticoids is not</td>
</tr>
</tbody>
</table>
Co-administered medicinal products (dose in mg) | Medicinal product assessed | AUC (90% CI) | C<sub>max</sub> (90% CI) | C<sub>min</sub> (90% CI) | Recommendations concerning co-administration
---|---|---|---|---|---

including Cushing’s syndrome and adrenal suppression have been reported in patients receiving ritonavir and inhaled or intranasally administered fluticasone propionate; this could also occur with other corticosteroids metabolized via the P450 3A pathway, e.g., budesonide. The effects of high fluticasone systemic exposure on ritonavir plasma levels are yet unknown. The mechanism of interaction is CYP3A4 inhibition.

**ERECTILE DYSFUNCTION**

**PDE5 Inhibitors**

| Sildenafil | Sildenafil is metabolised by CYP3A4. Co-administration with REYATAZ/ritonavir may result in increased concentrations of sildenafil and an increase in sildenafil-associated adverse events, including hypotension, visual changes, and priapism. The mechanism of the sildenafil/atazanavir interaction is CYP3A4 inhibition. | Patients should be warned about these possible side effects. |

**HERBAL PRODUCTS**

| St. John’s wort (Hypericum perforatum): | Concomitant use of St. John's wort with REYATAZ/ritonavir may be expected to result in significant reduction in plasma levels of atazanavir. This effect may be due to an induction of CYP3A4. There is a risk of loss of therapeutic effect and development of resistance (see section 4.3). | Co-administration of REYATAZ/ritonavir with products containing St. John's wort is contraindicated. |

**HORMONAL CONTRACEPTIVES**

| Ethinyloestradiol 25 μg + norgestimate (atazanavir 300 mg QD with ritonavir 100 mg QD) | ethinyloestradiol and norgestimate | If an oral contraceptive is administered with REYATAZ/ritonavir, it is recommended that the oral contraceptive contain at least 30 μg of ethinyloestradiol and that the patient be reminded of strict compliance with this contraceptive dosing regimen. Co-administration of REYATAZ/ritonavir with other hormonal contraceptives or oral contraceptives containing progestogens other than norgestimate has not been studied, and therefore should be avoided. An alternate reliable method of contraception is recommended. |

| Ethinyloestradiol 25 μg + norgestimate (atazanavir 300 mg QD with ritonavir 100 mg QD) | ethinyloestradiol and norgestimate | If an oral contraceptive is administered with REYATAZ/ritonavir, it is recommended that the oral contraceptive contain at least 30 μg of ethinyloestradiol and that the patient be reminded of strict compliance with this contraceptive dosing regimen. Co-administration of REYATAZ/ritonavir with other hormonal contraceptives or oral contraceptives containing progestogens other than norgestimate has not been studied, and therefore should be avoided. An alternate reliable method of contraception is recommended. |

- **Relevant dosages and concentrations:**
  - Ethinyloestradiol: ↓0.81 (0.75, 0.87) ↓0.84 (0.74, 0.95) ↓0.63 (0.55, 0.71)
  - Norgestimate: ↑1.85 (1.17, 2.05) ↓1.68 (1.51, 1.88) ↑2.02 (1.77, 2.31)

- **Recommendations:**
  - The increase in progestin exposure may lead to related side-effects (e.g. insulin resistance, dyslipidemia, acne and spotting), thus possibly affecting the compliance.

- **Additional considerations:**
  - While the concentration of ethinyloestradiol was increased with atazanavir given alone, due to both UGT and CYP3A4 inhibition by atazanavir, the net effect of atazanavir/ritonavir is a decrease in ethinyloestradiol levels because of the inducing effect of ritonavir.

- **Dosage adjustments:**
  - If an oral contraceptive is administered with REYATAZ/ritonavir, it is recommended that the oral contraceptive contain at least 30 μg of ethinyloestradiol and that the patient be reminded of strict compliance with this contraceptive dosing regimen. Co-administration of REYATAZ/ritonavir with other hormonal contraceptives or oral contraceptives containing progestogens other than norgestimate has not been studied, and therefore should be avoided. An alternate reliable method of contraception is recommended.
Co-administered medicinal products (dose in mg) | Medicinal product assessed | AUC (90% CI) | C<sub>max</sub> (90% CI) | C<sub>min</sub> (90% CI) | Recommendations concerning co-administration
---|---|---|---|---|---
**LIPID LOWERING AGENTS**
HMG-CoA reductase inhibitors

Simvastatin
Lovastatin
Simvastatin and lovastatin are highly dependent on CYP3A4 for their metabolism and co-administration with REYATAZ/ritonavir may result in increased concentrations.

Atorvastatin
The risk of myopathy including rhabdomyolysis may also be increased with atorvastatin, which is also metabolised by CYP3A4.

**OPIOIDS**

Buprenorphine, QD, stable maintenance dose, (atazanavir 300 mg QD with ritonavir 100 mg QD)

| buprenorphine | ↑1.67 | ↑1.37 | ↑1.69 | Co-administration warrants clinical monitoring for sedation and cognitive effects. A dose reduction of buprenorphine may be considered.
| norbuprenorphine | ↑2.05 | ↑1.61 | ↑2.01 | The mechanism of interaction is CYP3A4 and UGT1A1 inhibition. Concentrations of atazanavir were not significantly affected.

Methadone, stable maintenance dose (atazanavir 400 mg QD)
No significant effect on methadone concentrations was observed. Given that low dose ritonavir (100 mg twice daily) has been shown to have no significant effect on methadone concentrations, no interaction is expected if methadone is co-administered with REYATAZ and ritonavir, based on these data.

**SEDATIVES**

Benzodiazepines

Midazolam
Triazolam
Midazolam and triazolam are extensively metabolized by CYP3A4. Co-administration with REYATAZ/ritonavir may cause a large increase in the concentration of these benzodiazepines. No drug interaction study has been performed for the co-administration of REYATAZ/ritonavir with benzodiazepines. Based on data for other CYP3A4 inhibitors, plasma concentrations of midazolam are expected to be significantly higher when midazolam is given orally. Data from concomitant use of parenteral midazolam with other protease inhibitors suggest a possible 3-4 fold increase in midazolam plasma levels.

REYATAZ/ritonavir should not be co-administered with triazolam or orally administered midazolam (see section 4.3), whereas caution should be used with co-administration of REYATAZ/ritonavir and parenteral midazolam. If REYATAZ is co-administered with parenteral midazolam, it should be done in an intensive care unit (ICU) or similar setting which ensures close clinical monitoring and appropriate medical management in case of respiratory depression and/or prolonged sedation. Dosage adjustment for midazolam should be considered, especially
4.6 Pregnancy and lactation

There are no adequate data from the use of atazanavir in pregnant women. Studies in animals have not shown evidence of selective developmental toxicity or effects on reproductive function and fertility (see section 5.3). REYATAZ should be used during pregnancy only if the potential benefit justifies the potential risk.

It is not known whether REYATAZ administered to the mother during pregnancy will exacerbate physiological hyperbilirubinaemia and lead to kernicterus in neonates and infants. In the prepartum period, additional monitoring and alternative therapy to REYATAZ should be considered.

It is not known whether atazanavir is excreted in human milk. Studies in rats have demonstrated that atazanavir is excreted in the milk. It is therefore recommended that mothers being treated with REYATAZ not breast-feed their infants. As a general rule, it is recommended that HIV infected women not breast-feed their infants in order to avoid transmission of HIV.

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed. Patients should be informed that dizziness has been reported during treatment with regimens containing REYATAZ (see section 4.8).

4.8 Undesirable effects

REYATAZ has been evaluated for safety in combination therapy with other antiretroviral medicinal products in controlled clinical trials in 1,806 adult patients receiving REYATAZ 400 mg once daily (1,151 patients, 52 weeks median duration and 152 weeks maximum duration) or REYATAZ 300 mg with ritonavir 100 mg once daily (655 patients, 96 weeks median duration and 108 weeks maximum duration).

Adverse reactions were consistent between patients who received REYATAZ 400 mg once daily and patients who received REYATAZ 300 mg with ritonavir 100 mg once daily, except that jaundice and elevated total bilirubin levels were reported more frequently with REYATAZ plus ritonavir.

Among patients who received REYATAZ 400 mg once daily or REYATAZ 300 mg with ritonavir 100 mg once daily, the only adverse reactions of any severity reported very commonly with at least a possible relationship to regimens containing REYATAZ and one or more NRTIs were nausea (20%), diarrhoea (10%), and jaundice (13%). Among patients receiving REYATAZ 300 mg with ritonavir 100 mg, the frequency of jaundice was 19%. In the majority of cases, jaundice was reported within a few days to a few months after the initiation of treatment (see section 4.4).

Combination antiretroviral therapy has been associated with redistribution of body fat (lipodystrophy) in HIV patients, including loss of peripheral and facial subcutaneous fat, increased intra-abdominal and visceral fat, breast hypertrophy, and dorsocervical fat accumulation (buffalo hump).

Combination antiretroviral therapy has been associated with metabolic abnormalities such as hypertriglyceridaemia, hypercholesterolaemia, insulin resistance, hyperglycaemia, and hyperlactataemia (see sections 4.4 and 5.1).
**Adult patients**
The following adverse reactions of moderate intensity or greater with at least a possible relationship to regimens containing REYATAZ and one or more NRTIs have also been reported. The frequency of adverse reactions listed below is defined using the following convention: very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1,000 to < 1/100), rare (≥ 1/10,000 to < 1/1,000), or very rare (< 1/10,000). Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

<table>
<thead>
<tr>
<th>Cardiac disorders:</th>
<th>rare: oedema, palpitation</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Nervous system disorders:</strong></td>
<td>common: headache; uncommon: peripheral neuropathy, syncope, amnesia, dizziness, somnolence, dysgeusia</td>
</tr>
<tr>
<td><strong>Eye disorders:</strong></td>
<td>common: ocular icterus</td>
</tr>
<tr>
<td><strong>Respiratory, thoracic and mediastinal disorders:</strong></td>
<td>uncommon: dyspnoea</td>
</tr>
<tr>
<td><strong>Gastrointestinal disorders:</strong></td>
<td>common: vomiting, diarrhoea, abdominal pain, nausea, dyspepsia; uncommon: pancreatitis, gastritis, abdominal distension, stomatitis aphthous, flatulence, dry mouth</td>
</tr>
<tr>
<td><strong>Renal and urinary disorders:</strong></td>
<td>uncommon: nephrolithiasis, hematuria, proteinuria, pollakiuria; rare: kidney pain</td>
</tr>
<tr>
<td><strong>Skin and subcutaneous tissue disorders:</strong></td>
<td>common: rash; uncommon: urticaria, alopecia, pruritus; rare: vesiculobullous rash, eczema, vasodilatation</td>
</tr>
<tr>
<td><strong>Musculoskeletal and connective tissue disorders:</strong></td>
<td>uncommon: muscle atrophy, arthralgia, myalgia; rare: myopathy</td>
</tr>
<tr>
<td><strong>Metabolism and nutrition disorders:</strong></td>
<td>uncommon: weight decreased, weight gain, anorexia, appetite increased</td>
</tr>
<tr>
<td><strong>Vascular disorders:</strong></td>
<td>uncommon: hypertension</td>
</tr>
<tr>
<td><strong>General disorders and administration site conditions:</strong></td>
<td>common: lipodystrophy syndrome, fatigue; uncommon: chest pain, malaise, pyrexia, asthenia; rare: gait disturbance</td>
</tr>
<tr>
<td><strong>Immune system disorders:</strong></td>
<td>uncommon: hypersensitivity</td>
</tr>
<tr>
<td><strong>Hepatobiliary disorders:</strong></td>
<td>common: jaundice; uncommon: hepatitis; rare: hepatosplenomegaly</td>
</tr>
<tr>
<td><strong>Reproductive system and breast disorders:</strong></td>
<td>uncommon: gynaecomastia</td>
</tr>
<tr>
<td><strong>Psychiatric disorders:</strong></td>
<td>uncommon: depression, disorientation, anxiety, insomnia, sleep disorder, abnormal dream</td>
</tr>
</tbody>
</table>
In HIV-infected patients with severe immune deficiency at the time of initiation of combination antiretroviral therapy (CART), an inflammatory reaction to asymptomatic or residual opportunistic infections may arise (see section 4.4).

Cases of osteonecrosis have been reported, particularly in patients with generally acknowledged risk factors, advanced HIV disease or long-term exposure to combination antiretroviral therapy (CART). The frequency of this is unknown (see section 4.4).

**Laboratory abnormalities**
The most frequently reported laboratory abnormality in patients receiving regimens containing REYATAZ and one or more NRTIs was elevated total bilirubin reported predominantly as elevated indirect [unconjugated] bilirubin (87% Grade 1, 2, 3, or 4). Grade 3 or 4 elevation of total bilirubin was noted in 37% (6% Grade 4). Among experienced patients treated with REYATAZ 300 mg once daily with 100 mg ritonavir once daily for a median duration of 95 weeks, 53% had Grade 3-4 total bilirubin elevations. Among naive patients treated with REYATAZ 300 mg once daily with 100 mg ritonavir once daily for a median duration of 96 weeks, 48% had Grade 3-4 total bilirubin elevations (see section 4.4).

Other marked clinical laboratory abnormalities (Grade 3 or 4) reported in ≥ 2% of patients receiving regimens containing REYATAZ and one or more NRTIs included: elevated creatine kinase (7%), elevated alanine aminotransferase/serum glutamic-pyruvic transaminase (ALT/SGPT) (5%), low neutrophils (5%), elevated aspartate aminotransferase/serum glutamic-oxaloacetic transaminase (AST/SGOT) (3%), and elevated lipase (3%).

Two percent of patients treated with REYATAZ experienced concurrent Grade 3-4 ALT/AST and Grade 3-4 total bilirubin elevations.

**Patients co-infected with hepatitis B and/or hepatitis C virus**
Among 1,151 patients receiving atazanavir 400 mg once daily, 177 patients were co-infected with chronic hepatitis B or C, and among 655 patients receiving atazanavir 300 mg once daily with ritonavir 100 mg once daily, 97 patients were co-infected with chronic hepatitis B or C. Co-infected patients were more likely to have baseline hepatic transaminase elevations than those without chronic viral hepatitis. No differences in frequency of bilirubin elevations were observed between these patients and those without viral hepatitis. The frequency of treatment emergent hepatitis or transaminase elevations in co-infected patients was comparable between REYATAZ and comparator regimens (see section 4.4).

**Paediatric population**
In clinical studies, paediatric patients 3 months to less than 18 years of age had a mean duration of treatment with REYATAZ of 115 weeks. The safety profile in these studies was overall comparable to that seen in adults. Both asymptomatic first-degree (23%) and second-degree (1%) atrioventricular block were reported in paediatric patients. The most frequently reported laboratory abnormality in paediatric patients receiving REYATAZ was elevation of total bilirubin (≥ 2.6 times ULN, Grade 3-4) which occurred in 45% of patients.

**Postmarketing experience**
There have been postmarketing reports of unknown frequency for torsades de pointes, QTc prolongation, diabetes mellitus, hyperglycaemia, nephrolithiasis, and gallbladder disorders including choledolithiasis, cholecystitis, and cholestasis.

**4.9 Overdose**
Human experience of acute overdose with REYATAZ is limited. Single doses up to 1,200 mg have been taken by healthy volunteers without symptomatic untoward effects. At high doses that lead to high drug exposures, jaundice due to indirect (unconjugated) hyperbilirubinaemia (without associated liver function test changes) or PR interval prolongations may be observed (see sections 4.4 and 4.8).
Treatment of overdose with REYATAZ should consist of general supportive measures, including monitoring of vital signs and electrocardiogram (ECG), and observations of the patient's clinical status. If indicated, elimination of unabsorbed atazanavir should be achieved by emesis or gastric lavage. Administration of activated charcoal may also be used to aid removal of unabsorbed drug. There is no specific antidote for overdose with REYATAZ. Since atazanavir is extensively metabolised by the liver and is highly protein bound, dialysis is unlikely to be beneficial in significant removal of this medicinal product.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: protease inhibitor, ATC code: J05AE08

Mechanism of action: atazanavir is an azapeptide HIV-1 protease inhibitor (PI). The compound selectively inhibits the virus-specific processing of viral Gag-Pol proteins in HIV-1 infected cells, thus preventing formation of mature virions and infection of other cells.

Antiviral activity in vitro: atazanavir exhibits anti-HIV-1 (including all clades tested) and anti-HIV-2 activity in cell culture.

Resistance

Antiretroviral treatment naive adult patients
In clinical trials of antiretroviral treatment naive patients treated with unboosted atazanavir, the I50L substitution, sometimes in combination with an A71V change, is the signature resistance substitution for atazanavir. Resistance levels to atazanavir ranged from 3.5- to 29-fold without evidence of phenotypic cross resistance to other PIs. In clinical trials of antiretroviral treatment naive patients treated with boosted atazanavir, the I50L substitution did not emerge in any patient without baseline PI substitutions. The N88S substitution has been rarely observed in patients with virologic failure on atazanavir (with or without ritonavir). While it may contribute to decreased susceptibility to atazanavir when it occurs with other protease substitutions, in clinical studies N88S by itself does not always lead to phenotypic resistance to atazanavir or have a consistent impact on clinical efficacy.

Table 3. De novo substitutions in treatment naive patients failing therapy with atazanavir + ritonavir (Study 138, 96 weeks)

<table>
<thead>
<tr>
<th>Frequency</th>
<th>de novo PI substitution (n=26)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;20%</td>
<td>none</td>
</tr>
<tr>
<td>10-20%</td>
<td>none</td>
</tr>
</tbody>
</table>

* Number of patients with paired genotypes classified as virological failures (HIV RNA ≥ 400 copies/ml).

The M184I/V substitution emerged in 5/26 REYATAZ/ritonavir and 7/26 lopinavir/ritonavir virologic failure patients, respectively.

Antiretroviral treatment experienced adult patients
In antiretroviral treatment experienced patients from Studies 009, 043, and 045, 100 isolates from patients designated as virological failures on therapy that included either atazanavir, atazanavir + ritonavir, or atazanavir + saquinavir were determined to have developed resistance to atazanavir. Of the 60 isolates from patients treated with either atazanavir or atazanavir + ritonavir, 18 (30%) displayed the I50L phenotype previously described in naive patients.

Table 4. De novo substitutions in treatment experienced patients failing therapy with atazanavir + ritonavir (Study 045, 48 weeks)

<table>
<thead>
<tr>
<th>Frequency</th>
<th>de novo PI substitution (n=35)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;20%</td>
<td>M36, M46, I54, A71, V82</td>
</tr>
<tr>
<td>10-20%</td>
<td>L10, I15, K20, V32, E35, S37, F53, I62, G73, I84, L90</td>
</tr>
</tbody>
</table>

* Number of patients with paired genotypes classified as virological failures (HIV RNA ≥ 400 copies/ml).
Ten patients had baseline phenotypic resistance to atazanavir + ritonavir (fold change [FC]>5.2). FC susceptibility in cell culture relative to the wild-type reference was assayed using PhenoSenseSM (Monogram Biosciences, South San Francisco, California, USA).

None of the de novo substitutions (see Table 4) are specific to atazanavir and may reflect re-emergence of archived resistance on atazanavir + ritonavir in Study 045 treatment-experienced population.

The resistance in antiretroviral treatment experienced patients mainly occurs by accumulation of the major and minor resistance substitutions described previously to be involved in protease inhibitor resistance.

Clinical results

In antiretroviral naïve adult patients

Study 138 is an international randomised, open-label, multicenter, prospective trial of treatment naïve patients comparing REYATAZ/ritonavir (300 mg/100 mg once daily) to lopinavir/ritonavir (400 mg/100 mg twice daily), each in combination with fixed dose tenofovir/emtricitabine (300 mg/200 mg tablets once daily). The REYATAZ/ritonavir arm showed similar (non-inferior) antiviral efficacy compared to the lopinavir/ritonavir arm, as assessed by the proportion of patients with HIV RNA < 50 copies/ml at week 48 (Table 5). Analyses of data through 96 weeks of treatment demonstrated durability of antiviral activity (Table 5).
Table 5: Efficacy Outcomes in Study 138

<table>
<thead>
<tr>
<th>Parameter</th>
<th>REYATAZ/ritonavirb (300 mg/100 mg once daily)</th>
<th>Lopinavir/ritonavirc (400 mg/100 mg twice daily)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Week 48</td>
<td>Week 96</td>
</tr>
<tr>
<td>HIV RNA &lt;50 copies/ml, %</td>
<td></td>
<td></td>
</tr>
<tr>
<td>All patientsd</td>
<td>78</td>
<td>74</td>
</tr>
<tr>
<td>Difference estimate [95% CI]d</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Per protocol analysise</td>
<td>86 (n=392f)</td>
<td>91 (n=352)</td>
</tr>
<tr>
<td>Difference estimate [95% CI]e</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HIV RNA Mean Change from Baseline, log10 copies/ml</td>
<td></td>
<td></td>
</tr>
<tr>
<td>All patients</td>
<td>-3.09 (n=397)</td>
<td>-3.21 (n=360)</td>
</tr>
<tr>
<td>CD4 Mean Change from Baseline, cells/mm³</td>
<td></td>
<td></td>
</tr>
<tr>
<td>All patients</td>
<td>203 (n=370)</td>
<td>268 (n=336)</td>
</tr>
<tr>
<td>HIV RNA &lt;100,000 copies/ml</td>
<td>179 (n=183)</td>
<td>243 (n=163)</td>
</tr>
<tr>
<td>≥100,000 copies/ml</td>
<td>227 (n=187)</td>
<td>291 (n=173)</td>
</tr>
</tbody>
</table>

a Mean baseline CD4 cell count was 214 cells/mm³ (range 2 to 810 cells/mm³) and mean baseline plasma HIV-1 RNA was 4.94 log10 copies/ml (range 2.6 to 5.88 log10 copies/ml)
b REYATAZ/RTV with tenofovir/emtricitabine (fixed dose 300 mg/200 mg tablets once daily).
c Lopinavir/RTV with tenofovir/emtricitabine (fixed dose 300 mg/200 mg tablets once daily).
d Intent-to-treat analysis, with missing values considered as failures.
e Per protocol analysis: Excluding non-completers and patients with major protocol deviations.
f Number of patients evaluable.

In antiretroviral experienced adult patients

Study 045 is a randomised, multicenter trial comparing REYATAZ/ritonavir (300/100 mg once daily) and REYATAZ/saquinavir (400/1,200 mg once daily), to lopinavir + ritonavir (400/100 mg fixed dose combination twice daily), each in combination with tenofovir (see sections 4.5 and 4.8) and one NRTI, in patients with virologic failure on two or more prior regimens containing at least one PI, NRTI, and NNRTI. For randomised patients, the mean time of prior antiretroviral exposure was 138 weeks for PIs, 281 weeks for NRTIs, and 85 weeks for NNRTIs. At baseline, 34% of patients were receiving a PI and 60% were receiving an NNRTI. Fifteen of 120 (13%) patients in the REYATAZ + ritonavir treatment arm and 17 of 123 (14%) patients in the lopinavir + ritonavir arm had four or more of the PI substitutions L10, M46, I54, V82, I84, and L90. Thirty-two percent of patients in the study had a viral strain with fewer than two NRTI substitutions.

The primary endpoint was the time-averaged difference in change from baseline in HIV RNA through 48 weeks (Table 6).
Table 6: Efficacy Outcomes at Week 48 and at Week 96 (Study 045)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>ATV/RTV ((300 \text{ mg/100 mg once daily})) (n=120)</th>
<th>LPV/RTV ((400 \text{ mg/100 mg twice daily})) (n=123)</th>
<th>Time-averaged difference ATV/RTV-LPV/RTV (97.5% \text{ CI})</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV RNA Mean Change from Baseline, (\text{log}_{10} \text{ copies/ml})</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All patients</td>
<td>Week 48</td>
<td>Week 96</td>
<td>Week 48</td>
</tr>
<tr>
<td></td>
<td>-1.93 ((n=90))</td>
<td>-2.29 ((n=64))</td>
<td>-1.87 ((n=99))</td>
</tr>
<tr>
<td>HIV RNA &lt;50 copies/ml, %(^{f}) (responder/evaluable)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All patients</td>
<td>36 (43/120)</td>
<td>32 (38/120)</td>
<td>42 (52/123)</td>
</tr>
<tr>
<td>HIV RNA &lt;50 copies/ml by select baseline PI substitutions, (^{g}) % (responder/evaluable)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0-2</td>
<td>44 (28/63)</td>
<td>41 (26/63)</td>
<td>56 (32/57)</td>
</tr>
<tr>
<td>3</td>
<td>18 (2/11)</td>
<td>9 (1/11)</td>
<td>38 (6/16)</td>
</tr>
<tr>
<td>≥4</td>
<td>27 (12/45)</td>
<td>24 (11/45)</td>
<td>28 (14/50)</td>
</tr>
</tbody>
</table>

CD4 Mean Change from Baseline, cells/mm\(^3\)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>ATV/RTV ((300 \text{ mg/100 mg once daily})) (n=120)</th>
<th>LPV/RTV ((400 \text{ mg/100 mg twice daily})) (n=123)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients</td>
<td>Week 48</td>
<td>Week 96</td>
</tr>
<tr>
<td></td>
<td>110 (n=83)</td>
<td>122 (n=60)</td>
</tr>
</tbody>
</table>

a The mean baseline CD4 cell count was 337 cells/mm\(^3\) (range: 14 to 1,543 cells/mm\(^3\)) and the mean baseline plasma HIV-1 RNA level was 4.4 \(\text{log}_{10}\) copies/ml (range: 2.6 to 5.88 \(\text{log}_{10}\) copies/ml).
b ATV/RTV with tenofovir/emtricitabine (fixed dose 300 mg/200 mg tablets once daily).
c LPV/RTV with tenofovir/emtricitabine (fixed dose 300 mg/200 mg tablets once daily).
d Confidence interval.
e Number of patients evaluable.
f Intent-to-treat analysis, with missing values considered as failures. Responders on LPV/RTV who completed treatment before Week 96 are excluded from Week 96 analysis. The proportion of patients with HIV RNA < 400 copies/ml were 53% and 43% for ATV/RTV and LPV/RTV at weeks 48 and 96 respectively.
g Select substitutions include any change at positions L10, K20, L24, V32, L33, M36, M46, G48, I50, I54, L63, A71, G73, V82, I84, and L90 (0-2, 3, 4 or more) at baseline. NA = not applicable.

Through 48 weeks of treatment, the mean changes from baseline in HIV RNA levels for REYATAZ + ritonavir and lopinavir + ritonavir were similar (non-inferior). Consistent results were obtained with the last observation carried forward method of analysis (time-averaged difference of 0.11, 97.5% confidence interval [-0.15, 0.36]). By as-treated analysis, excluding missing values, the proportions of patients with HIV RNA < 400 copies/ml (< 50 copies/ml) in the REYATAZ + ritonavir arm and the lopinavir + ritonavir arm were 55% (40%) and 56% (46%), respectively.

Through 96 weeks of treatment, mean HIV RNA changes from baseline for REYATAZ + ritonavir and lopinavir + ritonavir met criteria for non-inferiority based on observed cases. Consistent results were obtained with the last observation carried forward method of analysis. By as-treated analysis, excluding missing values, the proportions of patients with HIV RNA <400 copies/ml (<50 copies/ml) for REYATAZ + ritonavir were 84% (72%) and for lopinavir + ritonavir were 82% (72%). It is important to note that at time of the 96-week analysis, 48 % of patients overall remained on study.

REYATAZ + saquinavir was shown to be inferior to lopinavir + ritonavir.

Paediatric population

Assessment of the pharmacokinetics, safety, tolerability, and efficacy of REYATAZ is based on data from the open-label, multicenter clinical trial PACTG 1020A conducted in patients from 3 months to 21 years of age. Overall in this study, 182 paediatric patients (81 antiretroviral-naive and 101 antiretroviral-experienced) received once daily REYATAZ (capsule or powder formulation), with or without ritonavir, in combination with two NRTIs.

The clinical data derived from this study are inadequate to support the use of atazanavir (with or without ritonavir) in children below 6 years of age.

Efficacy data observed in the 41 paediatric patients aged 6 years to less than 18 years that received REYATAZ capsules with ritonavir are presented in Table 7. For treatment-naive paediatric patients, the mean baseline CD4 cell count was 344 cells/mm\(^3\) (range: 2 to 800 cells/ mm\(^3\)) and mean baseline
plasma HIV 1 RNA was 4.67 log_{10} copies/ml (range: 3.70 to 5.00 log_{10} copies/ml). For treatment-experienced paediatric patients, the mean baseline CD4 cell count was 522 cells/mm³ (range: 100 to 1157 cells/ mm³) and mean baseline plasma HIV 1 RNA was 4.09 log_{10} copies/ml (range: 3.28 to 5.00 log_{10} copies/ml).

Table 7: Efficacy Outcomes (paediatric patients 6 years to less than 18 years of age) at Week 48 (Study PACTG 1020A)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Treatment-Naive REYATAZ Capsules/ritonavir (300 mg/100 mg once daily) n=16</th>
<th>Treatment-Experienced REYATAZ Capsules/ritonavir (300 mg/100 mg once daily) n=25</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV RNA &lt;50 copies/ml, % a</td>
<td>81 (13/16)</td>
<td>24 (6/25)</td>
</tr>
<tr>
<td>All patients</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HIV RNA &lt;400 copies/ml, % a</td>
<td>88 (14/16)</td>
<td>32 (8/25)</td>
</tr>
<tr>
<td>All patients</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CD4 Mean Change from Baseline, cells/mm³</td>
<td>293 (n=14 b)</td>
<td>229 (n=14 b)</td>
</tr>
<tr>
<td>All patients</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HIV RNA &lt;50 copies/ml by select baseline PI substitutions, c % (responder/evaluable d)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0-2</td>
<td>NA</td>
<td>27 (4/15)</td>
</tr>
<tr>
<td>3</td>
<td>NA</td>
<td>-</td>
</tr>
<tr>
<td>≥4</td>
<td>NA</td>
<td>0 (0/3)</td>
</tr>
</tbody>
</table>

a Intent-to-treat analysis, with missing values considered as failures.

b Number of patients evaluable.
d Includes patients with baseline resistance data.

Data in the paediatric population are very limited. Available data do suggest that atazanavir in combination with ritonavir may not be effective in treatment experienced children even with very few (<3) PI mutations.

5.2 Pharmacokinetic properties

The pharmacokinetics of atazanavir were evaluated in healthy adult volunteers and in HIV-infected patients; significant differences were observed between the two groups. The pharmacokinetics of atazanavir exhibit a non-linear disposition. In healthy subjects, the AUC of atazanavir from the capsules and oral powder were similar.

Absorption: in HIV-infected patients (n=33, combined studies), multiple dosing of REYATAZ 300 mg once daily with ritonavir 100 mg once daily with food produced a geometric mean (CV%) for atazanavir, C_{max} of 4466 (42%) ng/ml, with time to C_{max} of approximately 2.5 hours. The geometric mean (CV%) for atazanavir C_{min} and AUC was 654 (76%) ng/ml and 44185 (51%) ng•h/ml, respectively.

Food effect: co-administration of REYATAZ and ritonavir with food optimises the bioavailability of atazanavir. Co-administration of a single 300-mg dose of REYATAZ and 100-mg dose of ritonavir with a light meal resulted in a 33% increase in the AUC and a 40% increase in both the C_{max} and the 24-hour concentration of atazanavir relative to the fasting state. Co-administration with a high-fat meal did not affect the AUC of atazanavir relative to fasting conditions and the C_{max} was within 11% of fasting values. The 24-hour concentration following a high fat meal was increased by approximately 33% due to delayed absorption; the median T_{max} increased from 2.0 to 5.0 hours. Administration of REYATAZ with ritonavir with either a light or a high-fat meal decreased the coefficient of variation...
of AUC and $C_{\text{max}}$ by approximately 25% compared to the fasting state. To enhance bioavailability and minimise variability, REYATAZ is to be taken with food.

**Distribution:** atazanavir was approximately 86% bound to human serum proteins over a concentration range of 100 to 10,000 ng/ml. Atazanavir binds to both alpha-1-acid glycoprotein (AAG) and albumin to a similar extent (89% and 86%, respectively, at 1,000 ng/ml). In a multiple-dose study in HIV-infected patients dosed with 400 mg of atazanavir once daily with a light meal for 12 weeks, atazanavir was detected in the cerebrospinal fluid and semen.

**Metabolism:** studies in humans and *in vitro* studies using human liver microsomes have demonstrated that atazanavir is principally metabolised by CYP3A4 isozyme to oxygenated metabolites. Metabolites are then excreted in the bile as either free or glucuronidated metabolites. Additional minor metabolic pathways consist of N-dealkylation and hydrolysis. Two minor metabolites of atazanavir in plasma have been characterised. Neither metabolite demonstrated *in vitro* antiviral activity.

**Elimination:** following a single 400-mg dose of $^{14}$C-atazanavir, 79% and 13% of the total radioactivity was recovered in the faeces and urine, respectively. Unchanged drug accounted for approximately 20% and 7% of the administered dose in the faeces and urine, respectively. Mean urinary excretion of unchanged drug was 7% following 2 weeks of dosing at 800 mg once daily. In HIV-infected adult patients ($n=33$, combined studies) the mean half-life within a dosing interval for atazanavir was 12 hours at steady state following a dose of 300 mg daily with ritonavir 100 mg once daily with a light meal.

**Special populations**

**Paediatric patients:** The pharmacokinetics of atazanavir in paediatric patients exhibit an increased absorption rate compared to adults. There is a slight trend toward a higher clearance in younger children when normalised for body weight. As a result, greater peak to trough ratios are observed. The geometric mean AUC values in paediatric patients at recommended doses are expected to be similar to those observed in adults, with higher geometric mean $C_{\text{max}}$ (13-17%) and lower geometric mean $C_{\text{min}}$ (up to 30%) values compared to those in adults. The variability of pharmacokinetic parameters in younger children is higher.

**Impaired renal function:** in healthy subjects, the renal elimination of unchanged atazanavir was approximately 7% of the administered dose. There are no pharmacokinetic data available for REYATAZ with ritonavir in patients with renal insufficiency. REYATAZ (without ritonavir) has been studied in adult patients with severe renal impairment ($n=20$), including those on haemodialysis, at multiple doses of 400 mg once daily. Although this study presented some limitations (i.e., unbound drug concentrations not studied), results suggested that the atazanavir pharmacokinetic parameters were decreased by 30% to 50% in patients undergoing haemodialysis compared to patients with normal renal function. The mechanism of this decrease is unknown. (See sections 4.2 and 4.4.)

**Impaired hepatic function:** atazanavir is metabolised and eliminated primarily by the liver. The effects of hepatic impairment on the pharmacokinetics of atazanavir after a 300 mg dose with ritonavir have not been studied. Concentrations of atazanavir with or without ritonavir are expected to be increased in patients with moderately or severely impaired hepatic function (see sections 4.2, 4.3, and 4.4).

**Age/Gender:** a study of the pharmacokinetics of atazanavir was performed in 59 healthy male and female subjects (29 young, 30 elderly). There were no clinically important pharmacokinetic differences based on age or gender.

**Race:** a population pharmacokinetic analysis of samples from Phase II clinical trials indicated no effect of race on the pharmacokinetics of atazanavir.
5.3 Preclinical safety data

In repeat-dose toxicity studies, conducted in mice, rats, and dogs, atazanavir-related findings were generally confined to the liver and included generally minimal to mild increases in serum bilirubin and liver enzymes, hepatocellular vacuolation and hypertrophy, and, in female mice only, hepatic single-cell necrosis. Systemic exposures of atazanavir in mice (males), rats, and dogs at doses associated with hepatic changes were at least equal to that observed in humans given 400 mg once daily. In female mice, atazanavir exposure at a dose that produced single-cell necrosis was 12 times the exposure in humans given 400 mg once daily. Serum cholesterol and glucose were minimally to mildly increased in rats but not in mice or dogs.

During in vitro studies, cloned human cardiac potassium channel (hERG), was inhibited by 15% at a concentration (30 μM) of atazanavir corresponding to 30-fold the free drug concentration at Cmax in humans. Similar concentrations of atazanavir increased by 13% the action potential duration (APD90) in rabbit Purkinje fibres study. Electrocardiographic changes (sinus bradycardia, prolongation of PR interval, prolongation of QT interval, and prolongation of QRS complex) were observed only in an initial 2-week oral toxicity study performed in dogs. Subsequent 9-month oral toxicity studies in dogs showed no drug-related electrocardiographic changes. The clinical relevance of these non-clinical data is unknown. Potential cardiac effects of this product in humans cannot be ruled out (see sections 4.4 and 4.8). The potential for PR prolongation should be considered in cases of overdose (see section 4.9).

In a fertility and early embryonic development study in rats, atazanavir altered oestrus cycling with no effects on mating or fertility. No teratogenic effects were observed in rats or rabbits at maternally toxic doses. In pregnant rabbits, gross lesions of the stomach and intestines were observed in dead or moribund does at maternal doses 2 and 4 times the highest dose administered in the definitive embryo-development study. In the pre- and postnatal development assessment in rats, atazanavir produced a transient reduction in body weight in the offspring at a maternally toxic dose. Systemic exposure to atazanavir at doses that resulted in maternal toxicity was at least equal to or slightly greater than that observed in humans given 400 mg once daily.

Atazanavir was negative in an Ames reverse-mutation assay but did induce chromosomal aberrations in vitro in both the absence and presence of metabolic activation. In in vivo studies in rats, atazanavir did not induce micronuclei in bone marrow, DNA damage in duodenum (comet assay), or unscheduled DNA repair in liver at plasma and tissue concentrations exceeding those that were clastogenic in vitro.

In long-term carcinogenicity studies of atazanavir in mice and rats, an increased incidence of benign hepatic adenomas was seen in female mice only. The increased incidence of benign hepatic adenomas in female mice was likely secondary to cytotoxic liver changes manifested by single-cell necrosis and is considered to have no relevance for humans at intended therapeutic exposures. There were no tumorigenic findings in male mice or in rats.

Atazanavir increased opacity of bovine corneas in an in vitro ocular irritation study, indicating it may be an ocular irritant upon direct contact with the eye.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Capsule contents:
- Crospovidone
- Lactose monohydrate
- Magnesium stearate

Capsule shells:
- Gelatine
- Red iron oxide
Black iron oxide
Yellow iron oxide
Indigocarmin (E132)
Titanium dioxide (E171)

White ink containing:
Shellac
Titanium dioxide (E171)
Ammonium hydroxide
Propylene glycol
Simethicone

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years

6.4 Special precautions for storage

Do not store above 25°C.

6.5 Nature and contents of container

Each carton contains one high-density polyethylene (HDPE) bottle or three high-density polyethylene (HDPE) bottles closed with child-resistant polypropylene closure. Each bottle contains 30 hard capsules.

Each carton contains 30 x 1 capsules; 5 blister cards of 6 x 1 capsules each in Alu/Alu perforated unit dose blisters.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

Any unused product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

BRISTOL-MYERS SQUIBB PHARMA EEIG
Uxbridge Business Park
Sanderson Road
Uxbridge UB8 1DH
United Kingdom

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/03/267/008-010
9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 02 March 2004
Date of latest renewal: 02 March 2009

10. DATE OF REVISION OF THE TEXT

{month year}

Detailed information on this medicinal product is available on the website of the European Medicines Agency (EMEA) http://www.emea.europa.eu
1. NAME OF THE MEDICINAL PRODUCT

REYATAZ 50 mg/1.5 g oral powder

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One measuring spoon of 1.5 g oral powder contains 50 mg atazanavir (as sulphate).

Excipients: 150 mg of aspartame and 1,218.15 mg of sucrose per measuring spoon of 1.5 g oral powder

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Oral powder.
Off-white to pale yellow powder.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

REYATAZ is indicated for the treatment of HIV-1 infected adults in combination with other antiretroviral medicinal products.

In antiretroviral treatment experienced patients, the demonstration of efficacy is based on a study comparing REYATAZ 300 mg once daily in combination with ritonavir 100 mg once daily with lopinavir/ritonavir, each regimen in combination with tenofovir (see sections 4.8 and 5.1). Based on available virological and clinical data, no benefit is expected in patients with strains resistant to multiple protease inhibitors (≥ 4 PI mutations). The choice of REYATAZ in treatment experienced patients should be based on individual viral resistance testing and the patient’s treatment history (see section 5.1).

4.2 Posology and method of administration

Therapy should be initiated by a physician experienced in the management of HIV infection.

Adults: REYATAZ oral powder is available for patients who are unable to swallow capsules. The recommended dose of oral powder is 300 mg (6 level measuring spoons) once daily taken with ritonavir 100 mg once daily with food. Ritonavir is used as a booster of atazanavir pharmacokinetics (see sections 4.5 and 5.1). One measuring spoon of 1.5 g of oral powder contains 50 mg atazanavir.

If REYATAZ with ritonavir is co-administered with didanosine, it is recommended that didanosine be taken 2 hours after REYATAZ with ritonavir. REYATAZ with ritonavir must be taken with food (see section 4.5).

Infants, toddlers, children, and adolescents: the safety and efficacy of REYATAZ in paediatric patients has not been established (see section 5.2).

Patients with renal impairment: no dosage adjustment is needed. REYATAZ with ritonavir is not recommended in patients undergoing haemodialysis (see sections 4.4 and 5.2).
Patients with hepatic impairment: REYATAZ with ritonavir has not been studied in patients with hepatic impairment. REYATAZ with ritonavir should be used with caution in patients with mild hepatic impairment. REYATAZ should not be used in patients with moderate to severe hepatic impairment (see sections 4.3, 4.4 and 5.2).

The oral powder should be taken with food. The prescriber should advise the patient to scoop an overfilled spoon of loose powder from the bottle using the measuring spoon provided. The patient should then gently level the powder in the spoon by scraping the extra powder back into the bottle using a flat edge of a knife or spatula. Patients should be advised not to pack the powder into the spoon or to attempt to level the powder by shaking or tapping the spoon.

The oral powder may be mixed with water, milk, applesauce or yoghurt. Once the oral powder is mixed with these, it should be used within 6 hours.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients (see section 6.1).

Patients with moderate to severe hepatic insufficiency (see sections 4.2 and 4.4).

Combination of rifampicin and REYATAZ with concomitant low-dose ritonavir is contraindicated (see section 4.5).

REYATAZ with ritonavir must not be used in combination with medicinal products that are substrates of the CYP3A4 isoform of cytochrome P450 and have narrow therapeutic windows (e.g., astemizole, terfenadine, cisapride, pimozide, quinidine, bepridil, triazolam, midazolam administered orally (for caution on parenterally administered midazolam, see section 4.5), and ergot alkaloids, particularly, ergotamine, dihydroergotamine, ergonovine, methylergonovine) (see section 4.5).

REYATAZ must not be used in combination with products containing St. John’s wort (Hypericum perforatum) (see section 4.5).

4.4 Special warnings and precautions for use

Patients should be advised that current antiretroviral therapy has not been proven to prevent the risk of transmission of HIV to others through blood or sexual contact. Appropriate precautions should continue to be employed.

Co-administration of REYATAZ with ritonavir at doses greater than 100 mg once daily has not been clinically evaluated. The use of higher ritonavir doses may alter the safety profile of atazanavir (cardiac effects, hyperbilirubinaemia) and therefore is not recommended. Only when atazanavir with ritonavir is co-administered with efavirenz, a dose increase of ritonavir to 200 mg once daily could be considered. In this instance, close clinical monitoring is warranted (see Interaction with other Medicinal Products below).

Patients with coexisting conditions

Atazanavir is primarily hepatically metabolised and increased plasma concentrations were observed in patients with hepatic impairment (see sections 4.2 and 4.3). The safety and efficacy of REYATAZ has not been established in patients with significant underlying liver disorders. Patients with chronic hepatitis B or C and treated with combination antiretroviral therapy are at an increased risk for severe and potentially fatal hepatic adverse reactions. In case of concomitant antiviral therapy for hepatitis B or C, please refer also to the relevant Summary of Product Characteristics for these medicinal products (see section 4.8).

Patients with pre-existing liver dysfunction, including chronic active hepatitis, have an increased frequency of liver function abnormalities during combination antiretroviral therapy and should be
monitored according to standard practice. If there is evidence of worsening liver disease in such patients, interruption or discontinuation of treatment must be considered.

No dosage adjustment is needed in patients with renal impairment. However, REYATAZ with ritonavir is not recommended in patients undergoing haemodialysis (see sections 4.2 and 5.2).

Dose related asymptomatic prolongations in PR interval with REYATAZ have been observed in clinical studies. Caution should be used with medicinal products known to induce PR prolongations. In patients with pre-existing conduction problems (second degree or higher atroventricular or complex bundle-branch block), REYATAZ should be used with caution and only if the benefits exceed the risk (see section 5.1). Particular caution should be used when prescribing REYATAZ in association with medicinal products which have the potential to increase the QT interval and/or in patients with pre-existing risk factors (bradycardia, long congenital QT, electrolyte imbalances (see sections 4.8 and 5.3).

There have been reports of increased bleeding, including spontaneous skin haematomas and haemarthroses, in type A and B haemophiliac patients treated with protease inhibitors. In some patients additional factor VIII was given. In more than half of the reported cases, treatment with protease inhibitors was continued or reintroduced if treatment had been discontinued. A causal relationship has been suggested, although the mechanism of action has not been elucidated. Haemophiliac patients should therefore be made aware of the possibility of increased bleeding.

**Diabetics**
REYATAZ oral powder contains 7.3 g sucrose per 300 mg daily dose. This should be taken into account in patients with diabetes mellitus. Patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltase insufficiency should not take this medicine.

**Fat redistribution and metabolic disorders**
Combination antiretroviral therapy has been associated with the redistribution of body fat (lipodystrophy) in HIV patients. The long-term consequences of these reactions are currently unknown. Knowledge about the mechanism is incomplete. A connection between visceral lipomatosis and protease inhibitors and lipoatrophy and nucleoside reverse transcriptase inhibitors has been hypothesised. A higher risk of lipodystrophy has been associated with individual factors such as older age, and with drug related factors such as longer duration of antiretroviral treatment and associated metabolic disturbances. Clinical examination should include evaluation for physical signs of fat redistribution.

Combination antiretroviral therapy (CART), including REYATAZ (with or without ritonavir)-based CART, is associated with dyslipidaemia. Consideration should be given to the measurement of fasting serum lipids and blood glucose. Lipid disorders should be managed as clinically appropriate (see section 4.8).

In clinical studies, REYATAZ (with or without ritonavir) has been shown to induce dyslipidaemia to a lesser extent than comparators. The clinical impact of such findings has not been demonstrated in the absence of specific studies on cardiovascular risk. The selection of antiretroviral therapy must be guided principally by antiviral efficacy. Consultation with standard guidelines for management of dyslipidaemia is recommended.

**Hyperglycaemia**
New onset diabetes mellitus, hyperglycaemia, and exacerbation of existing diabetes mellitus have been reported in patients receiving protease inhibitors. In some of these, the hyperglycaemia was severe and in some cases also associated with ketoacidosis. Many patients had confounding medical conditions, some of which required therapy with medicinal products that have been associated with development of diabetes or hyperglycaemia.
**Hyperbilirubinaemia**

Reversible elevations in indirect (unconjugated) bilirubin related to inhibition of UDP-glucuronosyl transferase (UGT) have occurred in patients receiving REYATAZ (see section 4.8). Hepatic transaminase elevations that occur with elevated bilirubin in patients receiving REYATAZ should be evaluated for alternative etiologies. Alternative antiretroviral therapy to REYATAZ may be considered if jaundice or scleral icterus is unacceptable to a patient. Dose reduction of atazanavir is not recommended because it may result in a loss of therapeutic effect and development of resistance.

Indinavir is also associated with indirect (unconjugated) hyperbilirubinaemia due to inhibition of UGT. Combinations of REYATAZ and indinavir have not been studied and co-administration of these medicinal products is not recommended (see section 4.5).

**Nephrolithiasis**

Nephrolithiasis has been reported in patients receiving REYATAZ (see section 4.8). If signs or symptoms of nephrolithiasis occur, temporary interruption or discontinuation of treatment may be considered.

**Immune reactivation syndrome**

In HIV-infected patients with severe immune deficiency at the time of institution of combination antiretroviral therapy (CART), an inflammatory reaction to asymptomatic or residual opportunistic pathogens may arise and cause serious clinical conditions, or aggravation of symptoms. Typically, such reactions have been observed within the first few weeks or months of initiation of CART. Relevant examples are cytomegalovirus retinitis, generalised and/or focal mycobacterial infections, and *Pneumocystis carinii* pneumonia. Any inflammatory symptoms should be evaluated and treatment instituted when necessary.

**Osteonecrosis**

Although the etiology is considered to be multifactorial (including corticosteroid use, alcohol consumption, severe immunosuppression, higher body mass index), cases of osteonecrosis have been reported particularly in patients with advanced HIV-disease and/or long-term exposure to combination antiretroviral therapy (CART). Patients should be advised to seek medical advice if they experience joint aches and pain, joint stiffness or difficulty in movement.

**Interactions with other medicinal products**

Co-administration of REYATAZ with simvastatin or lovastatin is not recommended (see section 4.5).

Co-administration of REYATAZ with nevirapine or efavirenz is not recommended (see section 4.5). If the co-administration of REYATAZ with an NNRTI is required, an increase in the dose of both REYATAZ and ritonavir to 400 mg and 200 mg, respectively, in combination with efavirenz could be considered with close clinical monitoring.

Atazanavir is metabolised principally by CYP3A4. Co-administration of REYATAZ with ritonavir and medicinal products that induce CYP3A4 is not recommended (see sections 4.3 and 4.5).

Co-administration of voriconazole and REYATAZ with ritonavir is not recommended unless an assessment of the benefit/risk justifies the use of voriconazole (see section 4.5).

Concomitant use of REYATAZ/ritonavir and fluticasone or other glucocorticoids that are metabolized by CYP3A4 is not recommended unless the potential benefit of treatment outweighs the risk of systemic corticosteroid effects, including Cushing's syndrome and adrenal suppression (see section 4.5).

The absorption of atazanavir may be reduced in situations where gastric pH is increased irrespective of cause.

Co-administration of REYATAZ with proton pump inhibitors is not recommended (see section 4.5). If the combination of REYATAZ with a proton pump inhibitor is judged unavoidable, close clinical
monitoring is recommended in combination with an increase in the dose of REYATAZ to 400 mg with 100 mg of ritonavir; doses of proton pump inhibitors comparable to omeprazole 20 mg should not be exceeded.

Co-administration of REYATAZ/ritonavir in combination with tenofovir and an H₂-receptor antagonist should be avoided (see section 4.5).

Phenylketonuria
REYATAZ oral powder contains aspartame as a sweetening agent. Aspartame provides a source of phenylalanine and, therefore, may not be suitable for persons with phenylketonuria.

4.5 Interaction with other medicinal products and other forms of interaction

When REYATAZ and ritonavir are co-administered, the metabolic drug interaction profile for ritonavir may predominate because ritonavir is a more potent CYP3A4 inhibitor than atazanavir. The Summary of Product Characteristics for ritonavir must be consulted before initiation of therapy with REYATAZ and ritonavir.

Atazanavir is metabolised in the liver through CYP3A4. It inhibits CYP3A4. Therefore, REYATAZ with ritonavir is contraindicated with medicinal products that are substrates of CYP3A4 and have a narrow therapeutic index: astemizole, terfenadine, cisapride, pimozide, quinidine, bepridil, triazolam, orally administered midazolam, and ergot alkaloids, particularly ergotamine and dihydroergotamine (see section 4.3).

Other interactions

Interactions between atazanavir/ritonavir and protease inhibitors, antiretroviral agents other than protease inhibitors, and other non-antiretroviral medicinal products are listed in the tables below (increase is indicated as “↑”, decrease as “↓”, no change as “↔”, twice daily as “BID” and once daily as “QD”). If available, 90% confidence intervals (CI) are shown in parentheses. The studies presented in Table 1 were conducted in healthy subjects unless otherwise noted. Of importance, many studies were conducted with unboosted atazanavir, which is not the approved regimen of atazanavir.

**Table 1: Interactions between REYATAZ and other medicinal products**

<table>
<thead>
<tr>
<th>Co-administered medicinal products (dose in mg)</th>
<th>Medicinal product assessed</th>
<th>AUC (90% CI)</th>
<th>C&lt;sub&gt;max&lt;/sub&gt; (90% CI)</th>
<th>C&lt;sub&gt;min&lt;/sub&gt; (90% CI)</th>
<th>Recommendations concerning co-administration</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ANTI-INFECTIVES</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antiretrovirials</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Protease inhibitors:</strong> The co-administration of REYATAZ/ritonavir and other protease inhibitors has not been studied but would be expected to increase exposure to other protease inhibitors. Therefore, such co-administration is not recommended.</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ritonavir 100 mg QD (atazanavir 300 mg QD) studies conducted in HIV-infected patients</td>
<td>atazanavir</td>
<td>↑3.50* (2.44, 5.03)</td>
<td>↑2.20* (1.56, 3.11)</td>
<td>↑8.13* (4.59, 14.39)</td>
<td>Ritonavir 100 mg once daily is used as a booster of atazanavir pharmacokinetics.</td>
</tr>
<tr>
<td>* In a combined analysis, atazanavir 300 mg and ritonavir 100 mg (n=33) was compared to atazanavir 400 mg without ritonavir (n=28). The mechanism of interaction between atazanavir and ritonavir is CYP3A4 inhibition.</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Indinavir</td>
<td>Indinavir is associated with indirect unconjugated hyperbilirubinaemia due to inhibition of UGT.</td>
<td>Co-administration of REYATAZ/ritonavir and indinavir is not recommended (see section 4.4).</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs)</strong></td>
<td>Lamivudine 150 mg BID + zidovudine 300 mg BID (atazanavir 400 mg QD)</td>
<td>No significant effect on lamivudine and zidovudine concentrations was observed.</td>
<td>Based on these data and because ritonavir is not expected to have a significant impact on the pharmacokinetics of NRTIs, the...</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### Co-administered medicinal products (dose in mg)

<table>
<thead>
<tr>
<th>Medicinal product assessed</th>
<th>AUC (90% CI)</th>
<th>C&lt;sub&gt;max&lt;/sub&gt; (90% CI)</th>
<th>C&lt;sub&gt;min&lt;/sub&gt; (90% CI)</th>
<th>Recommendations concerning co-administration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abacavir</td>
<td></td>
<td></td>
<td></td>
<td>The co-administration of REYATAZ/ritonavir with abacavir is not expected to significantly alter the exposure of abacavir.</td>
</tr>
<tr>
<td>Didanosine (buffered tablets) 200 mg/stavudine 40 mg, both single dose (atazanavir 400 mg single dose)</td>
<td></td>
<td></td>
<td></td>
<td>Didanosine should be taken at the fasted state 2 hours after REYATAZ/ritonavir taken with food. The co-administration of REYATAZ/ritonavir with stavudine is not expected to significantly alter the exposure of stavudine. Atazanavir concentrations were greatly decreased when co-administered with didanosine (buffered tablets) and stavudine. The mechanism of interaction is a reduced solubility of atazanavir with increasing pH related to the presence of anti-acid agent in didanosine buffered tablets. No significant effect on didanosine and stavudine concentrations was observed.</td>
</tr>
<tr>
<td>Didanosine (enteric coated capsules) 400 mg single dose (atazanavir 300 mg QD with ritonavir 100 mg QD)</td>
<td>Didanosine (with food)</td>
<td>(0.66, 0.69)</td>
<td>(0.52, 0.74)</td>
<td>(0.92, 1.69)</td>
</tr>
<tr>
<td>Tenofovir disoproxil fumarate 300 mg QD (atazanavir 300 mg QD with ritonavir 100 mg QD) studies conducted in HIV-infected patients</td>
<td>Tenofovir disoproxil fumarate</td>
<td>(0.78, 1.37)</td>
<td>(0.70, 1.51)</td>
<td>(0.84, 1.50)</td>
</tr>
<tr>
<td>Tenofovir disoproxil fumarate 300 mg QD (atazanavir 300 mg QD with ritonavir 100 mg QD)</td>
<td>Tenofovir disoproxil fumarate</td>
<td>(1.06, 1.12)</td>
<td>(0.95, 1.26)</td>
<td>(0.84, 1.49)</td>
</tr>
</tbody>
</table>

### Non-nucleoside reverse transcriptase inhibitors (NNRTIs)

<table>
<thead>
<tr>
<th>Efavirenz 600 mg QD (atazanavir 400 mg QD with ritonavir 100 mg QD)</th>
<th>Efavirenz 600 mg QD (atazanavir 400 mg QD with ritonavir 200 mg QD)</th>
<th>All administered with food</th>
<th>Efavirenz (pm):</th>
<th>All administered with food</th>
<th>Efavirenz (pm):</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atazanavir (pm): all administered with food</td>
<td>Atazanavir (pm): all administered with food</td>
<td>↔1.00*</td>
<td>↔1.06**</td>
<td>↔1.09***</td>
<td>↔1.12**</td>
</tr>
<tr>
<td>(0.91, 1.10)</td>
<td>(0.90, 1.26)</td>
<td>(0.95, 1.26)</td>
<td>(0.84, 1.49)</td>
<td>(0.84, 1.49)</td>
<td>(0.84, 1.49)</td>
</tr>
</tbody>
</table>

* When compared to REYATAZ 300 mg/ritonavir 100 mg once daily in the evening without efavirenz. This decrease in atazanavir C<sub>min</sub> might negatively impact the efficacy of atazanavir. The mechanism of efavirenz/atazanavir interaction is CYP3A4 induction.

** based on historical comparison.
<table>
<thead>
<tr>
<th>Co-administered medicinal products (dose in mg)</th>
<th>Medicinal product assessed</th>
<th>AUC (90% CI)</th>
<th>C\text{max} (90% CI)</th>
<th>C\text{min} (90% CI)</th>
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</tr>
</thead>
<tbody>
<tr>
<td>Nevirapine 200 mg BID (atazanavir 400 mg QD with ritonavir 100 mg QD) study conducted in HIV infected patients</td>
<td>nevirapine</td>
<td>↑1.26 (1.17, 1.36)</td>
<td>↑1.21 (1.11, 1.32)</td>
<td>↑1.35 (1.25, 1.47)</td>
<td>Co-administration of nevirapine with REYATAZ/ritonavir is not recommended (see section 4.4)</td>
</tr>
<tr>
<td></td>
<td>atazanavir</td>
<td>↓0.81* (0.65, 1.02)</td>
<td>↔1.02* (0.85, 1.24)</td>
<td>↓0.41* (0.27, 0.60)</td>
<td></td>
</tr>
</tbody>
</table>
* When compared to REYATAZ 300 mg and ritonavir 100 mg without nevirapine. This decrease in atazanavir C\text{min} might negatively impact the efficacy of atazanavir. The mechanism of nevirapine/atazanavir interaction is CYP3A4 induction.

### Antibiotics

<table>
<thead>
<tr>
<th>Antibiotics</th>
<th>Medicinal product assessed</th>
<th>AUC (90% CI)</th>
<th>C\text{max} (90% CI)</th>
<th>C\text{min} (90% CI)</th>
<th>Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clarithromycin 500 mg BID (atazanavir 400 mg QD)</td>
<td>clarithromycin</td>
<td>↑1.94 (1.75, 2.16)</td>
<td>↑1.50 (1.32, 1.71)</td>
<td>↑2.60 (2.35, 2.88)</td>
<td>No recommendation regarding dose reduction can be made; therefore, caution should be exercised if REYATAZ/ritonavir is co-administered with clarithromycin.</td>
</tr>
<tr>
<td></td>
<td>14-OH clarithromycin</td>
<td>↓0.30 (0.26, 0.34)</td>
<td>↓0.28 (0.24, 0.33)</td>
<td>↓0.38 (0.34, 0.42)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>atazanavir</td>
<td>↑1.16 (1.16, 1.43)</td>
<td>↑1.06 (0.93, 1.20)</td>
<td>↑1.91 (1.66, 2.21)</td>
<td></td>
</tr>
</tbody>
</table>
A dose reduction of clarithromycin may result in subtherapeutic concentrations of 14-OH clarithromycin. The mechanism of the clarithromycin/atazanavir interaction is CYP3A4 inhibition.

### Antifungals

<table>
<thead>
<tr>
<th>Antifungals</th>
<th>Medicinal product assessed</th>
<th>AUC (90% CI)</th>
<th>C\text{max} (90% CI)</th>
<th>C\text{min} (90% CI)</th>
<th>Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ketoconazole 200 mg QD (atazanavir 400 mg QD)</td>
<td>No significant effect on atazanavir concentrations was observed.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Itraconazole</td>
<td>Itraconazole, like ketoconazole, is a potent inhibitor as well as a substrate of CYP3A4. Based on data obtained with other boosted PIs and ketoconazole, where ketoconazole AUC showed a 3-fold increase, REYATAZ/ritonavir is expected to increase ketoconazole or itraconazole concentrations.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Voriconazole</td>
<td>Co-administration of REYATAZ/ritonavir and voriconazole has not been studied. The effect of co-administration of oral voriconazole and low dose (100 mg) oral ritonavir was investigated in healthy volunteers. Low doses of ritonavir (100 mg BID) decreased the C\text{max} and AUC of voriconazole (90% CI) by an average of 24% (19% to 36%) and 39% (22% to 52%), respectively. Administration of voriconazole resulted in a minor decrease in steady state C\text{max} and AUC of ritonavir (90% CI) with an average of 24% (16% to 39%) and 14% (26% to 1%), respectively.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fluconazole 200 mg QD (atazanavir 300 mg and ritonavir 100 mg QD)</td>
<td>Atazanavir and fluconazole concentrations were not significantly modified when REYATAZ/ritonavir was co-administered with fluconazole.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Antimycobacterial

<table>
<thead>
<tr>
<th>Antimycobacterial</th>
<th>Medicinal product assessed</th>
<th>AUC (90% CI)</th>
<th>C\text{max} (90% CI)</th>
<th>C\text{min} (90% CI)</th>
<th>Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rifabutin 150 mg twice weekly (atazanavir 300 mg and ritonavir 100 mg QD)</td>
<td>rifabin</td>
<td>↑1.48 ** (1.19, 1.84)</td>
<td>↑2.49 ** (2.03, 3.06)</td>
<td>↑1.40 ** (1.05, 1.87)</td>
<td>When given with REYATAZ/ritonavir, the recommended dose of rifabutin is 150 mg 3 times per week on set days (for example Monday-Wednesday-Friday). Increased monitoring for rifabutin-associated adverse reactions including neutropenia is recommended.</td>
</tr>
</tbody>
</table>
** When compared to rifabutin 150 mg QD alone. Total rifabutin and 25-O-desacetyl-rifabutin AUC: ↑2.19 (1.78, 2.69). In previous studies, the pharmacokinetics of atazanavir was not altered by rifabutin. |
### Acute Exacerbations of HIV-Related Uveitis

When acute exacerbations of uveitis occur in patients on REYATAZ/ritonavir, recommendations concerning co-administration and uveitis is warranted due to an expected increase in exposure to rifabutin. Further dosage reduction of rifabutin to 150 mg twice weekly on set days is recommended for patients in whom the 150 mg dose 3 times per week is not tolerated. It should be kept in mind that the twice weekly dosage of 150 mg may not provide an optimal exposure to rifabutin thus leading to a risk of rifamycin resistance and a treatment failure. No dose adjustment is needed for REYATAZ/ritonavir.

### Rifampicin

Rifampicin is a strong CYP3A4 inducer and has been shown to cause a 72% decrease in atazanavir AUC which can result in virological failure and resistance development. During attempts to overcome the decreased exposure by increasing the dose of REYATAZ or other protease inhibitors with ritonavir, a high frequency of liver reactions was seen. The combination of rifampicin and REYATAZ with concomitant low-dose ritonavir is contraindicated (see section 4.3).

### Acid Reducing Agents

#### H₂-Receptor antagonists

**Without Tenofovir**

In HIV-infected patients with atazanavir/ritonavir at the recommended dose 300/100 mg QD

<table>
<thead>
<tr>
<th>Medicinal product assessed</th>
<th>AUC (90% CI)</th>
<th>Cmax (90% CI)</th>
<th>Cmin (90% CI)</th>
<th>Recommendations concerning co-administration</th>
</tr>
</thead>
<tbody>
<tr>
<td>famotidine 20 mg BID</td>
<td>0.82</td>
<td>0.80</td>
<td>0.89</td>
<td>The combination of rifampicin and REYATAZ with concomitant low-dose ritonavir is contraindicated (see section 4.3).</td>
</tr>
<tr>
<td>famotidine 40 mg BID</td>
<td>0.77</td>
<td>0.77</td>
<td>0.77</td>
<td></td>
</tr>
</tbody>
</table>

In Healthy volunteers with atazanavir/ritonavir at an increased dose of 400/100 mg QD

<table>
<thead>
<tr>
<th>Medicinal product assessed</th>
<th>AUC (90% CI)</th>
<th>Cmax (90% CI)</th>
<th>Cmin (90% CI)</th>
<th>Recommendations concerning co-administration</th>
</tr>
</thead>
<tbody>
<tr>
<td>famotidine 40 mg BID</td>
<td>0.86</td>
<td>0.86</td>
<td>0.86</td>
<td></td>
</tr>
</tbody>
</table>

**With Tenofovir 300 mg QD**

In HIV-infected patients with atazanavir/ritonavir at the recommended dose of 300/100 mg QD

<table>
<thead>
<tr>
<th>Medicinal product assessed</th>
<th>AUC (90% CI)</th>
<th>Cmax (90% CI)</th>
<th>Cmin (90% CI)</th>
<th>Recommendations concerning co-administration</th>
</tr>
</thead>
<tbody>
<tr>
<td>famotidine 20 mg BID</td>
<td>0.79*</td>
<td>0.79*</td>
<td>0.81*</td>
<td></td>
</tr>
<tr>
<td>famotidine 40 mg BID</td>
<td>0.76*</td>
<td>0.77*</td>
<td>0.75*</td>
<td></td>
</tr>
</tbody>
</table>

* When compared to atazanavir 300 mg QD with ritonavir 100 mg QD and tenofovir disoproxil fumarate 300 mg all as a single dose with food. When compared to atazanavir 300 mg with ritonavir 100 mg without tenofovir, atazanavir concentrations are expected to be additionally decreased by about 20%.

For patients who are taking tenofovir, Co-administration of REYATAZ/ritonavir in combination with tenofovir and an H₂-receptor antagonist should be avoided (see section 4.4). If the combination of REYATAZ/ritonavir

For patients not taking tenofovir, if REYATAZ 300 mg/ritonavir 100 mg and H₂-receptor antagonists are co-administered, a dose equivalent to famotidine 20 mg BID should not be exceeded. If a higher dose of an H₂-receptor antagonist is required (eg, famotidine 40 mg BID or equivalent) an increase of the REYATAZ/ritonavir dose from 300/100 mg to 400/100 mg can be considered.
### Co-administered medicinal products (dose in mg)

<table>
<thead>
<tr>
<th>Medicinal product assessed</th>
<th>AUC (90% CI)</th>
<th>C&lt;sub&gt;max&lt;/sub&gt; (90% CI)</th>
<th>C&lt;sub&gt;min&lt;/sub&gt; (90% CI)</th>
<th>Recommendations concerning co-administration</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>with both tenofovir and H&lt;sub&gt;2&lt;/sub&gt;-receptor antagonist is judged unavoidable, close clinical monitoring is recommended. A dose increase of REYATAZ to 400 mg with 100 mg of ritonavir may be considered but is still under evaluation.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Co-administration of REYATAZ/ritonavir with proton pump inhibitors is not recommended. If the combination of REYATAZ/ritonavir with a proton pump inhibitor is judged unavoidable, close clinical monitoring is recommended in combination with an increase in the dose of REYATAZ to 400 mg with 100 mg of ritonavir; doses of proton pump inhibitors comparable to omeprazole 20 mg should not be exceeded (see section 4.4).</td>
</tr>
</tbody>
</table>

### Proton pump inhibitors

<table>
<thead>
<tr>
<th>Omeprazole 40 mg QD (atazanavir 400 mg QD with ritonavir 100 mg QD)</th>
<th>atazanavir (am): 2 hr after omeprazole</th>
<th>↓0.39 (0.35, 0.45)</th>
<th>↓0.44 (0.38, 0.51)</th>
<th>↓0.35 (0.29, 0.41)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Omeprazole 20 mg QD (atazanavir 400 mg QD with ritonavir 100 mg QD)</td>
<td>atazanavir (am): 1 hr after omeprazole</td>
<td>↓0.70* (0.57, 0.86)</td>
<td>↓0.69* (0.58, 0.83)</td>
<td>↓0.69* (0.54, 0.88)</td>
</tr>
<tr>
<td>* When compared to atazanavir 300 mg QD with ritonavir 100 mg QD</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

The decrease in AUC, C<sub>max</sub>, and C<sub>min</sub> was not mitigated when an increased dose of REYATAZ/ritonavir (400/100 mg once daily) was temporally separated from omeprazole by 12 hours. Although not studied, similar results are expected with other proton pump inhibitors. This decrease in atazanavir exposure might negatively impact the efficacy of atazanavir. The mechanism of interaction is decreased solubility of atazanavir as intra-gastric pH increases with H<sub>2</sub> blockers.

### Antacids

<table>
<thead>
<tr>
<th>Antacids and medicinal products containing buffers</th>
<th>Reduced plasma concentrations of atazanavir may be the consequence of increased gastric pH if antacids, including buffered medicinal products, are administered with REYATAZ/ritonavir.</th>
</tr>
</thead>
</table>

### ANTICOAGULANTS

<table>
<thead>
<tr>
<th>Warfarin</th>
<th>Co-administration with REYATAZ/ritonavir has the potential to produce a decrease or, less often, an increase in INR (International Normalised Ratio).</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>It is recommended that the INR be monitored carefully during treatment with REYATAZ/ritonavir, especially when commencing therapy.</td>
</tr>
</tbody>
</table>

### ANTINEOPLASTICS AND IMMUNOSUPPRESSANTS

<table>
<thead>
<tr>
<th>Antineoplastics</th>
<th>Atazanavir inhibits UGT and may interfere with the metabolism of irinotecan, resulting in increased irinotecan toxicities.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Irinotecan</td>
<td>If REYATAZ/ritonavir is co-administered with irinotecan, patients should be closely monitored for adverse events related to irinotecan.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Immunosuppressants</th>
<th>Concentrations of these immunosuppressants may be increased when co-administered with REYATAZ/ritonavir due to CYP3A4 inhibition.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cyclosporin</td>
<td>More frequent therapeutic concentration monitoring of these medicinal products is recommended until</td>
</tr>
<tr>
<td>Tacrolimus</td>
<td></td>
</tr>
<tr>
<td>Sirolimus</td>
<td></td>
</tr>
</tbody>
</table>
### CARDIOVASCULAR AGENTS

#### Antiarrhythmics

<table>
<thead>
<tr>
<th>Medicinal product assessed</th>
<th>Co-administered medicinal products (dose in mg)</th>
<th>AUC (90% CI)</th>
<th>C&lt;sub&gt;max&lt;/sub&gt; (90% CI)</th>
<th>C&lt;sub&gt;min&lt;/sub&gt; (90% CI)</th>
<th>Recommendations concerning co-administration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amiodarone, Systemic lidocaine, Quinidine</td>
<td>Concentrations of these antiarrhythmics may be increased when co-administered with REYATAZ/ritonavir. The mechanism of amiodarone or systemic lidocaine/atazanavir interaction is CYP3A inhibition. Quinidine has a narrow therapeutic window and is contraindicated due to potential inhibition of CYP3A by REYATAZ/ritonavir.</td>
<td></td>
<td></td>
<td></td>
<td>Caution is warranted and therapeutic concentration monitoring is recommended when available. The concomitant use of quinidine is contraindicated (see section 4.3).</td>
</tr>
</tbody>
</table>

#### Calcium channel blockers

<table>
<thead>
<tr>
<th>Medicinal product assessed</th>
<th>Co-administered medicinal products (dose in mg)</th>
<th>AUC (90% CI)</th>
<th>C&lt;sub&gt;max&lt;/sub&gt; (90% CI)</th>
<th>C&lt;sub&gt;min&lt;/sub&gt; (90% CI)</th>
<th>Recommendations concerning co-administration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bepridil</td>
<td>REYATAZ/ritonavir should not be used in combination with medicinal products that are substrates of CYP3A4 and have a narrow therapeutic index.</td>
<td></td>
<td></td>
<td></td>
<td>Co-administration with bepridil is contraindicated (see section 4.3)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Medicinal product assessed</th>
<th>Co-administered medicinal products (dose in mg)</th>
<th>AUC (90% CI)</th>
<th>C&lt;sub&gt;max&lt;/sub&gt; (90% CI)</th>
<th>C&lt;sub&gt;min&lt;/sub&gt; (90% CI)</th>
<th>Recommendations concerning co-administration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diltiazem 180 mg QD (atazanavir 400 mg QD)</td>
<td>diltiazem</td>
<td>↑2.5 (2.09, 2.41)</td>
<td>↑1.98 (1.78, 2.19)</td>
<td>↑2.42 (2.14, 2.73)</td>
<td>An initial dose reduction of diltiazem by 50% is recommended, with subsequent titration as needed and ECG monitoring.</td>
</tr>
<tr>
<td></td>
<td>desacetyl-diltiazem</td>
<td>↑2.65 (2.45, 2.87)</td>
<td>↑2.72 (2.44, 3.03)</td>
<td>↑2.21 (2.02, 2.42)</td>
<td></td>
</tr>
</tbody>
</table>

No significant effect on atazanavir concentrations was observed. There was an increase in the maximum PR interval compared to atazanavir alone. Co-administration of diltiazem and REYATAZ/ritonavir has not been studied. The mechanism of diltiazem/atazanavir interaction is CYP3A4 inhibition.

<table>
<thead>
<tr>
<th>Medicinal product assessed</th>
<th>Co-administered medicinal products (dose in mg)</th>
<th>AUC (90% CI)</th>
<th>C&lt;sub&gt;max&lt;/sub&gt; (90% CI)</th>
<th>C&lt;sub&gt;min&lt;/sub&gt; (90% CI)</th>
<th>Recommendations concerning co-administration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Verapamil</td>
<td>Serum concentrations of verapamil may be increased by REYATAZ/ritonavir due to CYP3A4 inhibition.</td>
<td></td>
<td></td>
<td></td>
<td>Caution should be exercised when verapamil is co-administered with REYATAZ/ritonavir.</td>
</tr>
</tbody>
</table>

#### CORTICOSTEROIDS

<table>
<thead>
<tr>
<th>Medicinal product assessed</th>
<th>Co-administered medicinal products (dose in mg)</th>
<th>AUC (90% CI)</th>
<th>C&lt;sub&gt;max&lt;/sub&gt; (90% CI)</th>
<th>C&lt;sub&gt;min&lt;/sub&gt; (90% CI)</th>
<th>Recommendations concerning co-administration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fluticasone propionate intranasal 50 µg 4 times daily for 7 days (ritonavir 100 mg capsules BID)</td>
<td>The fluticasone propionate plasma levels increased significantly, whereas the intrinsic cortisol levels decreased by approximately 86% (90% confidence interval 82-89%). Greater effects may be expected when fluticasone propionate is inhaled. Systemic corticosteroid effects including Cushing’s syndrome and adrenal suppression have been reported in patients receiving ritonavir and inhaled or intranasally administered fluticasone propionate; this could also occur with other corticosteroids metabolized via the P450 3A pathway, e.g., budesonide. The effects of high fluticasone systemic exposure on ritonavir plasma levels are yet unknown. The mechanism of interaction is CYP3A4 inhibition.</td>
<td></td>
<td></td>
<td></td>
<td>Co-administration of REYATAZ/ritonavir and these glucocorticoids is not recommended unless the potential benefit of treatment outweighs the risk of systemic corticosteroid effects (see section 4.4). A dose reduction of the glucocorticoid should be considered with close monitoring of local and systemic effects or a switch to a glucocorticoid, which is not a substrate for CYP3A4 (e.g., beclomethasone). Moreover, in case of withdrawal of glucocorticoids, progressive dose reduction may have to be performed over a longer period.</td>
</tr>
</tbody>
</table>

#### ERECTILE DYSFUNCTION

#### PDE5 Inhibitors

<table>
<thead>
<tr>
<th>Medicinal product assessed</th>
<th>Co-administered medicinal products (dose in mg)</th>
<th>AUC (90% CI)</th>
<th>C&lt;sub&gt;max&lt;/sub&gt; (90% CI)</th>
<th>C&lt;sub&gt;min&lt;/sub&gt; (90% CI)</th>
<th>Recommendations concerning co-administration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sildenafil</td>
<td>Sildenafil is metabolised by CYP3A4. Co-administration with</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Patients should be
<table>
<thead>
<tr>
<th>Co-administered medicinal products (dose in mg)</th>
<th>Medicinal product assessed</th>
<th>AUC (90% CI)</th>
<th>C\text{max} (90% CI)</th>
<th>C\text{min} (90% CI)</th>
<th>Recommendations concerning co-administration</th>
</tr>
</thead>
<tbody>
<tr>
<td>REYATAZ/ritonavir may result in increased concentrations of sildenafil and an increase in sildenafil-associated adverse events, including hypotension, visual changes, and priapism. The mechanism of the sildenafil/atazanavir interaction is CYP3A4 inhibition.</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>warned about these possible side effects.</td>
</tr>
</tbody>
</table>

**HERBAL PRODUCTS**

St. John’s wort (Hypericum perforatum): Concomitant use of St. John’s wort with REYATAZ/ritonavir may be expected to result in significant reduction in plasma levels of atazanavir. This effect may be due to an induction of CYP3A4. There is a risk of loss of therapeutic effect and development of resistance (see section 4.3).

**HORMONAL CONTRACEPTIVES**

| Ethinyloestradiol 25 μg + norgestimate (atazanavir 300 mg QD with ritonavir 100 mg QD) | ethinyloestradiol | ↓0.81 (0.75, 0.87) | ↓0.84 (0.74, 0.95) | ↓0.63 (0.55, 0.71) | If an oral contraceptive is administered with REYATAZ/ritonavir, it is recommended that the oral contraceptive contain at least 30 μg of ethinyloestradiol and that the patient be reminded of strict compliance with this contraceptive dosing regimen. Co-administration of REYATAZ/ritonavir with other hormonal contraceptives or oral contraceptives containing progestogens other than norgestimate has not been studied, and therefore should be avoided. An alternate reliable method of contraception is recommended. |
| ethinyloestradiol | ↓0.81 (0.75, 0.87) |
| norgestimate | ↑1.85 (1.67, 2.05) |
| norgestimate | ↑1.85 (1.67, 2.05) |

While the concentration of ethinyloestradiol was increased with atazanavir given alone, due to both UGT and CYP3A4 inhibition by atazanavir, the net effect of atazanavir/ritonavir is a decrease in ethinyloestradiol levels because of the inducing effect of ritonavir.

The increase in progestin exposure may lead to related side-effects (e.g. insulin resistance, dyslipidemia, acne and spotting), thus possibly affecting the compliance.

**LIPID LOWERING AGENTS**

**HMG-CoA reductase inhibitors**

Simvastatin and lovastatin are highly dependent on CYP3A4 for their metabolism and co-administration with REYATAZ/ritonavir may result in increased concentrations.

Co-administration of simvastatin or lovastatin with REYATAZ/ritonavir is not recommended due to an increased risk of myopathy including rhabdomyolysis. The use of another HMG-CoA reductase inhibitor which does not undergo metabolism by CYP3A such as pravastatin or fluvastatin is recommended.

**OPIOIDS**

Buprenorphine, QD, stable maintenance dose, (atazanavir 300 mg QD with ritonavir 100 mg QD)

| buprenorphine | ↑1.67 |
| norbuprenorphine | ↑2.05 |

The mechanism of interaction is CYP3A4 and UGT1A1 inhibition.
<table>
<thead>
<tr>
<th>Co-administered medicinal products (dose in mg)</th>
<th>Medicinal product assessed</th>
<th>AUC (90% CI)</th>
<th>C&lt;sub&gt;max&lt;/sub&gt; (90% CI)</th>
<th>C&lt;sub&gt;min&lt;/sub&gt; (90% CI)</th>
<th>Recommendations concerning co-administration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methadone, stable maintenance dose (atazanavir 400 mg QD)</td>
<td>No significant effect on methadone concentrations was observed. Given that low dose ritonavir (100 mg twice daily) has been shown to have no significant effect on methadone concentrations, no interaction is expected if methadone is co-administered with REYATAZ and ritonavir, based on these data.</td>
<td></td>
<td></td>
<td></td>
<td>No dosage adjustment is necessary if methadone is co-administered with REYATAZ and ritonavir.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>SEDATIVES</th>
<th>Benzodiazepines</th>
</tr>
</thead>
<tbody>
<tr>
<td>Midazolam</td>
<td>Midazolam and triazolam are extensively metabolized by CYP3A4. Co-administration with REYATAZ/ritonavir may cause a large increase in the concentration of these benzodiazepines. No drug interaction study has been performed for the co-administration of REYATAZ/ritonavir with benzodiazepines. Based on data for other CYP3A4 inhibitors, plasma concentrations of midazolam are expected to be significantly higher when midazolam is given orally. Data from concomitant use of parenteral midazolam with other protease inhibitors suggest a possible 3-4 fold increase in midazolam plasma levels.</td>
</tr>
<tr>
<td>Triazolam</td>
<td></td>
</tr>
</tbody>
</table>

4.6 Pregnancy and lactation

There are no adequate data from the use of atazanavir in pregnant women. Studies in animals have not shown evidence of selective developmental toxicity or effects on reproductive function and fertility (see section 5.3). REYATAZ should be used during pregnancy only if the potential benefit justifies the potential risk.

It is not known whether REYATAZ administered to the mother during pregnancy will exacerbate physiological hyperbilirubinaemia and lead to kernicterus in neonates and infants. In the prepartum period, additional monitoring and alternative therapy to REYATAZ should be considered.

It is not known whether atazanavir is excreted in human milk. Studies in rats have demonstrated that atazanavir is excreted in the milk. It is therefore recommended that mothers being treated with REYATAZ not breast-feed their infants. As a general rule, it is recommended that HIV infected women not breast-feed their infants in order to avoid transmission of HIV.
4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed. Patients should be informed that dizziness has been reported during treatment with regimens containing REYATAZ (see section 4.8).

4.8 Undesirable effects

REYATAZ has been evaluated for safety in combination therapy with other antiretroviral medicinal products in controlled clinical trials in 1,806 adult patients receiving REYATAZ 400 mg once daily (1,151 patients, 52 weeks median duration and 152 weeks maximum duration) or REYATAZ 300 mg with ritonavir 100 mg once daily (655 patients, 96 weeks median duration and 108 weeks maximum duration).

Adverse reactions were consistent between patients who received REYATAZ 400 mg once daily and patients who received REYATAZ 300 mg with ritonavir 100 mg once daily, except that jaundice and elevated total bilirubin levels were reported more frequently with REYATAZ plus ritonavir.

Among patients who received REYATAZ 400 mg once daily or REYATAZ 300 mg with ritonavir 100 mg once daily, the only adverse reactions of any severity reported very commonly with at least a possible relationship to regimens containing REYATAZ and one or more NRTIs were nausea (20%), diarrhoea (10%), and jaundice (13%). Among patients receiving REYATAZ 300 mg with ritonavir 100 mg, the frequency of jaundice was 19%. In the majority of cases, jaundice was reported within a few days to a few months after the initiation of treatment (see section 4.4).

Combination antiretroviral therapy has been associated with redistribution of body fat (lipodystrophy) in HIV patients, including loss of peripheral and facial subcutaneous fat, increased intra-abdominal and visceral fat, breast hypertrophy, and dorsocervical fat accumulation (buffalo hump).

Combination antiretroviral therapy has been associated with metabolic abnormalities such as hypertriglyceridaemia, hypercholesterolaemia, insulin resistance, hyperglycaemia, and hyperlactataemia (see sections 4.4 and 5.1).

Adult patients
The following adverse reactions of moderate intensity or greater with at least a possible relationship to regimens containing REYATAZ and one or more NRTIs have also been reported. The frequency of adverse reactions listed below is defined using the following convention: very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1,000 to < 1/100), rare (≥ 1/10,000 to < 1/1,000), or very rare (< 1/10,000). Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Cardiac disorders: rare: oedema, palpitation

Nervous system disorders: common: headache;
uncommon: peripheral neuropathy, syncope, amnesia, dizziness, somnolence, dysgeusia

Eye disorders: common: ocular icterus

Respiratory, thoracic and mediastinal disorders: uncommon: dyspnoea

Gastrointestinal disorders: common: vomiting, diarrhoea, abdominal pain, nausea, dyspepsia;
uncommon: pancreatitis, gastritis, abdominal distension, stomatitis aphtous, flatulence, dry mouth
Renal and urinary disorders: uncommon: nephrolithiasis, hematuria, proteinuria, pollakiuria; rare: kidney pain

Skin and subcutaneous tissue disorders: common: rash; uncommon: urticaria, alopecia, pruritus; rare: vesicobullous rash, eczema, vasodilatation

Musculoskeletal and connective tissue disorders: uncommon: muscle atrophy, arthralgia, myalgia; rare: myopathy

Metabolism and nutrition disorders: uncommon: weight decreased, weight gain, anorexia, appetite increased

Vascular disorders: uncommon: hypertension

General disorders and administration site conditions: common: lipodystrophy syndrome, fatigue; uncommon: chest pain, malaise, pyrexia, asthenia; rare: gait disturbance

Immune system disorders: uncommon: hypersensitivity

Hepatobiliary disorders: common: jaundice; uncommon: hepatitis; rare: hepatosplenomegaly

Reproductive system and breast disorders: uncommon: gynaecomastia

Psychiatric disorders: uncommon: depression, disorientation, anxiety, insomnia, sleep disorder, abnormal dream

In HIV-infected patients with severe immune deficiency at the time of initiation of combination antiretroviral therapy (CART), an inflammatory reaction to asymptomatic or residual opportunistic infections may arise (see section 4.4).

Cases of osteonecrosis have been reported, particularly in patients with generally acknowledged risk factors, advanced HIV disease or long-term exposure to combination antiretroviral therapy (CART). The frequency of this is unknown (see section 4.4).

Laboratory abnormalities
The most frequently reported laboratory abnormality in patients receiving regimens containing REYATAZ and one or more NRTIs was elevated total bilirubin reported predominantly as elevated indirect [unconjugated] bilirubin (87% Grade 1, 2, 3, or 4). Grade 3 or 4 elevation of total bilirubin was noted in 37% (6% Grade 4). Among experienced patients treated with REYATAZ 300 mg once daily with 100 mg ritonavir once daily for a median duration of 95 weeks, 53% had Grade 3-4 total bilirubin elevations. Among naive patients treated with REYATAZ 300 mg once daily with 100 mg ritonavir once daily for a median duration of 96 weeks, 48% had Grade 3-4 total bilirubin elevations (see section 4.4).

Other marked clinical laboratory abnormalities (Grade 3 or 4) reported in ≥ 2% of patients receiving regimens containing REYATAZ and one or more NRTIs included: elevated creatine kinase (7%), elevated alanine aminotransferase/serum glutamic-pyruvic transaminase (ALT/SGPT) (5%), low neutrophils (5%), elevated aspartate aminotransferase/serum glutamic-oxaloacetic transaminase (AST/SGOT) (3%), and elevated lipase (3%).
Two percent of patients treated with REYATAZ experienced concurrent Grade 3-4 ALT/AST and Grade 3-4 total bilirubin elevations.

**Patients co-infected with hepatitis B and/or hepatitis C virus**

Among 1,151 patients receiving atazanavir 400 mg once daily, 177 patients were co-infected with chronic hepatitis B or C, and among 655 patients receiving atazanavir 300 mg once daily with ritonavir 100 mg once daily, 97 patients were co-infected with chronic hepatitis B or C. Co-infected patients were more likely to have baseline hepatic transaminase elevations than those without chronic viral hepatitis. No differences in frequency of bilirubin elevations were observed between these patients and those without viral hepatitis. The frequency of treatment emergent hepatitis or transaminase elevations in co-infected patients was comparable between REYATAZ and comparator regimens (see section 4.4).

**Postmarketing experience**

There have been postmarketing reports of unknown frequency for torsades de pointes, QTc prolongation, diabetes mellitus, hyperglycaemia, nephrolithiasis, and gallbladder disorders including cholelithiasis, cholecystitis, and cholestasis.

**4.9 Overdose**

Human experience of acute overdose with REYATAZ is limited. Single doses up to 1,200 mg have been taken by healthy volunteers without symptomatic untoward effects. At high doses that lead to high drug exposures, jaundice due to indirect (unconjugated) hyperbilirubinaemia (without associated liver function test changes) or PR interval prolongations may be observed (see sections 4.4 and 4.8).

Treatment of overdose with REYATAZ should consist of general supportive measures, including monitoring of vital signs and electrocardiogram (ECG), and observations of the patient's clinical status. If indicated, elimination of unabsorbed atazanavir should be achieved by emesis or gastric lavage. Administration of activated charcoal may also be used to aid removal of unabsorbed drug. There is no specific antidote for overdose with REYATAZ. Since atazanavir is extensively metabolised by the liver and is highly protein bound, dialysis is unlikely to be beneficial in significant removal of this medicinal product.

**5. PHARMACOLOGICAL PROPERTIES**

**5.1 Pharmacodynamic properties**

Pharmacotherapeutic group: protease inhibitor, ATC code: J05AE08

*Mechanism of action:* atazanavir is an azapeptide HIV-1 protease inhibitor (PI). The compound selectively inhibits the virus-specific processing of viral Gag-Pol proteins in HIV-1 infected cells, thus preventing formation of mature virions and infection of other cells.

*Antiviral activity in vitro:* atazanavir exhibits anti-HIV-1 (including all clades tested) and anti-HIV-2 activity in cell culture.

**Resistance**

*Antiretroviral treatment naive patients*

In clinical trials of antiretroviral treatment naive patients treated with unboosted atazanavir, the I50L substitution, sometimes in combination with an A71V change, is the signature resistance substitution for atazanavir. Resistance levels to atazanavir ranged from 3.5- to 29-fold without evidence of phenotypic cross resistance to other PIs. In clinical trials of antiretroviral treatment naive patients treated with boosted atazanavir, the I50L substitution did not emerge in any patient without baseline PI substitutions. The N88S substitution has been rarely observed in patients with virologic failure on atazanavir (with or without ritonavir). While it may contribute to decreased susceptibility to atazanavir...
when it occurs with other protease substitutions, in clinical studies N88S by itself does not always lead to phenotypic resistance to atazanavir or have a consistent impact on clinical efficacy.

Table 2. De novo substitutions in treatment naive patients failing therapy with atazanavir + ritonavir (Study 138, 96 weeks)

<table>
<thead>
<tr>
<th>Frequency</th>
<th>de novo PI substitution (n=26)(^a)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;20%</td>
<td>none</td>
</tr>
<tr>
<td>10-20%</td>
<td>none</td>
</tr>
</tbody>
</table>

\(^a\) Number of patients with paired genotypes classified as virological failures (HIV RNA ≥ 400 copies/ml).

The M184I/V substitution emerged in 5/26 REYATAZ/ritonavir and 7/26 lopinavir/ritonavir virologic failure patients, respectively.

**Antiretroviral treatment experienced patients**

In antiretroviral treatment experienced patients from Studies 009, 043, and 045, 100 isolates from patients designated as virological failures on therapy that included either atazanavir, atazanavir + ritonavir, or atazanavir + saquinavir were determined to have developed resistance to atazanavir. Of the 60 isolates from patients treated with either atazanavir or atazanavir + ritonavir, 18 (30%) displayed the I50L phenotype previously described in naive patients.

Table 3. De novo substitutions in treatment experienced patients failing therapy with atazanavir + ritonavir (Study 045, 48 weeks)

<table>
<thead>
<tr>
<th>Frequency</th>
<th>de novo PI substitution (n=35)(^a,b)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;20%</td>
<td>M36, M46, I54, A71, V82</td>
</tr>
<tr>
<td>10-20%</td>
<td>L10, L15, K20, V32, E35, S37, F53, I62, G73, I84, L90</td>
</tr>
</tbody>
</table>

\(^a\) Number of patients with paired genotypes classified as virological failures (HIV RNA ≥ 400 copies/ml).

\(^b\) Ten patients had baseline phenotypic resistance to atazanavir + ritonavir (fold change [FC] > 5.2). FC susceptibility in cell culture relative to the wild-type reference was assayed using PhenoSense\(^TM\) (Monogram Biosciences, South San Francisco, California, USA).

None of the de novo substitutions (see Table 3) are specific to atazanavir and may reflect re-emergence of archived resistance on atazanavir + ritonavir in Study 045 treatment-experienced population.

The resistance in antiretroviral treatment experienced patients mainly occurs by accumulation of the major and minor resistance substitutions described previously to be involved in protease inhibitor resistance.

**Clinical results**

**In antiretroviral naive patients**

*Study 138* is an international randomised, open-label, multicenter, prospective trial of treatment naïve patients comparing REYATAZ/ritonavir (300 mg/100 mg once daily) to lopinavir/ritonavir (400 mg/100 mg twice daily), each in combination with fixed dose tenofovir/emtricitabine (300 mg/200 mg tablets once daily). The REYATAZ/ritonavir arm showed similar (non-inferior) antiviral efficacy compared to the lopinavir/ritonavir arm, as assessed by the proportion of patients with HIV RNA < 50 copies/ml at week 48 (Table 4). Analyses of data through 96 weeks of treatment demonstrated durability of antiviral activity (Table 4).
Table 4: Efficacy Outcomes in Study 138

<table>
<thead>
<tr>
<th>Parameter</th>
<th>REYATAZ/ritonavir&lt;sup&gt;b&lt;/sup&gt; (300 mg/100 mg once daily) n=440</th>
<th>Lopinavir/ritonavir&lt;sup&gt;c&lt;/sup&gt; (400 mg/100 mg twice daily) n=443</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Week 48</td>
<td>Week 96</td>
</tr>
<tr>
<td>HIV RNA &lt;50 copies/ml, %</td>
<td></td>
<td></td>
</tr>
<tr>
<td>All patients&lt;sup&gt;d&lt;/sup&gt;</td>
<td>78</td>
<td>74</td>
</tr>
<tr>
<td>Difference estimate&lt;sup&gt;d&lt;/sup&gt;</td>
<td>Week 48: 1.7% [-3.8%, 7.1%]</td>
<td>Week 96: 6.1% [0.3%, 12.0%]</td>
</tr>
<tr>
<td>(95% CI)</td>
<td>(n=392&lt;sup&gt;f&lt;/sup&gt;)</td>
<td>(n=352)</td>
</tr>
<tr>
<td>Per protocol analysis&lt;sup&gt;e&lt;/sup&gt;</td>
<td>89</td>
<td>89</td>
</tr>
<tr>
<td>Difference estimate&lt;sup&gt;e&lt;/sup&gt;</td>
<td>Week 48: -3% [-7.6%, 1.5%]</td>
<td>Week 96: 2.2% [-2.3%, 6.7%]</td>
</tr>
<tr>
<td>(95% CI)</td>
<td>(n=358)</td>
<td>(n=322)</td>
</tr>
<tr>
<td>HIV RNA &lt;50 copies/ml, % by Baseline Characteristic&lt;sup&gt;d&lt;/sup&gt;</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HIV RNA &lt;100,000 copies/ml</td>
<td>82 (n=217)</td>
<td>75 (n=217)</td>
</tr>
<tr>
<td>≥100,000 copies/ml</td>
<td>74 (n=223&lt;sup&gt;f&lt;/sup&gt;)</td>
<td>74 (n=223)</td>
</tr>
<tr>
<td>CD4 count &lt;50 cells/mm&lt;sup&gt;3&lt;/sup&gt;</td>
<td>78 (n=58)</td>
<td>78 (n=58)</td>
</tr>
<tr>
<td>50 to &lt;100 cells/mm&lt;sup&gt;3&lt;/sup&gt;</td>
<td>76 (n=45)</td>
<td>71 (n=45)</td>
</tr>
<tr>
<td>100 to &lt;200 cells/mm&lt;sup&gt;3&lt;/sup&gt;</td>
<td>75 (n=106)</td>
<td>71 (n=106)</td>
</tr>
<tr>
<td>≥ 200 cells/mm&lt;sup&gt;3&lt;/sup&gt;</td>
<td>80 (n=222)</td>
<td>76 (n=222)</td>
</tr>
<tr>
<td>HIV RNA Mean Change from Baseline, log&lt;sub&gt;10&lt;/sub&gt; copies/ml</td>
<td></td>
<td></td>
</tr>
<tr>
<td>All patients</td>
<td>-3.09 (n=397)</td>
<td>-3.21 (n=360)</td>
</tr>
<tr>
<td>CD4 Mean Change from Baseline, cells/mm&lt;sup&gt;3&lt;/sup&gt;</td>
<td></td>
<td></td>
</tr>
<tr>
<td>All patients</td>
<td>203 (n=370)</td>
<td>268 (n=336)</td>
</tr>
<tr>
<td>HIV RNA &lt;100,000 copies/ml</td>
<td>179 (n=183)</td>
<td>243 (n=163)</td>
</tr>
<tr>
<td>≥100,000 copies/ml</td>
<td>227 (n=187)</td>
<td>291 (n=173)</td>
</tr>
</tbody>
</table>

<sup>a</sup> Mean baseline CD4 cell count was 214 cells/mm<sup>3</sup> (range 2 to 810 cells/mm<sup>3</sup> and mean baseline plasma HIV-1 RNA was 4.94 log<sub>10</sub> copies/ml (range 2.6 to 5.88 log<sub>10</sub> copies/ml)

<sup>b</sup> REYATAZ/RTV with tenofovir/emtricitabine (fixed dose 300 mg/200 mg tablets once daily).

<sup>c</sup> Lopinavir/RTV with tenofovir/emtricitabine (fixed dose 300 mg/200 mg tablets once daily).

<sup>d</sup> Intent-to-treat analysis, with missing values considered as failures.

<sup>e</sup> Per protocol analysis: Excluding non-completers and patients with major protocol deviations.

<sup>f</sup> Number of patients evaluable.

In antiretroviral experienced patients

Study 045 is a randomised, multicenter trial comparing REYATAZ/ritonavir (300/100 mg once daily) and REYATAZ/saquinavir (400/1,200 mg once daily), to lopinavir + ritonavir (400/100 mg fixed dose combination twice daily), each in combination with tenofovir (see sections 4.5 and 4.8) and one NRTI, in patients with virologic failure on two or more prior regimens containing at least one PI, NRTI, and NNRTI. For randomised patients, the mean time of prior antiretroviral exposure was 138 weeks for PIs, 281 weeks for NRTIs, and 85 weeks for NNRTIs. At baseline, 34% of patients were receiving a PI and 60% were receiving an NNRTI. Fifteen of 120 (13%) patients in the REYATAZ + ritonavir treatment arm and 17 of 123 (14%) patients in the lopinavir + ritonavir arm had four or more of the PI substitutions L10, M46, I54, V82, I84, and L90. Thirty-two percent of patients in the study had a viral strain with fewer than two NRTI substitutions.

The primary endpoint was the time-averaged difference in change from baseline in HIV RNA through 48 weeks (Table 5).
Table 5: Efficacy Outcomes at Week 48 and at Week 96 (Study 045)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>ATV/RTVb (300 mg/100 mg once daily) n=120</th>
<th>LPV/RTVc (400 mg/100 mg twice daily) n=123</th>
<th>Time-averaged difference ATV/RTV-LPV/RTV [97.5% CId]</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV RNA Mean Change from Baseline, log_{10} copies/ml</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Week 48</td>
<td>Week 96</td>
<td>Week 48</td>
<td>Week 96</td>
</tr>
<tr>
<td>All patients</td>
<td>-1.93 (n=90)</td>
<td>-2.29 (n=64)</td>
<td>-1.87 (n=99)</td>
</tr>
<tr>
<td>HIV RNA &lt;50 copies/ml, %f (responder/evaluable)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All patients</td>
<td>36 (43/120)</td>
<td>32 (38/120)</td>
<td>42 (52/123)</td>
</tr>
<tr>
<td>HIV RNA &lt;50 copies/ml by select baseline PI substitutions, f, g % (responder/evaluable)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0-2</td>
<td>44 (28/63)</td>
<td>41 (26/63)</td>
<td>56 (32/57)</td>
</tr>
<tr>
<td>3</td>
<td>18 (2/11)</td>
<td>9 (1/11)</td>
<td>38 (6/16)</td>
</tr>
<tr>
<td>≥4</td>
<td>27 (12/45)</td>
<td>24 (11/45)</td>
<td>28 (14/50)</td>
</tr>
<tr>
<td>CD4 Mean Change from Baseline, cells/mm³</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All patients</td>
<td>110 (n=83)</td>
<td>122 (n=60)</td>
<td>121 (n=94)</td>
</tr>
</tbody>
</table>

a The mean baseline CD4 cell count was 337 cells/mm³ (range: 14 to 1,543 cells/mm³) and the mean baseline plasma HIV-1 RNA level was 4.4 log_{10} copies/ml (range: 2.6 to 5.88 log_{10} copies/ml).
b ATV/RTV with tenofovir/emtricitabine (fixed dose 300 mg/200 mg tablets once daily).
c LPV/RTV with tenofovir/emtricitabine (fixed dose 300 mg/200 mg tablets once daily).
d Confidence interval.
e Number of patients evaluable.
f Intent-to-treat analysis, with missing values considered as failures. Responders on LPV/RTV who completed treatment before Week 96 are excluded from Week 96 analysis. The proportion of patients with HIV RNA < 400 copies/ml were 53% and 43% for ATV/RTV and 54% and 46% for LPV/RTV at weeks 48 and 96 respectively.
g Select substitutions include any change at positions L10, K20, L24, V32, L33, M36, M46, G48, I50, I54, L63, A71, G73, V82, I84, and L90 (0-2, 3, 4 or more) at baseline.

NA = not applicable.

Through 48 weeks of treatment, the mean changes from baseline in HIV RNA levels for REYATAZ + ritonavir and lopinavir + ritonavir were similar (non-inferior). Consistent results were obtained with the last observation carried forward method of analysis (time-averaged difference of 0.11, 97.5% confidence interval [-0.15, 0.36]). By as-treated analysis, excluding missing values, the proportions of patients with HIV RNA < 400 copies/ml (< 50 copies/ml) in the REYATAZ + ritonavir arm and the lopinavir + ritonavir arm were 55% (40%) and 56% (46%), respectively.

Through 96 weeks of treatment, mean HIV RNA changes from baseline for REYATAZ + ritonavir and lopinavir + ritonavir met criteria for non-inferiority based on observed cases. Consistent results were obtained with the last observation carried forward method of analysis. By as-treated analysis, excluding missing values, the proportions of patients with HIV RNA <400 copies/ml (<50 copies/ml) for REYATAZ + ritonavir were 84% (72%) and for lopinavir + ritonavir were 82% (72%). It is important to note that at time of the 96-week analysis, 48 % of patients overall remained on study.

REYATAZ + saquinavir was shown to be inferior to lopinavir + ritonavir.

5.2 Pharmacokinetic properties

The pharmacokinetics of atazanavir were evaluated in healthy adult volunteers and in HIV-infected patients; significant differences were observed between the two groups. The pharmacokinetics of atazanavir exhibit a non-linear disposition. In healthy subjects, the AUC of atazanavir from the capsules and oral powder were similar.

Absorption: in HIV-infected patients (n=33, combined studies), multiple dosing of REYATAZ 300 mg once daily with ritonavir 100 mg once daily with food produced a geometric mean (CV%) for atazanavir, C_{max} of 4466 (42%) ng/ml, with time to C_{max} of approximately 2.5 hours. The geometric mean (CV%) for atazanavir C_{min} and AUC was 654 (76%) ng/ml and 44185 (51%) ng•h/ml, respectively.
**Food effect:** co-administration of REYATAZ and ritonavir with food optimises the bioavailability of atazanavir. Co-administration of a single 300 mg dose of REYATAZ and 100 mg dose of ritonavir with a light meal resulted in a 33% increase in the AUC and a 40% increase in both the Cmax and the 24-hour concentration of atazanavir relative to the fasting state. Co-administration with a high-fat meal did not affect the AUC of atazanavir relative to fasting conditions and the Cmax was within 11% of fasting values. The 24-hour concentration following a high fat meal was increased by approximately 33% due to delayed absorption; the median Tmax increased from 2.0 to 5.0 hours. Administration of REYATAZ with ritonavir with either a light or a high-fat meal decreased the coefficient of variation of AUC and Cmax by approximately 25% compared to the fasting state. To enhance bioavailability and minimise variability, REYATAZ is to be taken with food.

**Distribution:** atazanavir was approximately 86% bound to human serum proteins over a concentration range of 100 to 10,000 ng/ml. Atazanavir binds to both alpha-1-acid glycoprotein (AAG) and albumin to a similar extent (89% and 86%, respectively, at 1,000 ng/ml). In a multiple-dose study in HIV-infected patients dosed with 400 mg of atazanavir once daily with a light meal for 12 weeks, atazanavir was detected in the cerebrospinal fluid and semen.

**Metabolism:** studies in humans and in vitro studies using human liver microsomes have demonstrated that atazanavir is principally metabolised by CYP3A4 isozyme to oxygenated metabolites. Metabolites are then excreted in the bile as either free or glucuronidated metabolites. Additional minor metabolic pathways consist of N-dealkylation and hydrolysis. Two minor metabolites of atazanavir in plasma have been characterised. Neither metabolite demonstrated in vitro antiviral activity.

**Elimination:** following a single 400-mg dose of 14C-atazanavir, 79% and 13% of the total radioactivity was recovered in the faeces and urine, respectively. Unchanged drug accounted for approximately 20% and 7% of the administered dose in the faeces and urine, respectively. Mean urinary excretion of unchanged drug was 7% following 2 weeks of dosing at 800 mg once daily. In HIV-infected adult patients (n=33, combined studies) the mean half-life within a dosing interval for atazanavir was 12 hours at steady state following a dose of 300 mg daily with ritonavir 100 mg once daily with a light meal.

**Special populations**

**Impaired renal function:** in healthy subjects, the renal elimination of unchanged atazanavir was approximately 7% of the administered dose. There are no pharmacokinetic data available for REYATAZ with ritonavir in patients with renal insufficiency. REYATAZ (without ritonavir) has been studied in adult patients with severe renal impairment (n=20), including those on haemodialysis, at multiple doses of 400 mg once daily. Although this study presented some limitations (i.e., unbound drug concentrations not studied), results suggested that the atazanavir pharmacokinetic parameters were decreased by 30% to 50% in patients undergoing haemodialysis compared to patients with normal renal function. The mechanism of this decrease is unknown. (See sections 4.2 and 4.4.)

**Impaired hepatic function:** atazanavir is metabolised and eliminated primarily by the liver. The effects of hepatic impairment on the pharmacokinetics of atazanavir after a 300 mg dose with ritonavir have not been studied. Concentrations of atazanavir with or without ritonavir are expected to be increased in patients with moderately or severely impaired hepatic function (see sections 4.2, 4.3 and 4.4).

**Age/Gender:** a study of the pharmacokinetics of atazanavir was performed in 59 healthy male and female subjects (29 young, 30 elderly). There were no clinically important pharmacokinetic differences based on age or gender.

**Race:** a population pharmacokinetic analysis of samples from Phase II clinical trials indicated no effect of race on the pharmacokinetics of atazanavir.

**Infants, toddlers, children, and adolescents:** the pharmacokinetics of atazanavir is being studied after multiple doses in paediatric patients, stratified by age. There are insufficient data at this time to recommend a dose (see section 4.2).
5.3 Preclinical safety data

In repeat-dose toxicity studies, conducted in mice, rats, and dogs, atazanavir-related findings were generally confined to the liver and included generally minimal to mild increases in serum bilirubin and liver enzymes, hepatocellular vacuolation and hypertrophy, and, in female mice only, hepatic single-cell necrosis. Systemic exposures of atazanavir in mice (males), rats, and dogs at doses associated with hepatic changes were at least equal to that observed in humans given 400 mg once daily. In female mice, atazanavir exposure at a dose that produced single-cell necrosis was 12 times the exposure in humans given 400 mg once daily. Serum cholesterol and glucose were minimally to mildly increased in rats but not in mice or dogs.

During in vitro studies, cloned human cardiac potassium channel (hERG), was inhibited by 15% at a concentration (30 μM) of atazanavir corresponding to 30-fold the free drug concentration at C_{max} in humans. Similar concentrations of atazanavir increased by 13% the action potential duration (APD_{90}) in rabbit Purkinje fibres study. Electrocardiographic changes (sinus bradycardia, prolongation of PR interval, prolongation of QT interval, and prolongation of QRS complex) were observed only in an initial 2-week oral toxicity study performed in dogs. Subsequent 9-month oral toxicity studies in dogs showed no drug-related electrocardiographic changes. The clinical relevance of these non-clinical data is unknown. Potential cardiac effects of this product in humans cannot be ruled out (see sections 4.4 and 4.8). The potential for PR prolongation should be considered in cases of overdose (see section 4.9).

In a fertility and early embryonic development study in rats, atazanavir altered oestrus cycling with no effects on mating or fertility. No teratogenic effects were observed in rats or rabbits at maternally toxic doses. In pregnant rabbits, gross lesions of the stomach and intestines were observed in dead or moribund does at maternal doses 2 and 4 times the highest dose administered in the definitive embryo-development study. In the pre- and postnatal development assessment in rats, atazanavir produced a transient reduction in body weight in the offspring at a maternally toxic dose. Systemic exposure to atazanavir at doses that resulted in maternal toxicity was at least equal to or slightly greater than that observed in humans given 400 mg once daily.

Atazanavir was negative in an Ames reverse-mutation assay but did induce chromosomal aberrations in vitro in both the absence and presence of metabolic activation. In in vivo studies in rats, atazanavir did not induce micronuclei in bone marrow, DNA damage in duodenum (comet assay), or unscheduled DNA repair in liver at plasma and tissue concentrations exceeding those that were clastogenic in vitro.

In long-term carcinogenicity studies of atazanavir in mice and rats, an increased incidence of benign hepatic adenomas was seen in female mice only. The increased incidence of benign hepatic adenomas in female mice was likely secondary to cytotoxic liver changes manifested by single-cell necrosis and is considered to have no relevance for humans at intended therapeutic exposures. There were no tumorigenic findings in male mice or in rats.

Atazanavir increased opacity of bovine corneas in an in vitro ocular irritation study, indicating it may be an ocular irritant upon direct contact with the eye.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Aspartame (E951)
Sucrose
Orange-vanilla flavour including:
Modified food starch
Dextrose
Butylhydroxytoluene (E321)
6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years
After opening: 2 months.

6.4 Special precautions for storage

Keep the bottle tightly closed.

6.5 Nature and contents of container

High density polyethylene (HDPE) bottles closed with a child-resistant polypropylene closure. Each bottle contains 180 g of REYATAZ and is packaged in a carton with a measuring spoon.

6.6 Special precautions for disposal

Any unused product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

BRISTOL-MYERS SQUIBB PHARMA EEIG
Uxbridge Business Park
Sanderson Road
Uxbridge UB8 1DH
United Kingdom

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/03/267/007

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 02 March 2004
Date of latest renewal: 02 March 2009

10. DATE OF REVISION OF THE TEXT

{month year}

Detailed information on this medicinal product is available on the website of the European Medicines Agency (EMEA) http://www.emea.europa.eu
ANNEX II

A. MANUFACTURING AUTHORISATION HOLDER RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OF THE MARKETING AUTHORISATION
A. MANUFACTURING AUTHORISATION HOLDER(S) RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer(s) responsible for batch release

Bristol-Myers Squibb, Champ “Lachaud”, La Goualle, F-19250 Meymac, France
Bristol-Myers Squibb, Rue du Docteur Gilles, F-28230 Epernon, France
Bristol-Myers Squibb S.r.l., Contrada Fontana del Ceraso, 03012 Anagni (FR), Italy

The printed package leaflet of the medicinal product must state the name and address of the manufacturer responsible for the release of the concerned batch.

B. CONDITIONS OF THE MARKETING AUTHORISATION

- CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE IMPOSED ON THE MARKETING AUTHORISATION HOLDER

Medicinal product subject to restricted medical prescription (See Annex I: Summary of Product Characteristics, section 4.2).

- CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

Not applicable.

- OTHER CONDITIONS

**Pharmacovigilance system**

The MAH must ensure that the system of pharmacovigilance, as described in version 3.3 presented in Module 1.8.1. of the Marketing Authorisation Application, is in place and functioning before and whilst the product is on the market.

**Risk Management plan**

The MAH commits to performing the studies and additional pharmacovigilance activities detailed in the Pharmacovigilance Plan, as agreed in version 2.2 of the Risk Management Plan (RMP) presented in Module 1.8.2. of the Marketing Authorisation Application and any subsequent updates of the RMP agreed by the CHMP.

As per the CHMP Guideline on Risk Management Systems for medicinal products for human use, the updated RMP should be submitted at the same time as the next Periodic Safety Update Report (PSUR).

In addition, an updated RMP should be submitted

- When new information is received that may impact on the current Safety Specification, Pharmacovigilance Plan or risk minimisation activities
- Within 60 days of an important (pharmacovigilance or risk minimisation) milestone being reached
- At the request of the EMEA
ANNEX III

LABELLING AND PACKAGE LEAFLET
A. LABELLING
PARTICULARS TO APPEAR ON THE OUTER PACKAGING AND THE IMMEDIATE PACKAGING

OUTER CARTON TEXT (BOTTLE AND BLISTER PRESENTATIONS) AND BOTTLE LABEL TEXT

1. NAME OF THE MEDICINAL PRODUCT

REYATAZ 100 mg hard capsules
atazanavir

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each capsule contains 100 mg of atazanavir (as sulphate).

3. LIST OF EXCIPIENTS

Excipients: contains lactose (see leaflet for further information).

4. PHARMACEUTICAL FORM AND CONTENTS

Carton and label bottle pack (1 bottle): 60 hard capsules
Blister pack: 60 hard capsules

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use.
Capsules should be swallowed whole. Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP {MM/YYYY}

9. SPECIAL STORAGE CONDITIONS

Bottle pack:
Do not store above 25°C.
Blister pack:
Do not store above 25°C.
Store in the original package

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

BRISTOL-MYERS SQUIBB PHARMA EEIG
Uxbridge Business Park
Sanderson Road
Uxbridge UB8 1DH
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

Bottle pack
60 hard capsules: EU/1/03/267/001

Blister pack:
60 hard capsules: EU/1/03/267/002

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Outer carton: REYATAZ 100 mg
**MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS**

1. **NAME OF THE MEDICINAL PRODUCT**
   
   REYATAZ 100 mg hard capsules
   atazanavir

2. **NAME OF THE MARKETING AUTHORISATION HOLDER**
   
   BRISTOL-MYERS SQUIBB PHARMA EEIG

3. **EXPIRY DATE**
   
   EXP {MM/YYYY}

4. **BATCH NUMBER**
   
   Lot

5. **OTHER**
| PARTICULARS TO APPEAR ON THE OUTER PACKAGING AND THE IMMEDIATE PACKAGING |
| OUTER CARTON TEXT (BOTTLE AND BLISTER PRESENTATIONS) AND BOTTLE LABEL TEXT |

1. **NAME OF THE MEDICINAL PRODUCT**

REYATAZ 150 mg hard capsules
atazanavir

2. **STATEMENT OF ACTIVE SUBSTANCE(S)**

Each capsule contains 150 mg of atazanavir (as sulphate).

3. **LIST OF EXCIPIENTS**

Excipients: contains lactose (see leaflet for further information).

4. **PHARMACEUTICAL FORM AND CONTENTS**

Carton and label bottle pack (1 bottle): 60 hard capsules

Blister pack: 60 hard capsules

5. **METHOD AND ROUTE(S) OF ADMINISTRATION**

Oral use.
Capsules should be swallowed whole. Read the package leaflet before use.

6. **SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN**

Keep out of the reach and sight of children.

7. **OTHER SPECIAL WARNING(S), IF NECESSARY**

8. **EXPIRY DATE**

EXP {MM/YYYY}

9. **SPECIAL STORAGE CONDITIONS**

Bottle pack:
Do not store above 25°C.
Blister pack:
Do not store above 25°C.
Store in the original package

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

BRISTOL-MYERS SQUIBB PHARMA EEIG
Uxbridge Business Park
Sanderson Road
Uxbridge UB8 1DH
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

Bottle pack
60 hard capsules: EU/1/03/267/003

Blister pack:
60 hard capsules: EU/1/03/267/004

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Outer carton: REYATAZ 150 mg
<table>
<thead>
<tr>
<th>MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>1. NAME OF THE MEDICINAL PRODUCT</strong></td>
</tr>
<tr>
<td>REYATAZ 150 mg hard capsules</td>
</tr>
<tr>
<td>atazanavir</td>
</tr>
<tr>
<td><strong>2. NAME OF THE MARKETING AUTHORITY HOLDER</strong></td>
</tr>
<tr>
<td>BRISTOL-MYERS SQUIBB PHARMA EEIG</td>
</tr>
<tr>
<td><strong>3. EXPIRY DATE</strong></td>
</tr>
<tr>
<td>EXP {MM/YYYY}</td>
</tr>
<tr>
<td><strong>4. BATCH NUMBER</strong></td>
</tr>
<tr>
<td>Lot</td>
</tr>
<tr>
<td><strong>5. OTHER</strong></td>
</tr>
</tbody>
</table>
**PARTICULARS TO APPEAR ON THE OUTER PACKAGING AND THE IMMEDIATE PACKAGING**

**OUTER CARTON TEXT (BOTTLE AND BLISTER PRESENTATIONS) AND BOTTLE LABEL TEXT**

<table>
<thead>
<tr>
<th>1. NAME OF THE MEDICINAL PRODUCT</th>
</tr>
</thead>
<tbody>
<tr>
<td>REYATAZ 200 mg hard capsules</td>
</tr>
<tr>
<td>atazanavir</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>2. STATEMENT OF ACTIVE SUBSTANCE(S)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Each capsule contains 200 mg of atazanavir (as sulphate).</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>3. LIST OF EXCIPIENTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Excipients: contains lactose (see leaflet for further information).</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>4. PHARMACEUTICAL FORM AND CONTENTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carton and label bottle pack (1 bottle): 60 hard capsules</td>
</tr>
<tr>
<td>Blister pack: 60 hard capsules</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>5. METHOD AND ROUTE(S) OF ADMINISTRATION</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral use.</td>
</tr>
<tr>
<td>Capsules should be swallowed whole. Read the package leaflet before use.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN</th>
</tr>
</thead>
<tbody>
<tr>
<td>Keep out of the reach and sight of children.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>7. OTHER SPECIAL WARNING(S), IF NECESSARY</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>8. EXPIRY DATE</th>
</tr>
</thead>
<tbody>
<tr>
<td>EXP {MM/YYYY}</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>9. SPECIAL STORAGE CONDITIONS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bottle pack:</td>
</tr>
<tr>
<td>Do not store above 25°C.</td>
</tr>
</tbody>
</table>
Blister pack:
Do not store above 25°C.
Store in the original package

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

BRISTOL-MYERS SQUIBB PHARMA EEIG
Uxbridge Business Park
Sanderson Road
Uxbridge UB8 1DH
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

Bottle pack
60 hard capsules: EU/1/03/267/005

Blister pack:
60 hard capsules: EU/1/03/267/006

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Outer carton: REYATAZ 200 mg
<table>
<thead>
<tr>
<th></th>
<th>MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>NAME OF THE MEDICINAL PRODUCT</td>
</tr>
<tr>
<td></td>
<td>REYATAZ 200 mg hard capsules</td>
</tr>
<tr>
<td></td>
<td>atazanavir</td>
</tr>
<tr>
<td>2.</td>
<td>NAME OF THE MARKETING AUTHORISATION HOLDER</td>
</tr>
<tr>
<td></td>
<td>BRISTOL-MYERS SQUIBB PHARMA EEIG</td>
</tr>
<tr>
<td>3.</td>
<td>EXPIRY DATE</td>
</tr>
<tr>
<td></td>
<td>EXP {MM/YYYY}</td>
</tr>
<tr>
<td>4.</td>
<td>BATCH NUMBER</td>
</tr>
<tr>
<td></td>
<td>Lot</td>
</tr>
<tr>
<td>5.</td>
<td>OTHER</td>
</tr>
<tr>
<td>PARTICULARS TO APPEAR ON THE OUTER PACKAGING AND THE IMMEDIATE PACKAGING</td>
<td></td>
</tr>
<tr>
<td>OUTER CARTON TEXT (BOTTLE AND BLISTER PRESENTATIONS) AND BOTTLE LABEL TEXT</td>
<td></td>
</tr>
</tbody>
</table>

1. **NAME OF THE MEDICINAL PRODUCT**

   REYATAZ 300 mg hard capsules  
   atazanavir

2. **STATEMENT OF ACTIVE SUBSTANCE(S)**

   Each capsule contains 300 mg of atazanavir (as sulphate).

3. **LIST OF EXCIPIENTS**

   Excipients: contains lactose (see leaflet for further information).

4. **PHARMACEUTICAL FORM AND CONTENTS**

   Carton and label bottle pack (1 bottle): 30 hard capsules  
   Carton Bottle pack: (3 bottles): 3 x 30 hard capsules (3 bottles of 30 hard capsules)  
   Label Bottle pack: (3 bottles): 30 hard capsules from a multi-pack comprising 3 bottles  
   **Blister pack:** 30 hard capsules

5. **METHOD AND ROUTE(S) OF ADMINISTRATION**

   Oral use.  
   Capsules should be swallowed whole. Read the package leaflet before use.

6. **SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN**

   Keep out of the reach and sight of children.

7. **OTHER SPECIAL WARNING(S), IF NECESSARY**

8. **EXPIRY DATE**

   EXP {MM/YYYY}

9. **SPECIAL STORAGE CONDITIONS**

   **Bottle pack:**
Do not store above 25°C.

**Blister pack:**
Do not store above 25°C.
Store in the original package

### 10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

### 11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

BRISTOL-MYERS SQUIBB PHARMA EEIG
Uxbridge Business Park
Sanderson Road
Uxbridge UB8 1DH
United Kingdom

### 12. MARKETING AUTHORISATION NUMBER(S)

**Bottle pack**
- 30 hard capsules: EU/1/03/267/008
- 3 x 30 hard capsules: EU/1/03/267/010

**Blister pack:**
- 30 hard capsules: EU/1/03/267/009

### 13. BATCH NUMBER

Lot

### 14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

### 15. INSTRUCTIONS ON USE

### 16. INFORMATION IN BRAILLE

**Outer carton:** REYATAZ 300 mg
<table>
<thead>
<tr>
<th>MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. <strong>NAME OF THE MEDICINAL PRODUCT</strong></td>
</tr>
<tr>
<td>REYATAZ 300 mg hard capsules</td>
</tr>
<tr>
<td>atazanavir</td>
</tr>
<tr>
<td>2. <strong>NAME OF THE MARKETING AUTHORISATION HOLDER</strong></td>
</tr>
<tr>
<td>BRISTOL-MYERS SQUIBB PHARMA EEIG</td>
</tr>
<tr>
<td>3. <strong>EXPIRY DATE</strong></td>
</tr>
<tr>
<td>EXP {MM/YYYY}</td>
</tr>
<tr>
<td>4. <strong>BATCH NUMBER</strong></td>
</tr>
<tr>
<td>Lot</td>
</tr>
<tr>
<td>5. <strong>OTHER</strong></td>
</tr>
</tbody>
</table>

PARTICULARS TO APPEAR ON THE OUTER PACKAGING AND THE IMMEDIATE PACKAGING
CARTON AND LABEL FOR BOTTLE WITH ORAL POWDER

1. NAME OF THE MEDICINAL PRODUCT

REYATAZ 50 mg/1.5 g oral powder
atazanavir

2. STATEMENT OF ACTIVE SUBSTANCE(S)

One measuring spoon of 1.5 g oral powder contains 50 mg of atazanavir (as sulphate).

3. LIST OF EXCIPIENTS

Also contains aspartame (E951) and sucrose (see leaflet for further information).

4. PHARMACEUTICAL FORM AND CONTENTS

180 g oral powder

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP {MM/YYYY}

9. SPECIAL STORAGE CONDITIONS

Keep the bottle tightly closed.
10. **SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE**

11. **NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER**

   BRISTOL-MYERS SQUIBB PHARMA EEIG  
   Uxbridge Business Park  
   Sanderson Road  
   Uxbridge UB8 1DH  
   United Kingdom

12. **MARKETING AUTHORISATION NUMBER(S)**

   EU/1/03/267/007

13. **BATCH NUMBER**

   Lot

14. **GENERAL CLASSIFICATION FOR SUPPLY**

   Medicinal product subject to medical prescription.

15. **INSTRUCTIONS ON USE**

16. **INFORMATION IN BRAILLE**

   Outer carton: REYATAZ 50 mg/1.5 g
B. PACKAGE LEAFLET
REYATAZ 100 mg hard capsules
atazanavir

Read all of this leaflet carefully before you start taking this medicine.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others.
- It may harm them, even if their symptoms are the same as yours.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor.

In this leaflet:
1. What REYATAZ is and what it is used for
2. Before you take REYATAZ
3. How to take REYATAZ
4. Possible side effects
5. How to store REYATAZ
6. Further information

1. WHAT REYATAZ IS AND WHAT IT IS USED FOR

REYATAZ is an antiviral (or antiretroviral) medicine. It is one of a group called protease inhibitors. These medicines control Human Immunodeficiency Virus (HIV) infection by stopping a protein that the HIV needs for its multiplication. They work by reducing the amount of HIV in your body and this in turn, strengthens your immune system. In this way REYATAZ reduces the risk of developing illnesses linked to HIV infection.

Reyataz capsules may be used by adults and children 6 years of age and older. Your doctor has prescribed REYATAZ for you because you are infected by the HIV that causes Acquired Immunodeficiency Syndrome (AIDS). It is normally used in combination with other anti-HIV medicines. Your doctor will discuss with you which combination of these medicines with REYATAZ is best for you.

REYATAZ is not a cure for HIV infection. You may continue to develop infections or other illnesses linked to HIV infection. Treatment with REYATAZ does not reduce the risk of passing HIV to others through sexual contact or blood contamination. You must continue to take appropriate precautions to avoid giving the virus to others.

2 BEFORE YOU TAKE REYATAZ

Do not take REYATAZ
- if you are allergic (hypersensitive) to atazanavir or any of the other ingredients of REYATAZ
- if you have moderate to severe liver problems. Your doctor will evaluate how severe your liver disease is before deciding whether you can take REYATAZ
- if you are taking any of these medicines: see also Taking other medicines with REYATAZ
  - rifampicin, an antibiotic used to treat tuberculosis
  - astemizole or terfenadine (commonly used to treat allergy symptoms, these medicines may be available without prescription); cisapride (used to treat gastric reflux, sometimes called heartburn); pimozide (used to treat schizophrenia); quinidine or bepridil (used to correct heart rhythm); ergotamine, dihydroergotamine, ergonovine, methylergonovine (used to treat headaches)
  - medicines containing St. John’s wort (Hypericum perforatum, a herbal preparation).
- triazolam and oral (taken by mouth) midazolam (used to help you sleep and/or to relieve anxiety).

Tell your doctor at once if any of these apply to you.

**Take special care with REYATAZ**

Some people will need special care before or while taking REYATAZ. Before taking this medicine, make sure your doctor knows:
- if you have hepatitis B or C
- if you have type A or B haemophilia
- if you have diabetes
- if you require haemodialysis
- if you are taking oral contraceptives ("the Pill") to prevent pregnancy
- if you are taking omeprazole or other proton pump inhibitors; or famotidine or other H2-receptor antagonists (used to treat diseases related to the acid in the stomach)
- if you notice changes in body fat. Redistribution, accumulation, or loss of body fat may occur in patients receiving antiretroviral therapy

Kidney stones have been reported in patients taking REYATAZ. If you develop signs or symptoms of kidney stones (pain in your side, blood in your urine, pain when you urinate), please inform your doctor immediately.

In some patients with advanced HIV infection (AIDS) and a history of opportunistic infection, signs and symptoms of inflammation from previous infections may occur soon after anti-HIV treatment is started. It is believed that these symptoms are due to an improvement in the body’s immune response, enabling the body to fight infections that may have been present with no obvious symptoms. If you notice any symptoms of infection, please inform your doctor immediately.

Some patients taking combination antiretroviral therapy may develop a bone disease called osteonecrosis (death of bone tissue caused by loss of blood supply to the bone). The length of combination antiretroviral therapy, corticosteroid use, alcohol consumption, severe immunosuppression, higher body mass index, among others, may be some of the many risk factors for developing this disease. Signs of osteonecrosis are joint stiffness, aches and pains (especially of the hip, knee and shoulder) and difficulty in movement. If you notice any of these symptoms please inform your doctor.

Hyperbilirubinaemia (an increase in the level of bilirubin in the blood) has occurred in patients receiving REYATAZ. The signs may be a mild yellowing of the skin or eyes. If you notice any of these symptoms please inform your doctor.

If you notice a change in the way your heart beats (heart rhythm changes), please inform your doctor.

**Use in Children**

REYATAZ capsules can be taken by children at least 6 years of age and older and weighing at least 15 kg who are able to swallow the capsules (see How to take REYATAZ).

Children receiving REYATAZ may require their heart to be monitored. Your child's doctor will decide this.

**Taking other medicines**

**You must not take REYATAZ with certain medicines.** These are listed under Do not take REYATAZ, at the start of Section 2.

There are other medicines that may not mix with REYATAZ. Please tell your doctor if you are taking or have recently taken any other medicines including medicines obtained without a prescription. It is especially important to mention these:
- other medicines to treat HIV infection
- sildenafil (used by men to treat impotence (erectile dysfunction))
- if you are taking an oral contraceptive ("the Pill") with REYATAZ, be sure to take it exactly as instructed by your doctor and not miss any doses.
- any medicines used to treat diseases related to the acid in the stomach (e.g. antacids, H₂-blockers and proton pump inhibitors)
- medicines to lower blood pressure, to slow heart rate, or to correct heart rhythm
- simvastatin, lovastatin, and atorvastatin (used to lower blood cholesterol)
- nevirapine and efavirenz (used to treat HIV)
- cyclosporin, tacrolimus, and sirolimus (medicines to decrease the effects of body's immune system)
- certain antibiotics (rifabutin, clarithromycin)
- ketoconazole, itraconazole, and voriconazole (antifungals)
- warfarin (anticoagulant, used to reduce the blood clots)
- irinotecan (used to treat cancer)
- sedative agents (e.g. midazolam administered by injection)
- buprenorphine (used to treat opioid addiction and pain).

Some medicines may interact with ritonavir, a medicine that is taken with REYATAZ. It is important to tell your doctor if you are taking fluticasone or budesonide (given by nose or inhaled to treat allergic symptoms or asthma).

**Taking REYATAZ with food and drink**

It is important that you take REYATAZ with food (a meal or a substantial snack) as this helps the body absorb the medicine.

**Pregnancy and breast-feeding**

Tell your doctor if you are pregnant or planning to become pregnant. Also be sure to tell your doctor if you are breast-feeding. It is recommended that women infected with HIV do not breast-feed because the virus might be transmitted through the breast milk.

**Driving and using machines**

No studies on the effects on the ability to drive and use machines have been performed. If you feel dizzy or lightheaded, contact your doctor immediately.

**Important information about some of the ingredients of REYATAZ**

If you have been told by your doctor that you have an intolerance to some sugars (e.g. lactose), contact your doctor before taking this medicinal product.

**3. HOW TO TAKE REYATAZ**

Always take REYATAZ exactly as your doctor has told you. You should check with your doctor if you are not sure. This way, you can be sure your medicine is fully effective and you reduce the risk of the virus developing resistance to the treatment.

The usual adult dose of REYATAZ capsules is 300 mg once daily with 100 mg ritonavir once daily and with food, in combination with other anti-HIV medicines. Your doctor may adjust the dose of REYATAZ according to your anti-HIV therapy.

For children (6 to less than 18 years of age), your child's doctor will decide the right dose based on your child's weight. The dose of REYATAZ capsules for children is calculated by body weight and is taken once daily with food and 100 mg ritonavir as shown below:
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<th>Ritonavir Dose* once daily (mg)</th>
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<td>150</td>
<td>100</td>
</tr>
<tr>
<td>20 to less than 40</td>
<td>200</td>
<td>100</td>
</tr>
<tr>
<td>at least 40</td>
<td>300</td>
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*Ritonavir capsules, tablets or oral solution may be used.

There are no dosing recommendations for REYATAZ in paediatric patients less than 6 years of age or weighing less than 15 kg.

**Take REYATAZ capsules with food** (a meal or a substantial snack). Swallow the capsules whole. **Do not open the capsules.**

**If you take more REYATAZ than you should**

If you accidentally take more REYATAZ capsules than your doctor recommended, contact your HIV doctor at once or contact the nearest hospital for advice.

**If you forget to take REYATAZ**

If you miss a dose, take the missed dose as soon as possible with food and then take your next scheduled dose at its regular time. If it is almost time for your next dose, do not take the missed dose. Wait and take the next dose at its regular time. **Do not take a double dose to make up for a forgotten dose.**

**If you stop taking REYATAZ**

Do not stop taking REYATAZ before talking to your doctor.

**If you have any further questions on the use of this product, ask your doctor.**

4. **POSSIBLE SIDE EFFECTS**

Like all medicines, REYATAZ can cause side effects, although not everybody gets them. When treating HIV infection, it is not always easy to identify what side effects are caused by REYATAZ, by the other medicines you are taking, or by the HIV infection itself. Tell your doctor if you notice anything unusual about your health.

The frequency of possible side effects listed below is defined using the following convention:

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<tr>
<td>not known:</td>
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</tr>
</tbody>
</table>

Patients treated with REYATAZ have reported the following side effects:

- **Common:**
  - headache
  - ocular icterus (presence of jaundice seen in the white part of the eyes)
  - vomiting, diarrhoea, abdominal pain (stomach pain of discomfort), nausea, dyspepsia (indigestion)
- jaundice (yellowing of the skin and/or eyes)
- rash
- lipodystrophy syndrome (body changes due to fat redistribution, accumulation, or loss of body fat), fatigue (extreme tiredness)

Uncommon:
- peripheral neuropathy (numbness, weakness, tingling or pain in the arms and legs)
- hypersensitivity (allergic reaction)
- asthenia (unusual tiredness or weakness)
- weight decreased, weight gain, anorexia (loss of appetite), appetite increased
- depression, anxiety, sleep disorder
- disorientation, amnesia (loss of memory), dizziness, somnolence (sleepiness), abnormal dream
- syncope (fainting), hypertension (high blood pressure)
- dyspnoea (shortness of breath)
- pancreatitis (inflammation of the pancreas), gastritis (inflammation of the stomach), stomatitis aphthous (mouth ulcers and cold sores), dysgeusia (impairment of the sense of taste), flatulence (wind), dry mouth, abdominal distension
- hepatitis (inflammation of the liver)
- urticaria (itchy rash), alopecia (unusual hair loss or thinning), pruritus (itching)
- muscle atrophy (muscle shrinkage), arthralgia (joint pain), myalgia (aching muscles)
- nephrolithiasis (formation of kidney stones), hematuria (blood in the urine), proteinuria (excess protein in the urine), pollakiuria (increased frequency of urination)
- gynaecomastia (breast enlargement in men)
- chest pain, malaise (generally feeling unwell), fever
- insomnia (difficulty sleeping)

Rare:
- gait disturbance (abnormal manner of walking)
- oedema (swelling), palpitation (fast or irregular heart beat)
- hepatosplenomegaly (enlargement of the liver and spleen)
- vesiculobullous rash (visible accumulation of fluid under the skin), eczema (skin rash), vasodilatation (widening of blood vessels)
- myopathy (aching muscles, muscle tenderness of weakness, not caused by exercise)
- kidney pain

Not known:
- Torsades de pointes (life threatening irregular heart beat)
- QTc prolongation (irregular heart beat)
- Diabetes mellitus (body cannot remove sugar from the blood normally)
- Hyperglycaemia (high sugar levels in the blood)
- Nephrolithiasis (kidney stones)

People who already have type A or B haemophilia may notice increased bleeding.

There have been reports of raised blood sugar and developing or worsening of diabetes in people using protease inhibitors. Also, there have been reports of unusual heart beat in both adult and paediatric patients using REYATAZ.

Changes in body fat have been seen in some patients taking antiretroviral therapy. These changes include increased amounts of fat in the upper back and neck ("buffalo hump"), breast, and around the abdomen ("belly"). Loss of fat from the legs, arms and face may also happen. The cause and long-term health effects of these conditions are not known at this time.

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your HIV doctor or nurse.
5. **HOW TO STORE REYATAZ**

- Keep out of the reach and sight of children.
- Do not use REYATAZ after the expiry date which is stated on the label, carton or blister. The expiry date refers to the last day of that month.
- Do not store above 25°C.

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6. **FURTHER INFORMATION**

**What REYATAZ contains**

- The active substance is atazanavir. Each capsule contains 100 mg of atazanavir (as sulphate).
- The other ingredients are crospovidone, lactose monohydrate, and magnesium stearate. The capsule shell and printing ink contain gelatine, shellac, ammonium hydroxide, simethicone, propylene glycol, indigocarmin (E132) and titanium dioxide (E171).

**What REYATAZ looks like and contents of the pack**

Each capsule of REYATAZ 100 mg contains 100 mg atazanavir.
Opaque blue and white capsule printed with white and blue inks, with "BMS 100 mg" on one half and with "3623" on the other half.

REYATAZ 100 mg hard capsules are supplied in bottles of 60 capsules.

REYATAZ 100 mg hard capsules are also supplied in blister strips in packs of 60 capsules.

REYATAZ also comes as a powder for adult patients who have difficulty swallowing capsules. REYATAZ oral powder must not be used in children who can not swallow the capsules.

Not all pack sizes may be marketed in all countries.

**The marketing authorisation holder of REYATAZ is:**

BRISTOL-MYERS SQUIBB PHARMA EEIG
Uxbridge Business Park
Sanderson Road
Uxbridge UB8 1DH
United Kingdom

**The manufacturer of REYATAZ is:**

BRISTOL-MYERS SQUIBB
Champ “Lachaud”, La Goualle
F-19250 Meymac
France

BRISTOL-MYERS SQUIBB
Rue du Docteur Gilles
F-28230 Epernon
France
BRISTOL-MYERS SQUIBB S.R.L.
Contrada Fontana del Cersao
03012 Anagni (FR)
Italy

For any further information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

**Belgique/België/Belgien**
BRISTOL-MYERS SQUIBB BELGIUM S.A./N.V.
Tél/Tel: + 32 2 352 76 11

**Luxembourg/Luxemburg**
BRISTOL-MYERS SQUIBB BELGIUM S.A./N.V.
Tél/Tel: + 32 2 352 76 11

**България**
BRISTOL-MYERS SQUIBB
ГЬОГЪЙСЪРКЕРЕСКЕДЕМЪ КФ.
Тел.: + 359 800 12 400

**Magyarország**
BRISTOL-MYERS SQUIBB
ГЬОГЪЙСЪРКЕРЕСКЕДЕМЪ КФ.
Тел.: + 36 1 301 9700

**Česká republika**
BRISTOL-MYERS SQUIBB SPOL. S R.O.
Tel: + 420 221 016 111

**Malta**
BRISTOL-MYERS SQUIBB S.R.L.
Tel: + 39 06 50 39 61

**Danmark**
BRISTOL-MYERS SQUIBB
Tlf: + 45 45 93 05 06

**Nederland**
BRISTOL-MYERS SQUIBB BV
Tel: + 31 34 857 42 22

**Deutschland**
BRISTOL-MYERS SQUIBB GMBH & CO. KGAA
Tel: + 49 89 121 42-0

**Norge**
BRISTOL-MYERS SQUIBB NORWAY LTD
Tlf: + 47 67 55 53 50

**Естонія**
BRISTOL-MYERS SQUIBB
ГЬОГЪЙСЪРКЕРЕСКЕДЕМЪ КФ.
Тел: + 372 6827 400

**Österreich**
BRISTOL-MYERS SQUIBB GESMBH
Tel: + 43 1 60 14 30

**Ελλάδα**
BRISTOL-MYERS SQUIBB A.E.
Τηλ: + 30 210 6074300

**Polska**
BRISTOL-MYERS SQUIBB POLSKA SP. Z O.O.
Tel.: + 48 22 5796666

**España**
BRISTOL-MYERS SQUIBB, S.A.
Tel: + 34 91 456 53 00

**Portugal**
BRISTOL-MYERS SQUIBB FARMACÊUTICA PORTUGUESA, S.A.
Tel: + 351 21 440 70 00

**France**
BRISTOL-MYERS SQUIBB SARL
Tél: + 33 (0)810 410 500

**România**
BRISTOL-MYERS SQUIBB
ГЬОГЪЙСЪРКЕРЕСКЕДЕМЪ КФ.
Тел: + 40 (0)21 272 16 00

**Ireland**
BRISTOL-MYERS SQUIBB PHARMACEUTICALS LTD
Tel: + 353 (1 800) 749 749

**Slovenija**
BRISTOL-MYERS SQUIBB SPOL. S R.O.
Tel: + 386 1 236 47 00

**Ísland**
VISTOR HF
Sími: + 354 535 7000

**Slovenská republika**
BRISTOL-MYERS SQUIBB SPOL. S R.O.
Tel: + 421 2 59298411
This leaflet was last approved in

Detailed information on this medicine is available on the European Medicines Agency (EMEA) website: http://www.emea.europa.eu/.
1. WHAT REYATAZ IS AND WHAT IT IS USED FOR

REYATAZ is an antiviral (or antiretroviral) medicine. It is one of a group called protease inhibitors. These medicines control Human Immunodeficiency Virus (HIV) infection by stopping a protein that the HIV needs for its multiplication. They work by reducing the amount of HIV in your body and this in turn, strengthens your immune system. In this way REYATAZ reduces the risk of developing illnesses linked to HIV infection.

Reyataz capsules may be used by adults and children 6 years of age and older. Your doctor has prescribed REYATAZ for you because you are infected by the HIV that causes Acquired Immunodeficiency Syndrome (AIDS). It is normally used in combination with other anti-HIV medicines. Your doctor will discuss with you which combination of these medicines with REYATAZ is best for you.

REYATAZ is not a cure for HIV infection. You may continue to develop infections or other illnesses linked to HIV infection. Treatment with REYATAZ does not reduce the risk of passing HIV to others through sexual contact or blood contamination. You must continue to take appropriate precautions to avoid giving the virus to others.

2 BEFORE YOU TAKE REYATAZ

Do not take REYATAZ

- if you are allergic (hypersensitive) to atazanavir or any of the other ingredients of REYATAZ
- if you have moderate to severe liver problems. Your doctor will evaluate how severe your liver disease is before deciding whether you can take REYATAZ
- if you are taking any of these medicines: see also Taking other medicines with REYATAZ
  - rifampicin, an antibiotic used to treat tuberculosis
  - astemizole or terfenadine (commonly used to treat allergy symptoms, these medicines may be available without prescription); cisapride (used to treat gastric reflux, sometimes called heartburn); pimozide (used to treat schizophrenia); quinidine or bepridil (used to correct heart rhythm); ergotamine, dihydroergotamine, ergonovine, methylergonovine (used to treat headaches)
  - medicines containing St. John’s wort (Hypericum perforatum, a herbal preparation).
- triazolam and oral (taken by mouth) midazolam (used to help you sleep and/or to relieve anxiety).

Tell your doctor at once if any of these apply to you.

**Take special care with REYATAZ**

Some people will need special care before or while taking REYATAZ. Before taking this medicine, make sure your doctor knows:

- if you have hepatitis B or C
- if you have type A or B haemophilia
- if you have diabetes
- if you require haemodialysis
- if you are taking oral contraceptives ("the Pill") to prevent pregnancy
- if you are taking omeprazole or other proton pump inhibitors; or famotidine or other H2-receptor antagonists (used to treat diseases related to the acid in the stomach)
- if you notice changes in body fat. Redistribution, accumulation, or loss of body fat may occur in patients receiving antiretroviral therapy

Kidney stones have been reported in patients taking REYATAZ. If you develop signs or symptoms of kidney stones (pain in your side, blood in your urine, pain when you urinate), please inform your doctor immediately.

In some patients with advanced HIV infection (AIDS) and a history of opportunistic infection, signs and symptoms of inflammation from previous infections may occur soon after anti-HIV treatment is started. It is believed that these symptoms are due to an improvement in the body’s immune response, enabling the body to fight infections that may have been present with no obvious symptoms. If you notice any symptoms of infection, please inform your doctor immediately.

Some patients taking combination antiretroviral therapy may develop a bone disease called osteonecrosis (death of bone tissue caused by loss of blood supply to the bone). The length of combination antiretroviral therapy, corticosteroid use, alcohol consumption, severe immunosuppression, higher body mass index, among others, may be some of the many risk factors for developing this disease. Signs of osteonecrosis are joint stiffness, aches and pains (especially of the hip, knee and shoulder) and difficulty in movement. If you notice any of these symptoms please inform your doctor.

Hyperbilirubinaemia (an increase in the level of bilirubin in the blood) has occurred in patients receiving REYATAZ. The signs may be a mild yellowing of the skin or eyes. If you notice any of these symptoms please inform your doctor.

If you notice a change in the way your heart beats (heart rhythm changes), please inform your doctor.

**Use in Children**

REYATAZ capsules can be taken by children at least 6 years of age and older and weighing at least 15 kg who are able to swallow the capsules (see How to take REYATAZ).

Children receiving REYATAZ may require their heart to be monitored. Your child's doctor will decide this.

**Taking other medicines**

**You must not take REYATAZ with certain medicines.** These are listed under Do not take REYATAZ, at the start of Section 2.

There are other medicines that may not mix with REYATAZ. Please tell your doctor if you are taking or have recently taken any other medicines including medicines obtained without a prescription. It is especially important to mention these:
other medicines to treat HIV infection
sildenafil (used by men to treat impotence (erectile dysfunction))
if you are taking an oral contraceptive ("the Pill") with REYATAZ, be sure to take it exactly as instructed by your doctor and not miss any doses.
any medicines used to treat diseases related to the acid in the stomach (e.g. antacids, H2-blockers and proton pump inhibitors)
medicines to lower blood pressure, to slow heart rate, or to correct heart rhythm
simvastatin, lovastatin, and atorvastatin (used to lower blood cholesterol)
nevirapine and efavirenz (used to treat HIV)
cyclosporin, tacrolimus, and sirolimus (medicines to decrease the effects of body's immune system)
certain antibiotics (rifabutin, clarithromycin)
ketoconazole, itraconazole, and voriconazole (antifungals)
warfarin (anticoagulant, used to reduce the blood clots)
irinotecan (used to treat cancer)
sedative agents (e.g. midazolam administered by injection)
buprenorphine (used to treat opioid addiction and pain).

Some medicines may interact with ritonavir, a medicine that is taken with REYATAZ. It is important to tell your doctor if you are taking fluticasone or budesonide (given by nose or inhaled to treat allergic symptoms or asthma).

Taking REYATAZ with food and drink

It is important that you take REYATAZ with food (a meal or a substantial snack) as this helps the body absorb the medicine.

Pregnancy and breast-feeding

Tell your doctor if you are pregnant or planning to become pregnant. Also be sure to tell your doctor if you are breast-feeding. It is recommended that women infected with HIV do not breast-feed because the virus might be transmitted through the breast milk.

Driving and using machines

No studies on the effects on the ability to drive and use machines have been performed. If you feel dizzy or lightheaded, contact your doctor immediately.

Important information about some of the ingredients of REYATAZ

If you have been told by your doctor that you have an intolerance to some sugars (e.g. lactose), contact your doctor before taking this medicinal product.

3. HOW TO TAKE REYATAZ

Always take REYATAZ exactly as your doctor has told you. You should check with your doctor if you are not sure. This way, you can be sure your medicine is fully effective and you reduce the risk of the virus developing resistance to the treatment.

The usual adult dose of REYATAZ capsules is 300 mg once daily with 100 mg ritonavir once daily and with food, in combination with other anti-HIV medicines. Your doctor may adjust the dose of REYATAZ according to your anti-HIV therapy.

For children (6 to less than 18 years of age), your child's doctor will decide the right dose based on your child's weight. The dose of REYATAZ capsules for children is calculated by body weight and is taken once daily with food and 100 mg ritonavir as shown below:
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*Ritonavir capsules, tablets or oral solution may be used.

There are no dosing recommendations for REYATAZ in paediatric patients less than 6 years of age or weighting less than 15 kg.

**Take REYATAZ capsules with food** (a meal or a substantial snack). Swallow the capsules whole. 
**Do not open the capsules.**

**If you take more REYATAZ than you should**

If you accidentally take more REYATAZ capsules than your doctor recommended, contact your HIV doctor at once or contact the nearest hospital for advice.

**If you forget to take REYATAZ**

If you miss a dose, take the missed dose as soon as possible with food and then take your next scheduled dose at its regular time. If it is almost time for your next dose, do not take the missed dose. Wait and take the next dose at its regular time. **Do not take a double dose to make up for a forgotten dose.**

**If you stop taking REYATAZ**

Do not stop taking REYATAZ before talking to your doctor.

**If you have any further questions on the use of this product, ask your doctor.**

4. **POSSIBLE SIDE EFFECTS**

Like all medicines, REYATAZ can cause side effects, although not everybody gets them. When treating HIV infection, it is not always easy to identify what side effects are caused by REYATAZ, by the other medicines you are taking, or by the HIV infection itself. Tell your doctor if you notice anything unusual about your health.

The frequency of possible side effects listed below is defined using the following convention:

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Patients treated with REYATAZ have reported the following side effects:

**Common:**
- headache
- ocular icterus (presence of jaundice seen in the white part of the eyes)
- vomiting, diarrhoea, abdominal pain (stomach pain of discomfort), nausea, dyspepsia (indigestion)
• jaundice (yellowing of the skin and/or eyes)
• rash
• lipodistrophy syndrome (body changes due to fat redistribution, accumulation, or loss of body fat), fatigue (extreme tiredness)

Uncommon:
• peripheral neuropathy (numbness, weakness, tingling or pain in the arms and legs)
• hypersensitivity (allergic reaction)
• asthenia (unusual tiredness or weakness)
• weight decreased, weight gain, anorexia (loss of appetite), appetite increased
• depression, anxiety, sleep disorder
• disorientation, amnesia (loss of memory), dizziness, somnolence (sleepiness), abnormal dream
• syncope (fainting), hypertension (high blood pressure)
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• pancreatitis (inflammation of the pancreas), gastritis (inflammation of the stomach), stomatitis aphthous (mouth ulcers and cold sores), dysgeusia (impairment of the sense of taste), flatulence (wind), dry mouth, abdominal distension
• hepatitis (inflammation of the liver)
• urticaria (itchy rash), alopecia (unusual hair loss or thinning), pruritus (itching)
• muscle atrophy (muscle shrinkage), arthralgia (joint pain), myalgia (aching muscles)
• nephrolithiasis (formation of kidney stones), hematuria (blood in the urine), proteinuria (excess protein in the urine), pollakiuria (increased frequency of urination)
• gynaecomastia (breast enlargement in men)
• chest pain, malaise (generally feeling unwell), fever
• insomnia (difficulty sleeping)

Rare:
• gait disturbance (abnormal manner of walking)
• oedema (swelling), palpitation (fast or irregular heart beat)
• hepatosplenomegaly (enlargement of the liver and spleen)
• vesiculobullous rash (visible accumulation of fluid under the skin), eczema (skin rash), vasodilatation (widening of blood vessels)
• myopathy (aching muscles, muscle tenderness of weakness, not caused by exercise)
• kidney pain

Not known:
• Torsades de pointes (life threatening irregular heart beat)
• QTc prolongation (irregular heart beat)
• Diabetes mellitus (body cannot remove sugar from the blood normally)
• Hyperglycaemia (high sugar levels in the blood)
• Nephrolithiasis (kidney stones)
• Gallbladder disorders (gallstones and gallbladder inflammation)

People who already have type A or B haemophilia may notice increased bleeding.

There have been reports of raised blood sugar and developing or worsening of diabetes in people using protease inhibitors. Also, there have been reports of unusual heart beat in both adult and paediatric patients using REYATAZ.

Changes in body fat have been seen in some patients taking antiretroviral therapy. These changes include increased amounts of fat in the upper back and neck ("buffalo hump"), breast, and around the abdomen ("belly"). Loss of fat from the legs, arms and face may also happen. The cause and long-term health effects of these conditions are not known at this time.

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your HIV doctor or nurse.
5. **HOW TO STORE REYATAZ**

- Keep out of the reach and sight of children.
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- Do not store above 25°C.

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6. **FURTHER INFORMATION**

**What REYATAZ contains**

- The active substance is atazanavir. Each capsule contains 150 mg of atazanavir (as sulphate).
- The other ingredients are crospovidone, lactose monohydrate, and magnesium stearate. The capsule shell and printing ink contain gelatine, shellac, ammonium hydroxide, simethicone, propylene glycol, indigocarmin (E132) and titanium dioxide (E171).

**What REYATAZ looks like and contents of the pack**

Each capsule of REYATAZ 150 mg contains 150 mg atazanavir.
Opaque blue and powder blue capsule printed with white and blue inks, with "BMS 150 mg" on one half and with "3624" on the other half.

REYATAZ 150 mg hard capsules are supplied in bottles of 60 capsules.
REYATAZ 150 mg hard capsules are also supplied in blister strips in packs of 60 capsules.
REYATAZ also comes as a powder for adult patients who have difficulty swallowing capsules. REYATAZ oral powder must not be used in children who can not swallow the capsules.

Not all pack sizes may be marketed in all countries.

**The marketing authorisation holder of REYATAZ is:**

BRISTOL-MYERS SQUIBB PHARMA EEIG
Uxbridge Business Park
Sanderson Road
Uxbridge UB8 1DH
United Kingdom

**The manufacturer of REYATAZ is:**

BRISTOL-MYERS SQUIBB
Champ “Lachaud”, La Goualle
F-19250 Meymac
France

BRISTOL-MYERS SQUIBB
Rue du Docteur Gilles
F-28230 Epernon
France
For any further information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

<table>
<thead>
<tr>
<th>Country</th>
<th>BRISTOL-MYERS SQUIBB S.R.L.</th>
<th>Tél/Tel:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Belgium</td>
<td>BRISTOL-MYERS SQUIBB BELGIUM S.A./N.V.</td>
<td>+ 32 2 352 76 11</td>
</tr>
<tr>
<td>Bulgaria</td>
<td>BRISTOL-MYERS SQUIBB</td>
<td>+ 359 800 12 400</td>
</tr>
<tr>
<td>Czech Republic</td>
<td>BRISTOL-MYERS SQUIBB SPOL. S.R.O.</td>
<td>+ 420 221 016 111</td>
</tr>
<tr>
<td>Denmark</td>
<td>BRISTOL-MYERS SQUIBB</td>
<td>+ 45 45 93 05 06</td>
</tr>
<tr>
<td>Estonia</td>
<td>BRISTOL-MYERS SQUIBB</td>
<td>+ 372 6827 400</td>
</tr>
<tr>
<td>Greece</td>
<td>BRISTOL-MYERS SQUIBB A.E.</td>
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</tr>
<tr>
<td>Spain</td>
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<td>+ 34 91 456 53 00</td>
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<tr>
<td>France</td>
<td>BRISTOL-MYERS SQUIBB SARL</td>
<td>+ 33 (0)810 410 500</td>
</tr>
<tr>
<td>Ireland</td>
<td>BRISTOL-MYERS SQUIBB PHARMACEUTICALS LTD</td>
<td>+ 353 (1 800) 749 749</td>
</tr>
<tr>
<td>Iceland</td>
<td>VISTOR HF</td>
<td>+ 354 535 7000</td>
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<td>Luxembourg</td>
<td>BRISTOL-MYERS SQUIBB BELGIUM S.A./N.V.</td>
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</tr>
<tr>
<td>Hungary</td>
<td>BRISTOL-MYERS SQUIBB</td>
<td>+ 36 1 301 9700</td>
</tr>
<tr>
<td>Malta</td>
<td>BRISTOL-MYERS SQUIBB S.R.L.</td>
<td>+ 39 06 50 39 61</td>
</tr>
<tr>
<td>The Netherlands</td>
<td>BRISTOL-MYERS SQUIBB BV</td>
<td>+ 31 34 857 42 22</td>
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<tr>
<td>Norway</td>
<td>BRISTOL-MYERS SQUIBB NORWAY LTD</td>
<td>+ 47 67 55 53 50</td>
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<tr>
<td>Austria</td>
<td>BRISTOL-MYERS SQUIBB GESMBH</td>
<td>+ 43 1 60 14 30</td>
</tr>
<tr>
<td>Poland</td>
<td>BRISTOL-MYERS SQUIBB POLSKA SP. Z.O.O.</td>
<td>+ 48 22 5796666</td>
</tr>
<tr>
<td>Portugal</td>
<td>BRISTOL-MYERS SQUIBB FARMACÊUTICA</td>
<td>+ 351 21 440 70 00</td>
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<tr>
<td>Romania</td>
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<td>+ 40 (0)21 272 16 00</td>
</tr>
<tr>
<td>Slovenia</td>
<td>BRISTOL-MYERS SQUIBB</td>
<td>+ 386 1 236 47 00</td>
</tr>
<tr>
<td>Slovak Republic</td>
<td>BRISTOL-MYERS SQUIBB</td>
<td>+ 421 2 59298411</td>
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</table>
Italia
BRISTOL-MYERS SQUIBB S.R.L.
Tel: + 39 06 50 39 61

Suomi/Finland
OY BRISTOL-MYERS SQUIBB (FINLAND) AB
Puh/Tel: + 358 9 251 21 230

Κύπρος
BRISTOL-MYERS SQUIBB A.E
Τηλ: + 357 800 92666

Sverige
BRISTOL-MYERS SQUIBB AB
Tel: + 46 8 704 71 00

Latvija
BRISTOL-MYERS SQUIBB
GYÓGYSZERKERESKEDELMI KFT.
Tel: + 371 67 50 21 85

United Kingdom
BRISTOL-MYERS SQUIBB PHARMACEUTICALS LTD
Tel: + 44 (0800) 731 1736

Lietuva
BRISTOL-MYERS SQUIBB
GYÓGYSZERKERESKEDELMI KFT.
Tel: + 370 5 2790 762

This leaflet was last approved in

Detailed information on this medicine is available on the European Medicines Agency (EMEA) web site: http://www.emea.europa.eu/.
Read all of this leaflet carefully before you start taking this medicine.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others.
- It may harm them, even if their symptoms are the same as yours.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor.

In this leaflet:
1. What REYATAZ is and what it is used for
2. Before you take REYATAZ
3. How to take REYATAZ
4. Possible side effects
5. How to store REYATAZ
6. Further information

1. WHAT REYATAZ IS AND WHAT IT IS USED FOR

REYATAZ is an antiviral (or antiretroviral) medicine. It is one of a group called protease inhibitors. These medicines control Human Immunodeficiency Virus (HIV) infection by stopping a protein that the HIV needs for its multiplication. They work by reducing the amount of HIV in your body and this in turn, strengthens your immune system. In this way REYATAZ reduces the risk of developing illnesses linked to HIV infection.

Reyataz capsules may be used by adults and children 6 years of age and older. Your doctor has prescribed REYATAZ for you because you are infected by the HIV that causes Acquired Immunodeficiency Syndrome (AIDS). It is normally used in combination with other anti-HIV medicines. Your doctor will discuss with you which combination of these medicines with REYATAZ is best for you.

REYATAZ is not a cure for HIV infection. You may continue to develop infections or other illnesses linked to HIV infection. Treatment with REYATAZ does not reduce the risk of passing HIV to others through sexual contact or blood contamination. You must continue to take appropriate precautions to avoid giving the virus to others.

2. BEFORE YOU TAKE REYATAZ

Do not take REYATAZ

- if you are allergic (hypersensitive) to atazanavir or any of the other ingredients of REYATAZ
- if you have moderate to severe liver problems. Your doctor will evaluate how severe your liver disease is before deciding whether you can take REYATAZ
- if you are taking any of these medicines: see also Taking other medicines with REYATAZ
  - rifampicin, an antibiotic used to treat tuberculosis
  - astemizole or terfenadine (commonly used to treat allergy symptoms, these medicines may be available without prescription); cisapride (used to treat gastric reflux, sometimes called heartburn); pimozide (used to treat schizophrenia); quinidine or bepridil (used to correct heart rhythm); ergotamine, dihydroergotamine, ergonovine, methylergonovine (used to treat headaches)
  - medicines containing St. John’s wort (Hypericum perforatum, a herbal preparation).
- triazolam and oral (taken by mouth) midazolam (used to help you sleep and/or to relieve anxiety).

Tell your doctor at once if any of these apply to you.

**Take special care with REYATAZ**

Some people will need special care before or while taking REYATAZ. Before taking this medicine, make sure your doctor knows:
- if you have hepatitis B or C
- if you have type A or B haemophilia
- if you have diabetes
- if you require haemodialysis
- if you are taking oral contraceptives ("the Pill") to prevent pregnancy
- if you are taking omeprazole or other proton pump inhibitors; or famotidine or other H2-receptor antagonists (used to treat diseases related to the acid in the stomach)
- if you notice changes in body fat. Redistribution, accumulation, or loss of body fat may occur in patients receiving antiretroviral therapy

Kidney stones have been reported in patients taking REYATAZ. If you develop signs or symptoms of kidney stones (pain in your side, blood in your urine, pain when you urinate), please inform your doctor immediately.

In some patients with advanced HIV infection (AIDS) and a history of opportunistic infection, signs and symptoms of inflammation from previous infections may occur soon after anti-HIV treatment is started. It is believed that these symptoms are due to an improvement in the body’s immune response, enabling the body to fight infections that may have been present with no obvious symptoms. If you notice any symptoms of infection, please inform your doctor immediately.

Some patients taking combination antiretroviral therapy may develop a bone disease called osteonecrosis (death of bone tissue caused by loss of blood supply to the bone). The length of combination antiretroviral therapy, corticosteroid use, alcohol consumption, severe immunosuppression, higher body mass index, among others, may be some of the many risk factors for developing this disease. Signs of osteonecrosis are joint stiffness, aches and pains (especially of the hip, knee and shoulder) and difficulty in movement. If you notice any of these symptoms please inform your doctor.

Hyperbilirubinaemia (an increase in the level of bilirubin in the blood) has occurred in patients receiving REYATAZ. The signs may be a mild yellowing of the skin or eyes. If you notice any of these symptoms please inform your doctor.

If you notice a change in the way your heart beats (heart rhythm changes), please inform your doctor.

**Use in Children**

REYATAZ capsules can be taken by children at least 6 years of age and older and weighing at least 15 kg who are able to swallow the capsules (see How to take REYATAZ).

Children receiving REYATAZ may require their heart to be monitored. Your child's doctor will decide this.

**Taking other medicines**

**You must not take REYATAZ with certain medicines.** These are listed under Do not take REYATAZ, at the start of Section 2.

There are other medicines that may not mix with REYATAZ. Please tell your doctor if you are taking or have recently taken any other medicines including medicines obtained without a prescription. It is especially important to mention these:
- other medicines to treat HIV infection
- sildenafil (used by men to treat impotence (erectile dysfunction))
- if you are taking an oral contraceptive ("the Pill") with REYATAZ, be sure to take it exactly as instructed by your doctor and not miss any doses.
- any medicines used to treat diseases related to the acid in the stomach (e.g. antacids, H2-blockers and proton pump inhibitors)
- medicines to lower blood pressure, to slow heart rate, or to correct heart rhythm
- simvastatin, lovastatin, and atorvastatin (used to lower blood cholesterol)
- nevirapine and efavirenz (used to treat HIV)
- cyclosporin, tacrolimus, and sirolimus (medicines to decrease the effects of body's immune system)
- certain antibiotics (rifabutin, clarithromycin)
- ketoconazole, itraconazole, and voriconazole (antifungals)
- warfarin (anticoagulant, used to reduce the blood clots)
- irinotecan (used to treat cancer)
- sedative agents (e.g. midazolam administered by injection)
- buprenorphine (used to treat opioid addiction and pain).

Some medicines may interact with ritonavir, a medicine that is taken with REYATAZ. It is important to tell your doctor if you are taking fluticasone or budesonide (given by nose or inhaled to treat allergic symptoms or asthma).

**Taking REYATAZ with food and drink**

It is important that you take REYATAZ with food (a meal or a substantial snack) as this helps the body absorb the medicine.

**Pregnancy and breast-feeding**

Tell your doctor if you are pregnant or planning to become pregnant. Also be sure to tell your doctor if you are breast-feeding. It is recommended that women infected with HIV do not breast-feed because the virus might be transmitted through the breast milk.

**Driving and using machines**

No studies on the effects on the ability to drive and use machines have been performed. If you feel dizzy or lightheaded, contact your doctor immediately.

**Important information about some of the ingredients of REYATAZ**

If you have been told by your doctor that you have an intolerance to some sugars (e.g. lactose), contact your doctor before taking this medicinal product.

3. **HOW TO TAKE REYATAZ**

Always take REYATAZ exactly as your doctor has told you. You should check with your doctor if you are not sure. This way, you can be sure your medicine is fully effective and you reduce the risk of the virus developing resistance to the treatment.

**The usual adult dose of REYATAZ capsules is 300 mg once daily with 100 mg ritonavir once daily and with food,** in combination with other anti-HIV medicines. Your doctor may adjust the dose of REYATAZ according to your anti-HIV therapy.

For children (6 to less than 18 years of age), your child's doctor will decide the right dose based on your child's weight. The dose of REYATAZ capsules for children is calculated by body weight and is taken once daily with food and 100 mg ritonavir as shown below:
<table>
<thead>
<tr>
<th>Body Weight (kg)</th>
<th>REYATAZ Dose once daily (mg)</th>
<th>Ritonavir Dose* once daily (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>15 to less than 20</td>
<td>150</td>
<td>100</td>
</tr>
<tr>
<td>20 to less than 40</td>
<td>200</td>
<td>100</td>
</tr>
<tr>
<td>at least 40</td>
<td>300</td>
<td>100</td>
</tr>
</tbody>
</table>

*Ritonavir capsules, tablets or oral solution may be used.

There are no dosing recommendations for REYATAZ in paediatric patients less than 6 years of age or weighing less than 15 kg.

**Take REYATAZ capsules with food** (a meal or a substantial snack). Swallow the capsules whole. **Do not open the capsules.**

**If you take more REYATAZ than you should**

If you accidentally take more REYATAZ capsules than your doctor recommended, contact your HIV doctor at once or contact the nearest hospital for advice.

**If you forget to take REYATAZ**

If you miss a dose, take the missed dose as soon as possible with food and then take your next scheduled dose at its regular time. If it is almost time for your next dose, do not take the missed dose. Wait and take the next dose at its regular time. **Do not take a double dose to make up for a forgotten dose.**

**If you stop taking REYATAZ**

Do not stop taking REYATAZ before talking to your doctor.

**If you have any further questions on the use of this product, ask your doctor.**

### 4. POSSIBLE SIDE EFFECTS

Like all medicines, REYATAZ can cause side effects, although not everybody gets them. When treating HIV infection, it is not always easy to identify what side effects are caused by REYATAZ, by the other medicines you are taking, or by the HIV infection itself. Tell your doctor if you notice anything unusual about your health.

The frequency of possible side effects listed below is defined using the following convention:

<table>
<thead>
<tr>
<th>Frequency</th>
<th>Description</th>
</tr>
</thead>
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<tr>
<td>very common:</td>
<td>affects more than 1 user in 10</td>
</tr>
<tr>
<td>common:</td>
<td>affects 1 to less than 10 users in 100</td>
</tr>
<tr>
<td>uncommon:</td>
<td>affects 1 to less than 10 users in 1,000</td>
</tr>
<tr>
<td>rare:</td>
<td>affects 1 to less than 10 users in 10,000</td>
</tr>
<tr>
<td>very rare:</td>
<td>affects less than 1 user in 10,000</td>
</tr>
<tr>
<td>not known:</td>
<td>frequency cannot be estimated from the available data</td>
</tr>
</tbody>
</table>

Patients treated with REYATAZ have reported the following side effects:

**Common:**
- headache
- ocular icterus (presence of jaundice seen in the white part of the eyes)
- vomiting, diarrhoea, abdominal pain (stomach pain of discomfort), nausea, dyspepsia (indigestion)
- jaundice (yellowing of the skin and/or eyes)
- rash
- lipodistrophy syndrome (body changes due to fat redistribution, accumulation, or loss of body fat), fatigue (extreme tiredness)

Uncommon:
- peripheral neuropathy (numbness, weakness, tingling or pain in the arms and legs)
- hypersensitivity (allergic reaction)
- asthenia (unusual tiredness or weakness)
- weight decreased, weight gain, anorexia (loss of appetite), appetite increased
- depression, anxiety, sleep disorder
- disorientation, amnesia (loss of memory), dizziness, somnolence (sleepiness), abnormal dream
- syncope (fainting), hypertension (high blood pressure)
- dyspnoea (shortness of breath)
- pancreatitis (inflammation of the pancreas), gastritis (inflammation of the stomach), stomatitis aphthous (mouth ulcers and cold sores), dysgeusia (impairment of the sense of taste), flatulence (wind), dry mouth, abdominal distension
- hepatitis (inflammation of the liver)
- urticaria (itchy rash), alopecia (unusual hair loss or thinning), pruritus (itching)
- muscle atrophy (muscle shrinkage), arthralgia (joint pain), myalgia (aching muscles)
- nephrolithiasis (formation of kidney stones), hematuria (blood in the urine), proteinuria (excess protein in the urine), pollakiuria (increased frequency of urination)
- gynaecomastia (breast enlargement in men)
- chest pain, malaise (generally feeling unwell), fever
- insomnia (difficulty sleeping)

Rare:
- gait disturbance (abnormal manner of walking)
- oedema (swelling), palpitation (fast or irregular heart beat)
- hepatosplenomegaly (enlargement of the liver and spleen)
- vesiculobullous rash (visible accumulation of fluid under the skin), eczema (skin rash), vasodilatation (widening of blood vessels)
- myopathy (aching muscles, muscle tenderness of weakness, not caused by exercise)
- kidney pain

Not known:
- Torsades de pointes (life threatening irregular heart beat)
- QTc prolongation (irregular heart beat)
- Diabetes mellitus (body cannot remove sugar from the blood normally)
- Hyperglycaemia (high sugar levels in the blood)
- Nephrolithiasis (kidney stones)
- Gallbladder disorders (gallstones and gallbladder inflammation)

People who already have type A or B haemophilia may notice increased bleeding.

There have been reports of raised blood sugar and developing or worsening of diabetes in people using protease inhibitors. Also, there have been reports of unusual heart beat in both adult and paediatric patients using REYATAZ.

Changes in body fat have been seen in some patients taking antiretroviral therapy. These changes include increased amounts of fat in the upper back and neck ("buffalo hump"), breast, and around the abdomen ("belly"). Loss of fat from the legs, arms and face may also happen. The cause and long-term health effects of these conditions are not known at this time.

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your HIV doctor or nurse.
5. **HOW TO STORE REYATAZ**

- Keep out of the reach and sight of children.
- Do not use REYATAZ after the expiry date which is stated on the label, carton or blister. The expiry date refers to the last day of that month.
- Do not store above 25°C.

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6. **FURTHER INFORMATION**

**What REYATAZ contains**

- The active substance is atazanavir. Each capsule contains 200 mg of atazanavir (as sulphate).
- The other ingredients are crospovidone, lactose monohydrate, and magnesium stearate. The capsule shell and printing ink contain gelatine, shellac, ammonium hydroxide, simethicone, propylene glycol, indigocarmin (E132) and titanium dioxide (E171).

**What REYATAZ looks like and contents of the pack**

Each capsule of REYATAZ 200 mg contains 200 mg atazanavir.
Opaque blue capsule printed with white ink, with "BMS 200 mg" on one half and with "3631" on the other half.

REYATAZ 200 mg hard capsules are supplied in bottles of 60 capsules.

REYATAZ 200 mg hard capsules are also supplied in blister strips in packs of 60 capsules.

REYATAZ also comes as a powder for adult patients who have difficulty swallowing capsules.
REYATAZ oral powder must not be used in children who can not swallow the capsules.

Not all pack sizes may be marketed in all countries.

**The marketing authorisation holder of REYATAZ is:**

BRISTOL-MYERS SQUIBB PHARMA EEIG
Uxbridge Business Park
Sanderson Road
Uxbridge UB8 1DH
United Kingdom

**The manufacturer of REYATAZ is:**

BRISTOL-MYERS SQUIBB
Champ “Lachaud”, La Goualle
F-19250 Meymac
France

BRISTOL-MYERS SQUIBB
Rue du Docteur Gilles
F-28230 Epernon
France
BRISTOL-MYERS SQUIBB S.R.L.
Contrada Fontana del Ceraso
03012 Anagni (FR)
Italy

For any further information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

**Belgique/België/Belgien**
BRISTOL-MYERS SQUIBB BELGIUM S.A./N.V.
Tél/Tel: + 32 2 352 76 11

**Hungary**
BRISTOL-MYERS SQUIBB
GYÓGYSZERKERESKEDELMI KFT.
Tel.: + 36 1 301 9700

**Czech republic**
BRISTOL-MYERS SQUIBB spol. s r.o.
Tel: + 420 221 016 111

**Danmark**
BRISTOL-MYERS SQUIBB
Tlf: + 45 45 93 05 06

**Deutschland**
BRISTOL-MYERS SQUIBB GMBH & CO. KGAA
Tel: + 49 89 121 42-0

**Estonia**
BRISTOL-MYERS SQUIBB
GYÓGYSZERKERESKEDELMI KFT.
Tel: + 372 6827 400

**Elláda**
BRISTOL-MYERS SQUIBB A.E.
Τηλ: + 30 210 6074300

**España**
BRISTOL-MYERS SQUIBB, S.A.
Tel: + 34 91 456 53 00

**France**
BRISTOL-MYERS SQUIBB SARL
Tél: + 33 (0)810 410 500

**Ireland**
BRISTOL-MYERS SQUIBB PHARMACEUTICALS LTD
Tel: + 353 (1 800) 749 749

**Ísland**
VISTOR HF
Sími: + 354 535 7000

**Luxembourg/Luxemburg**
BRISTOL-MYERS SQUIBB BELGIUM S.A./N.V.
Tél/Tel: + 32 2 352 76 11

**Magyarország**
BRISTOL-MYERS SQUIBB
GYÓGYSZERKERESKEDELMI KFT.
Tel.: + 36 1 301 9700

**Malta**
BRISTOL-MYERS SQUIBB S.R.L.
Tel: + 39 06 50 39 61

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BRISTOL-MYERS SQUIBB BV
Tel: + 31 34 857 42 22

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BRISTOL-MYERS SQUIBB NORWAY LTD
Tlf: + 47 67 55 53 50

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Tel: + 43 1 60 14 30

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BRISTOL-MYERS SQUIBB POLSKA SP. Z O.O.
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**Slovenská republika**
BRISTOL-MYERS SQUIBB spol. s r.o.
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- sildenafil (used by men to treat impotence (erectile dysfunction))
- if you are taking an oral contraceptive ("the Pill") with REYATAZ, be sure to take it exactly as instructed by your doctor and not miss any doses.
- any medicines used to treat diseases related to the acid in the stomach (e.g. antacids, H₂-blockers and proton pump inhibitors)
- medicines to lower blood pressure, to slow heart rate, or to correct heart rhythm
- simvastatin, lovastatin, and atorvastatin (used to lower blood cholesterol)
- nevirapine and efavirenz (used to treat HIV)
- cyclosporin, tacrolimus, and sirolimus (medicines to decrease the effects of body's immune system)
- certain antibiotics (rifabutin, clarithromycin)
- ketoconazole, itraconazole, and voriconazole (antifungals)
- warfarin (anticoagulant, used to reduce the blood clots)
- irinotecan (used to treat cancer)
- sedative agents (e.g. midazolam administered by injection)
- buprenorphine (used to treat opioid addiction and pain).

Some medicines may interact with ritonavir, a medicine that is taken with REYATAZ. It is important to tell your doctor if you are taking fluticasone or budesonide (given by nose or inhaled to treat allergic symptoms or asthma).

**Taking REYATAZ with food and drink**

It is important that you take REYATAZ with food (a meal or a substantial snack) as this helps the body absorb the medicine.

**Pregnancy and breast-feeding**

Tell your doctor if you are pregnant or planning to become pregnant. Also be sure to tell your doctor if you are breast-feeding. It is recommended that women infected with HIV do not breast-feed because the virus might be transmitted through the breast milk.

**Driving and using machines**

No studies on the effects on the ability to drive and use machines have been performed. If you feel dizzy or lightheaded, contact your doctor immediately.

**Important information about some of the ingredients of REYATAZ**

If you have been told by your doctor that you have an intolerance to some sugars (e.g. lactose), contact your doctor before taking this medicinal product.

### 3. HOW TO TAKE REYATAZ

Always take REYATAZ exactly as your doctor has told you. You should check with your doctor if you are not sure. This way, you can be sure your medicine is fully effective and you reduce the risk of the virus developing resistance to the treatment.

**The usual adult dose of REYATAZ capsules is 300 mg once daily with 100 mg ritonavir once daily and with food,** in combination with other anti-HIV medicines. Your doctor may adjust the dose of REYATAZ according to your anti-HIV therapy.

For children (6 to less than 18 years of age), your child's doctor will decide the right dose based on your child's weight. The dose of REYATAZ capsules for children is calculated by body weight and is taken once daily with food and 100 mg ritonavir as shown below:
### Body Weight

<table>
<thead>
<tr>
<th>Body Weight (kg)</th>
<th>REYATAZ Dose once daily (mg)</th>
<th>Ritonavir Dose* once daily (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>15 to less than 20</td>
<td>150</td>
<td>100</td>
</tr>
<tr>
<td>20 to less than 40</td>
<td>200</td>
<td>100</td>
</tr>
<tr>
<td>at least 40</td>
<td>300</td>
<td>100</td>
</tr>
</tbody>
</table>

*Ritonavir capsules, tablets or oral solution may be used.

There are no dosing recommendations for REYATAZ in paediatric patients less than 6 years of age or weighing less than 15 kg.

**Take REYATAZ capsules with food** (a meal or a substantial snack). Swallow the capsules whole. **Do not open the capsules.**

**If you take more REYATAZ than you should**

If you accidentally take more REYATAZ capsules than your doctor recommended, contact your HIV doctor at once or contact the nearest hospital for advice.

**If you forget to take REYATAZ**

If you miss a dose, take the missed dose as soon as possible with food and then take your next scheduled dose at its regular time. If it is almost time for your next dose, do not take the missed dose. Wait and take the next dose at its regular time. **Do not take a double dose to make up for a forgotten dose.**

**If you stop taking REYATAZ**

Do not stop taking REYATAZ before talking to your doctor.

**If you have any further questions on the use of this product, ask your doctor.**

### 4. POSSIBLE SIDE EFFECTS

Like all medicines, REYATAZ can cause side effects, although not everybody gets them. When treating HIV infection, it is not always easy to identify what side effects are caused by REYATAZ, by the other medicines you are taking, or by the HIV infection itself. Tell your doctor if you notice anything unusual about your health.

The frequency of possible side effects listed below is defined using the following convention:

<table>
<thead>
<tr>
<th>Category</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>very common:</td>
<td>affects more than 1 user in 10</td>
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<tr>
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<td>affects 1 to less than 10 users in 100</td>
</tr>
<tr>
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<td>affects 1 to less than 10 users in 1,000</td>
</tr>
<tr>
<td>rare:</td>
<td>affects 1 to less than 10 users in 10,000</td>
</tr>
<tr>
<td>very rare:</td>
<td>affects less than 1 user in 10,000</td>
</tr>
<tr>
<td>not known:</td>
<td>frequency cannot be estimated from the available data</td>
</tr>
</tbody>
</table>

Patients treated with REYATAZ have reported the following side effects:

**Common:**
- headache
- ocular icterus (presence of jaundice seen in the white part of the eyes)
- vomiting, diarrhoea, abdominal pain (stomach pain of discomfort), nausea, dyspepsia (indigestion)
jaundice (yellowing of the skin and/or eyes)
- rash
- lipodistrophy syndrome (body changes due to fat redistribution, accumulation, or loss of body fat), fatigue (extreme tiredness)

Uncommon:
- peripheral neuropathy (numbness, weakness, tingling or pain in the arms and legs)
- hypersensitivity (allergic reaction)
- asthenia (unusual tiredness or weakness)
- weight decreased, weight gain, anorexia (loss of appetite), appetite increased
- depression, anxiety, sleep disorder
- disorientation, amnesia (loss of memory), dizziness, somnolence (sleepiness), abnormal dream
- syncope (fainting), hypertension (high blood pressure)
- dyspnoea (shortness of breath)
- pancreatitis (inflammation of the pancreas), gastritis (inflammation of the stomach), stomatitis aphthous (mouth ulcers and cold sores), dysgeusia (impairment of the sense of taste), flatulence (wind), dry mouth, abdominal distension
- hepatitis (inflammation of the liver)
- urticaria (itchy rash), alopecia (unusual hair loss or thinning), pruritus (itching)
- muscle atrophy (muscle shrinkage), arthralgia (joint pain), myalgia (aching muscles)
- nephrolithiasis (formation of kidney stones), hematuria (blood in the urine), proteinuria (excess protein in the urine), polliakiuria (increased frequency of urination)
- gynaecomastia (breast enlargement in men)
- chest pain, malaise (generally feeling unwell), fever
- insomnia (difficulty sleeping)

Rare:
- gait disturbance (abnormal manner of walking)
- oedema (swelling), palpitation (fast or irregular heart beat)
- hepatosplenomegaly (enlargement of the liver and spleen)
- vesiculobullous rash (visible accumulation of fluid under the skin), eczema (skin rash), vasodilatation (widening of blood vessels)
- myopathy (aching muscles, muscle tenderness of weakness, not caused by exercise)
- kidney pain

Not known:
- Torsades de pointes (life threatening irregular heart beat)
- QTc prolongation (irregular heart beat)
- Diabetes mellitus (body cannot remove sugar from the blood normally)
- Hyperglycaemia (high sugar levels in the blood)
- Nephrolithiasis (kidney stones)
- Gallbladder disorders (gallstones and gallbladder inflammation)

People who already have type A or B haemophilia may notice increased bleeding.

There have been reports of raised blood sugar and developing or worsening of diabetes in people using protease inhibitors. Also, there have been reports of unusual heart beat in both adult and paediatric patients using REYATAZ.

Changes in body fat have been seen in some patients taking antiretroviral therapy. These changes include increased amounts of fat in the upper back and neck ("buffalo hump"), breast, and around the abdomen ("belly"). Loss of fat from the legs, arms and face may also happen. The cause and long-term health effects of these conditions are not known at this time.

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your HIV doctor or nurse.
5. HOW TO STORE REYATAZ

- Keep out of the reach and sight of children.
- Do not use REYATAZ after the expiry date which is stated on the label, carton or blister. The expiry date refers to the last day of that month.
- Do not store above 25°C.

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6. FURTHER INFORMATION

What REYATAZ contains

- The active substance is atazanavir. Each capsule contains 300 mg of atazanavir (as sulphate).
- The other ingredients are crospovidone, lactose monohydrate, and magnesium stearate. The capsule shell and printing ink contain gelatine, shellac, ammonium hydroxide, simethicone, red iron oxide, black iron oxide, yellow iron oxide, propylene glycol, indigocarmine (E132) and titanium dioxide (E171).

What REYATAZ looks like and contents of the pack

Each capsule of REYATAZ 300 mg contains 300 mg atazanavir. Opaque red and blue capsule printed with white ink, with "BMS 300 mg" on one half and with "3622" on the other half.

REYATAZ 300 mg hard capsules are supplied in bottles of 30 capsules. Either one or three bottles of 30 hard capsules are provided in one carton.

REYATAZ 300 mg hard capsules are also supplied in blister strips in packs of 30 capsules.

REYATAZ also comes as a powder for adult patients who have difficulty swallowing capsules. REYATAZ oral powder must not be used in children who can not swallow the capsules.

Not all pack sizes may be marketed in all countries.

The marketing authorisation holder of REYATAZ is:

BRISTOL-MYERS SQUIBB PHARMA EEIG
Uxbridge Business Park
Sanderson Road
Uxbridge UB8 1DH
United Kingdom

The manufacturer of REYATAZ is:

BRISTOL-MYERS SQUIBB
Champ “Lachaud”, La Goualle
F-19250 Meymac
France

BRISTOL-MYERS SQUIBB
Rue du Docteur Gilles
F-28230 Epernon
France
For any further information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

**Belgique/België/Belgien**
BRISTOL-MYSQUIBB BELGIUM S.A./N.V.
Tél/Tel: + 32 2 352 76 11

**Luxembourg/Luxemburg**
BRISTOL-MYSQUIBB BELGIUM S.A./N.V.
Tél/Tel: + 32 2 352 76 11

**България**
BRISTOL-MYSQUIBB
ГЙОГЪЙЗЕРКЕРСЕКЕДЕЛМІ KFT.
Тел.: + 359 800 12 400

**Magyarország**
BRISTOL-MYSQUIBB
ГЙОГЪЙЗЕРКЕРСЕКЕДЕЛМІ KFT.
Tel.: + 36 1 301 9700

**Česká republika**
BRISTOL-MYSQUIBB SPOL. S R.O.
Tel: + 420 221 016 111

**Malta**
BRISTOL-MYSQUIBB S.R.L.
Tel: + 39 06 50 39 61

**Danmark**
BRISTOL-MYSQUIBB
Tel: + 45 45 93 05 06

**Nederland**
BRISTOL-MYSQUIBB BV
Tel: + 31 34 857 42 22

**Deutschland**
BRISTOL-MYSQUIBB GMBH & CO. KGAA
Tel: + 49 89 121 42-0

**Norge**
BRISTOL-MYSQUIBB NORWAY LTD
Tel: + 47 67 55 53 50

**Eesti**
BRISTOL-MYSQUIBB
ГЙОГЪЙЗЕРКЕРСЕКЕДЕЛМІ KFT.
Tel: + 372 6827 400

**Österreich**
BRISTOL-MYSQUIBB GESMBH
Tel: + 43 1 60 14 30

**Ελλάδα**
BRISTOL-MYSQUIBB A.E.
Τηλ.: + 30 210 6074300

**Polska**
BRISTOL-MYSQUIBB POLSKA SP. Z O.O.
Tel.: + 48 22 5796666

**España**
BRISTOL-MYSQUIBB, S.A.
Tel: + 34 91 456 53 00

**Portugal**
BRISTOL-MYSQUIBB FARMACÊUTICA
PORTUGUESA, S.A.
Tel: + 351 21 440 70 00

**France**
BRISTOL-MYSQUIBB SARL
Tél: + 33 (0)810 410 500

**România**
BRISTOL-MYSQUIBB
ГЙОГЪЙЗЕРКЕРСЕКЕДЕЛМІ KFT.
Tel: + 40 (0)21 272 16 00

**Ireland**
BRISTOL-MYSQUIBB PHARMACEUTICALS LTD
Tel: + 353 (1 800) 749 749

**Slovenija**
BRISTOL-MYSQUIBB SPOL. S R.O.
Tel: + 386 1 236 47 00

**Ísland**
VISTOR HF
Simi: + 354 535 7000

**Slovenská republika**
BRISTOL-MYSQUIBB SPOL. S R.O.
Tel: + 421 2 59298411
This leaflet was last approved in

Detailed information on this medicine is available on the European Medicines Agency (EMEA) website: http://www.emea.europa.eu/.
REYATAZ 50 mg/1.5 g oral powder
atazanavir

Read all of this leaflet carefully before you start taking this medicine.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor.

In this leaflet:
1. What REYATAZ is and what it is used for
2. Before you take REYATAZ
3. How to take REYATAZ
4. Possible side effects
5. How to store REYATAZ
6. Further information

1. WHAT REYATAZ IS AND WHAT IT IS USED FOR

REYATAZ is an antiviral (or antiretroviral) medicine. It is one of a group called protease inhibitors. These medicines control Human Immunodeficiency Virus (HIV) infection by stopping a protein that the HIV needs for its multiplication. They work by reducing the amount of HIV in your body and this in turn, strengthens your immune system. In this way REYATAZ reduces the risk of developing illnesses linked to HIV infection.

Your doctor has prescribed REYATAZ for you because you are infected by the HIV that causes Acquired Immunodeficiency Syndrome (AIDS). It is normally used in combination with other anti-HIV medicines. Your doctor will discuss with you which combination of these medicines with REYATAZ is best for you.

REYATAZ is not a cure for HIV infection. You may continue to develop infections or other illnesses linked to HIV infection. Treatment with REYATAZ does not reduce the risk of passing HIV to others through sexual contact or blood contamination. You must continue to take appropriate precautions to avoid giving the virus to others.

2. BEFORE YOU TAKE REYATAZ

Do not take REYATAZ

- if you are allergic (hypersensitive) to atazanavir or any of the other ingredients of REYATAZ
- if you have moderate to severe liver problems. Your doctor will evaluate how severe your liver disease is before deciding whether you can take REYATAZ
- if you are taking any of these medicines: see also Taking other medicines with REYATAZ
  - rifampicin, an antibiotic used to treat tuberculosis
  - astemizole or terfenadine (commonly used to treat allergy symptoms, these medicines may be available without prescription); cisapride (used to treat gastric reflux, sometimes called heartburn); pimozide (used to treat schizophrenia); quinidine or bepridil (used to correct heart rhythm); ergotamine, dihydroergotamine, ergonovine, methylergonovine (used to treat headaches)
  - medicines containing St. John’s wort (Hypericum perforatum, a herbal preparation)
• triazolam and oral (taken by mouth) midazolam (used to help you sleep and/or to relieve anxiety).

Tell your doctor at once if any of these apply to you.

**Take special care with REYATAZ**

Some people will need special care before or while taking REYATAZ. Before taking this medicine, make sure your doctor knows:
- if you have hepatitis B or C
- if you have type A or B haemophilia
- if you have diabetes
- if you require haemodialysis
- if you are taking oral contraceptives ("the Pill") to prevent pregnancy
- if you are taking omeprazole or other proton pump inhibitors; or famotidine or other H2-receptor antagonists (used to treat diseases related to the acid in the stomach)
- if you notice changes in body fat. Redistribution, accumulation, or loss of body fat may occur in patients receiving antiretroviral therapy.

Kidney stones have been reported in patients taking REYATAZ. If you develop signs or symptoms of kidney stones (pain in your side, blood in your urine, pain when you urinate), please inform your doctor immediately.

In some patients with advanced HIV infection (AIDS) and a history of opportunistic infection, signs and symptoms of inflammation from previous infections may occur soon after anti-HIV treatment is started. It is believed that these symptoms are due to an improvement in the body’s immune response, enabling the body to fight infections that may have been present with no obvious symptoms. If you notice any symptoms of infection, please inform your doctor immediately.

Some patients taking combination antiretroviral therapy may develop a bone disease called osteonecrosis (death of bone tissue caused by loss of blood supply to the bone). The length of combination antiretroviral therapy, corticosteroid use, alcohol consumption, severe immunosuppression, higher body mass index, among others, may be some of the many risk factors for developing this disease. Signs of osteonecrosis are joint stiffness, aches and pains (especially of the hip, knee and shoulder) and difficulty in movement. If you notice any of these symptoms please inform your doctor.

Hyperbilirubinaemia (an increase in the level of bilirubin in the blood) has occurred in patients receiving REYATAZ. The signs may be a mild yellowing of the skin or eyes. If you notice any of these symptoms please inform your doctor.

If you notice a change in the way your heart beats (heart rhythm changes), please inform your doctor.

**Taking other medicines**

There are some medicines you cannot take at all with REYATAZ: rifampicin, an antibiotic used to treat tuberculosis, astemizole or terfenadine (commonly used to treat allergy symptoms, these medicines may be available without prescription); cisapride (used to treat gastric reflux, sometimes called heartburn); pimozide (used to treat schizophrenia); quinidine or bepridil (used to correct heart rhythm); ergotamine, dihydroergotamine, ergonovine, methylergonovine (used to treat migraine headaches), medicines containing St. John’s wort (Hypericum perforatum, a herbal preparation), triazolam and oral (taken by mouth) midazolam (used to help you sleep) (see section 2, under Do not take REYATAZ).

There are other medicines that may not mix with REYATAZ. Please tell your doctor if you are taking or have recently taken any other medicines including medicines obtained without a prescription. It is especially important to mention these:
- other medicines to treat HIV infection
sildenafil (used by men to treat impotence (erectile dysfunction))
if you are taking an oral contraceptive ("the Pill") with REYATAZ, be sure to take it exactly as instructed by your doctor and not miss any doses.
any medicines used to treat diseases related to the acid in the stomach (e.g. antacids, H2-blockers and proton pump inhibitors)
medicines to lower blood pressure, to slow heart rate, or to correct heart rhythm
simvastatin, lovastatin, and atorvastatin (used to lower blood cholesterol)
nevirapine and efavirenz (used to treat HIV)
cyclosporin, tacrolimus, and sirolimus (medicines to decrease the effects of body's immune system)
certain antibiotics (rifabutin, clarithromycin)
ketonazole, itraconazole, and voriconazole (antifungals)
warfarin (anticoagulant, used to reduce the blood clots)
irinotecan (used to treat cancer)
sedative agents (e.g. midazolam administered by injection)
buprenorphine (used to treat opioid addiction and pain).

Some medicines may interact with ritonavir, a medicine that is taken with REYATAZ. It is important to tell your doctor if you are taking fluticasone or budesonide (given by nose or inhaled to treat allergic symptoms or asthma).

Taking REYATAZ with food and drink

It is important that you take REYATAZ with food (a meal or a substantial snack) as this helps the body absorb the medicine.

Pregnancy and breast-feeding

Tell your doctor if you are pregnant or planning to become pregnant. Also be sure to tell your doctor if you are breast-feeding. It is recommended that women infected with HIV do not breast-feed because the virus might be transmitted through the breast milk.

Driving and using machines

No studies on the effect of effects on the ability to drive and use machines have been performed. If you feel dizzy or lightheaded, contact your doctor immediately.

Important information about some of the ingredients of REYATAZ

This medicine contains a sweetening agent called aspartame. Aspartame provides a source of phenylalanine that may not be suitable for persons with phenylketonuria.

REYATAZ oral powder contains 7.3 g sucrose per 300 mg daily dose. This should be taken into account in patients with diabetes mellitus.

3. HOW TO TAKE REYATAZ

Always take REYATAZ exactly as your doctor has told you. You should check with your doctor if you are not sure. This way, you can be sure your medicine is fully effective and you reduce the risk of the virus developing resistance to the treatment.

The usual adult dose of REYATAZ is 300 mg oral powder once daily with 100 mg ritonavir once daily and with food, in combination with other anti-HIV medicines. 300 mg REYATAZ oral powder equals to 6 level measuring spoons of powder (each spoon makes 50 mg of atazanavir). Your doctor may adjust the dose of REYATAZ according to your anti-HIV therapy. There is not enough information to recommend a dose in children.
Take REYATAZ with food (a meal or a substantial snack).

Scoop an overfilled spoon of loose powder from the bottle using the measuring spoon provided (see picture below). Then gently level the powder in the spoon by scraping the extra powder back into the bottle using a flat edge of a knife or spatula. Do not try to pack the powder into the spoon or attempt to level the powder by shaking or tapping the spoon. REYATAZ oral powder should be taken at about the same time each day with a meal. It may be mixed with water, milk, infant formula, applesauce, or yoghurt. Once the powder is mixed, it must be consumed within 6 hours. Do not mix the powder inside the bottles of REYATAZ.

If you take more REYATAZ than you should

If you accidentally take more REYATAZ oral powder than your doctor recommended, contact your HIV doctor at once or contact the nearest hospital for advice.

If you forget to take REYATAZ

If you miss a dose, take the missed dose as soon as possible with food and then take your next scheduled dose at its regular time. If it is almost time for your next dose, do not take the missed dose. Wait and take the next dose at its regular time. Do not take a double dose to make up for a forgotten dose.

If you stop taking REYATAZ

Do not stop taking REYATAZ before talking to your doctor.

If you have any further questions on the use of this product, ask your doctor.

4. POSSIBLE SIDE EFFECTS

Like all medicines, REYATAZ can cause side effects, although not everybody gets them. When treating HIV infection, it is not always easy to identify what side effects are caused by REYATAZ, by the other medicines you are taking, or by the HIV infection itself. Tell your doctor if you notice anything unusual about your health.

The frequency of possible side effects listed below is defined using the following convention:

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Patients treated with REYATAZ have reported the following side effects:
Common:
- headache
- ocular icterus (presence of jaundice seen in the white part of the eyes)
- vomiting, diarrhoea, abdominal pain (stomach pain of discomfort), nausea, dyspepsia (indigestion)
- jaundice (yellowing of the skin and/or eyes)
- rash
- lipodistrophy syndrome (body changes due to fat redistribution, accumulation, or loss of body fat), fatigue (extreme tiredness)
Uncommon:
- peripheral neuropathy (numbness, weakness, tingling or pain in the arms and legs)
- hypersensitivity (allergic reaction)
- asthenia (unusual tiredness or weakness)
- weight decreased, weight gain, anorexia (loss of appetite), appetite increased
- depression, anxiety, sleep disorder
- disorientation, amnesia (loss of memory), dizziness, somnolence (sleepiness), abnormal dream
- syncope (fainting), hypertension (high blood pressure)
- dyspnoea (shortness of breath)
- pancreatitis (inflammation of the pancreas), gastritis (inflammation of the stomach), stomatitis
- aphthous (mouth ulcers and cold sores), dysgeusia (impairment of the sense of taste), flatulence
- (wind), dry mouth, abdominal distension
- hepatitis (inflammation of the liver)
- urticaria (itchy rash), alopecia (unusual hair loss or thinning), pruritus (itching)
- muscle atrophy (muscle shrinkage), arthralgia (joint pain), myalgia (aching muscles)
- nephrolithiasis (formation of kidney stones), hematuria (blood in the urine), proteinuria (excess
- protein in the urine), pollakiuria (increased frequency of urination)
- gynaecomastia (breast enlargement in men)
- chest pain, malaise (generally feeling unwell), fever
- insomnia (difficulty sleeping)

Rare:
- gait disturbance (abnormal manner of walking)
- oedema (swelling), palpitation (fast or irregular heart beat)
- hepatosplenomegaly (enlargement of the liver and spleen)
- vesiculobullous rash (visible accumulation of fluid under the skin), eczema (skin rash),
- vasodilatation (widening of blood vessels)
- myopathy (aching muscles, muscle tenderness of weakness, not caused by exercise)
- kidney pain

Not known:
- Torsades de pointes (life threatening irregular heart beat)
- QTc prolongation (irregular heart beat)
- Diabetes mellitus (body cannot remove sugar from the blood normally)
- Hyperglycaemia (high sugar levels in the blood)
- Nephrolithiasis (kidney stones)
- Gallbladder disorders (gallstones and gallbladder inflammation)

People who already have type A or B haemophilia may notice increased bleeding.

There have been reports of raised blood sugar and developing or worsening of diabetes in people using protease inhibitors. Also, there have been reports of unusual heart beat in patients using REYATAZ.

Changes in body fat have been seen in some patients taking antiretroviral therapy. These changes include increased amounts of fat in the upper back and neck ("buffalo hump"), breast, and around the abdomen ("belly"). Loss of fat from the legs, arms and face may also happen. The cause and long-term health effects of these conditions are not known at this time.

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your HIV doctor or nurse.

5. HOW TO STORE REYATAZ
- Keep out of the reach and sight of children.
- Do not use REYATAZ after the expiry date stated on the package and on the bottle label. The expiry date refers to the last day of that month.
- Keep the bottle tightly closed.
Do not use REYATAZ oral powder if you notice the product has turned into a dark yellow or brown powder aggregated into one clump.

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6. FURTHER INFORMATION

What REYATAZ contains

The active substance in REYATAZ is atazanavir. One measuring spoon of 1.5 g oral powder contains 50 mg of atazanavir (as sulphate). The other ingredients are aspartame (E951), sucrose, and orange vanilla flavour.

What REYATAZ looks like and contents of the pack

REYATAZ oral powder is supplied in bottles containing 180 g of powder together with a plastic measuring spoon. The colour of the powder is off-white to pale yellow. REYATAZ also exists in capsules. However, not all pack sizes may be marketed in all countries.

The marketing authorisation holder of REYATAZ is:

BRISTOL-MYERS SQUIBB PHARMA EEIG
Uxbridge Business Park
Sanderson Road
Uxbridge UB8 1DH
United Kingdom

The manufacturer of REYATAZ is:

BRISTOL-MYERS SQUIBB
Champ “Lachaud”, La Goualle
F-19250 Meymac
France

For any further information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

Belgique/België/Belgien
BRISTOL-MYERS SQUIBB BELGIUM S.A./N.V.
Tél/Tel: + 32 2 352 76 11

Luxembourg/Luxemburg
BRISTOL-MYERS SQUIBB BELGIUM S.A./N.V.
Tél/Tel: + 32 2 352 76 11

България
BRISTOL-MYERS SQUIBB
GYOGYSZERKERESKEDELMI KFT.
Tel.: + 359 800 12 400

Magyarország
BRISTOL-MYERS SQUIBB
GYOGYSZERKERESKEDELMI KFT.
Tel.: + 36 1 301 9700

Česká republika
BRISTOL-MYERS SQUIBB SPOL. S R.O.
Tel: + 420 221 016 111

Malta
BRISTOL-MYERS SQUIBB S.R.L.
Tel: + 39 06 50 39 61

Danmark
BRISTOL-MYERS SQUIBB
Tlf: + 45 45 93 05 06

Nederland
BRISTOL-MYERS SQUIBB BV
Tel: + 31 34 857 42 22
Deutschland  
BRISTOL-MYERS SQUIBB GMBH & CO. KGAA  
Tel: + 49 89 121 42-0

Norge  
BRISTOL-MYERS SQUIBB NORWAY LTD  
Tel: + 47 67 55 53 50

Eesti  
BRISTOL-MYERS SQUIBB  
GYÖGYSZERKERESKEDELMI KFT.  
Tel: + 372 6827 400

Österreich  
BRISTOL-MYERS SQUIBB GESMBH  
Tel: + 43 1 60 14 30

Ελλάδα  
BRISTOL-MYERS SQUIBB A.E.  
Τηλ: + 30 210 6074300

Polska  
BRISTOL-MYERS SQUIBB POLSKA SP. Z O.O.  
Tel.: + 48 22 5796666

España  
BRISTOL-MYERS SQUIBB, S.A.  
Tel: + 34 91 456 53 00

Portugal  
BRISTOL-MYERS SQUIBB FARMACÊUTICA PORTUGUESA, S.A.  
Tel: + 351 21 440 70 00

France  
BRISTOL-MYERS SQUIBB SARL  
Tél: + 33 (0)810 410 500

România  
BRISTOL-MYERS SQUIBB  
GYÖGYSZERKERESKEDELMI KFT.  
Tel: + 40 (0)21 272 16 00

Ireland  
BRISTOL-MYERS SQUIBB PHARMACEUTICALS LTD  
Tel: + 353 (1 800) 749 749

Slovenija  
BRISTOL-MYERS SQUIBB spol. s r.o.  
Tel: + 386 1 236 47 00

Ísland  
VISTOR hf  
Sími: + 354 535 7000

Slovenská republika  
BRISTOL-MYERS SQUIBB spol. s r.o.  
Tel: + 421 2 59298411

Italia  
BRISTOL-MYERS SQUIBB S.R.L.  
Tel: + 39 06 50 39 61

Suomi/Finland  
OY BRISTOL-MYERS SQUIBB (FINLAND) AB  
Puh/Tel: + 358 9 251 21 230

Κύπρος  
BRISTOL-MYERS SQUIBB A.E  
Τηλ: + 357 800 92666

Sverige  
BRISTOL-MYERS SQUIBB AB  
Tel: + 46 8 704 71 00

Latvija  
BRISTOL-MYERS SQUIBB  
GYÖGYSZERKERESKEDELMI KFT.  
Tel: + 371 67 50 21 85

United Kingdom  
BRISTOL-MYERS SQUIBB PHARMACEUTICALS LTD  
Tel: + 44 (0800) 731 1736

Lietuva  
BRISTOL-MYERS SQUIBB  
GYÖGYSZERKERESKEDELMI KFT.  
Tel: + 370 5 2790 762

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