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 (corresponding to 113.9 mg atazanavir sulphate). For excipients, see 6.1.

3. PHARMACEUTICAL FORM

Capsule, hard. The capsules are opaque blue and white. They are printed with edible white and blue inks, with "BMS 100" on one half and with "3623" on the other half.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

REYATAZ is indicated for the treatment of HIV-1 infected, antiretroviral treatment experienced 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 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 should be based on individual viral resistance testing and the patient’s treatment history (see 5.1).

4.2 Posology and method of administration

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

Oral use.

*Adults:* the recommended dose of REYATAZ is 300 mg (REYATAZ is available as 100 mg, 150 mg and 200 mg hard capsules) once daily taken with ritonavir 100 mg once daily and with food. Ritonavir is used as a booster of atazanavir pharmacokinetics (see 4.5 and 5.1).

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

*Infants, toddlers, children, and adolescents:* the efficacy and safety of REYATAZ have not been established in this population (see 5.2).

*Patients with renal impairment:* no dosage adjustment is needed (see 5.2).

*Patients with hepatic impairment:* REYATAZ with ritonavir should be used with caution in patients with mild hepatic insufficiency. REYATAZ should not be used in patients with moderate to severe hepatic insufficiency (see 4.3, 4.4, and 5.2). REYATAZ with ritonavir has not been studied in patients with hepatic insufficiency.
Method of administration: for oral administration. The capsules should be swallowed whole. REYATAZ oral powder is available for patients who are unable to swallow capsules. (See Summary of Product Characteristics for REYATAZ oral powder).

4.3 Contraindications

Hypersensitivity to atazanavir or to any of the excipients (see 6.1).

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

REYATAZ with ritonavir should not be used in combination with rifampicin (see 4.5).

REYATAZ with ritonavir should 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, and ergot alkaloids, particularly, ergotamine, dihydroergotamine, ergonovine, methylergonovine) (see 4.5).

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

4.4 Special warnings and special 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.

There are insufficient data to recommend a dose in antiretroviral treatment-naive patients at present.

Co-administration of REYATAZ with ritonavir in doses greater than 100 mg once daily has not been clinically evaluated. The use of higher ritonavir doses might alter the safety profile of atazanavir (cardiac effects, hyperbilirubinemia) and therefore is not recommended.

Patients with coexisting conditions

Atazanavir is primarily hepatically metabolised and increased plasma concentrations were observed in patients with hepatic impairment (see 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 events. 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 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.

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 5.1).

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.

Consideration should be given to the measurement of fasting serum lipids and blood glucose. Lipid disorders should be managed as clinically appropriate (see 4.8).

In clinical studies, REYATAZ (with or without ritonavir) has been shown to induce dyslipidemia to a lesser extent than comparators (see 5.1). However, the clinical impact of such findings has not been demonstrated in the absence of specific studies on cardiovascular risk.

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.

Hyperbilirubinemia
Reversible elevations in indirect (unconjugated) bilirubin related to inhibition of UDP-glucuronosyl transferase (UGT) have occurred in patients receiving REYATAZ (see 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) hyperbilirubinemia 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 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.

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

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

The concomitant use of REYATAZ and oral contraceptives should be avoided (see 4.5).
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 and ergot alkaloids, particularly ergotamine and dihydroergotamine (see 4.3).

Antiretroviral agents

Nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs):

Interaction studies with stavudine, lamivudine and zidovudine have been performed with REYATAZ without ritonavir. Based on data derived from these studies and because ritonavir is not expected to have a significant impact on the pharmacokinetics of NRTIs, the co-administration of REYATAZ and ritonavir with these medicinal products is not expected to significantly alter the exposure of the co-administered drugs. The same conclusion applies to the co-administration with abacavir. Considering that REYATAZ with ritonavir should be administered with food, didanosine should be taken 2 hours after REYATAZ with ritonavir.

Tenofovir disoproxil fumarate: atazanavir concentrations (AUC and C_min) are decreased when tenofovir is co-administered with REYATAZ (decrease of 25% and 40% of AUC and C_min respectively compared to atazanavir 400 mg). When ritonavir was added to atazanavir, the negative impact of tenofovir on atazanavir C_min was significantly reduced, whereas the decrease of AUC was of the same magnitude (decrease of 25% and 26% of AUC and C_min respectively compared to atazanavir/ritonavir 300/100 mg). The efficacy of REYATAZ with ritonavir in combination with tenofovir in treatment-experienced patients has been demonstrated in the clinical study 045 (see 4.8 and 5.1).

Non-nucleoside reverse transcriptase inhibitors (NNRTIs)

Efavirenz: if REYATAZ is to be co-administered with efavirenz, which decreases atazanavir exposure, it is recommended that REYATAZ 400 mg with ritonavir 100 mg be co-administered with efavirenz 600 mg (all as a single daily dose with food), as this combination is anticipated to result in atazanavir exposure that approximates the mean exposure to atazanavir produced by 300 mg of REYATAZ given with ritonavir 100 mg. No efficacy and safety data are available to support the co-administration of efavirenz and REYATAZ at the increased dose of 400 mg with ritonavir.

Nevirapine: The effects of co-administration of REYATAZ and nevirapine have not been studied. Nevirapine is a metabolic inducer of CYP3A4 and is expected to decrease atazanavir exposure. Therefore, in the absence of data regarding the expected interaction between REYATAZ with ritonavir and nevirapine, this co-administration is not recommended.

Protease inhibitors

Indinavir: indinavir is also associated with indirect (unconjugated) hyperbilirubinemia due to inhibition of UGT. Co-administration of REYATAZ and indinavir is not recommended (see 4.4).

Ritonavir: based on data in healthy volunteers, the addition of ritonavir 100 mg to atazanavir 300 mg has been shown to significantly increase the pharmacokinetic parameters of atazanavir (approximately, 2 fold increase of AUC and 7 fold increase of C_min in comparison to atazanavir 400 mg without ritonavir). In patients, the limited pharmacokinetic data currently available suggest that the impact of ritonavir might be less noticeable on the C_min (approximately, 3 fold increase).
The co-administration of REYATAZ with 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.

Other medicinal products

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 with ritonavir. REYATAZ with ritonavir should be administered 2 hours before or 1 hour after buffered medicinal products.

Antiarrhythmics (amiodarone, systemic lidocaine, quinidine): concentrations may be increased when co-administered with REYATAZ with ritonavir. Caution is warranted and therapeutic concentration monitoring is recommended when available. The concomitant use of quinidine is contraindicated (see 4.3).

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

Calcium channel blockers: co-administration of bepridil with REYATAZ is not recommended (see 4.3). Co-administration of diltiazem (180 mg once daily) with atazanavir (400 mg once daily) in healthy subjects resulted in a 2 to 3 fold increase in diltiazem and desacetyl-diltiazem exposure and no change in the pharmacokinetics of atazanavir. There was an increase in the maximum PR interval compared to atazanavir alone. Co-administration of diltiazem and REYATAZ with ritonavir has not been studied. An initial dose reduction of diltiazem by 50% is recommended, with subsequent titration as needed and ECG monitoring. Verapamil may also have its serum concentrations increased by REYATAZ with ritonavir; therefore, caution should be exercised when verapamil is co-administered with REYATAZ with ritonavir.

HMG-CoA reductase inhibitors (simvastatin, lovastatin, atorvastatin): simvastatin and lovastatin are highly dependent on CYP3A4 for their metabolism and co-administration with REYATAZ with ritonavir may result in increased concentrations. Concomitant use of simvastatin or lovastatin is not recommended due to an increased risk of myopathy including rhabdomyolysis. The risk of myopathy including rhabdomyolysis may also be increased when protease inhibitors, including REYATAZ with ritonavir, are used in combination with atorvastatin, which is also metabolised by CYP3A4. Caution should be exercised.

H2-Receptor antagonists and proton pump inhibitors: the effects of H2-receptor antagonists, proton pump inhibitors, or other gastric acid suppressors on REYATAZ have not been studied; however, reduced plasma concentrations of atazanavir may result due to increased gastric pH if these medicinal products are administered with REYATAZ with ritonavir. Caution should be exercised.

Immunosuppressants (cyclosporin, tacrolimus, sirolimus): concentrations of cyclosporin, tacrolimus, or sirolimus may be increased when co-administered with REYATAZ with ritonavir. More frequent therapeutic concentration monitoring of these medicinal products is recommended until plasma levels have been stabilised.

Macrolide antibiotics: co-administration of clarithromycin (500 mg twice daily) with atazanavir (400 mg once daily) resulted in a 2 fold increase in exposure to clarithromycin and a 70% decrease in exposure to 14-OH clarithromycin, with a 28% increase in the AUC of atazanavir. Dose reduction of clarithromycin may result in subtherapeutic concentrations of 14-OH clarithromycin. No recommendation regarding dose reduction can be made; therefore, caution should be exercised if REYATAZ plus ritonavir is co-administered with clarithromycin.

Oral contraceptives (ethinyl estradiol, norethindrone): the mean concentration of ethinyl estradiol, when co-administered as a 35-µg dose with atazanavir 400 mg once daily, was increased to a level
between mean concentrations produced by a 35-µg and a 50-µg ethinyl estradiol dose, and the AUC of norethindrone was increased about 2 fold. In contrast, ritonavir may decrease ethinyl estradiol concentrations. The effects of co-administration of oral contraceptives and REYATAZ with ritonavir have not been studied. The concomitant use of REYATAZ and oral contraceptives should be avoided (see 4.4). Alternate reliable methods of contraception should be considered.

**Rifabutin:** simultaneous administration of 400 mg of atazanavir and 150 mg of rifabutin once daily for 14 days resulted in no clinically important change in the C\(_{\text{max}}\) or AUC for atazanavir. No dose adjustment is needed for REYATAZ. The rifabutin C\(_{\text{max}}\) for the 150-mg dose was 1.5 fold higher and the AUC was 2.3 fold higher than historical data for a standard 300-mg dose. A rifabutin dose reduction of up to 75% (e.g., 150 mg every other day or 3 times per week) is recommended when administered with REYATAZ with ritonavir.

**Rifampicin:** although the effect of rifampicin on REYATAZ has not been studied, rifampicin decreases plasma concentrations and AUC of most protease inhibitors by about 90%. This may result in loss of therapeutic effect and development of resistance. The concomitant use of REYATAZ and rifampicin is contraindicated (see 4.3).

**Sildenafil:** sildenafil is metabolised by CYP3A4. Co-administration with REYATAZ may result in increased concentrations of sildenafil and an increase in sildenafil-associated adverse events, including hypotension, visual changes, and priapism. Patients should be warned about these possible side effects.

**Triazole antifungal agents:** co-administration with ketoconazole has only been studied with REYATAZ without ritonavir. Co-administration of 200 mg of ketoconazole with 400 mg of atazanavir in healthy subjects resulted in negligible increases in atazanavir AUC and C\(_{\text{max}}\) (respectively 11% and 3%). Plasma levels of both atazanavir and ritonavir may be increased by ketoconazole and itraconazole. High doses of ketoconazole and itraconazole (> 200 mg/day) should be used cautiously with atazanavir and ritonavir, by assessing the risk versus the benefit of such a combination.

**Warfarin:** co-administration with REYATAZ with 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 and ritonavir, especially when commencing therapy.

**St. John’s wort (Hypericum perforatum):** REYATAZ should not be used concomitantly with products containing St. John's wort since it 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 4.3).

### 4.6 Pregnancy and lactation

There are no adequate and well-controlled studies in pregnant women. Studies in animals have not shown evidence of selective developmental toxicity or effects on reproductive function and fertility (see 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 hyperbilirubinemia 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

There are no data to suggest that atazanavir affects the ability to drive or use machines. However, patients should be informed that dizziness has been reported during treatment with regimens containing REYATAZ (see 4.8).

4.8 Undesirable effects

Data on the safety and tolerability of REYATAZ 300 mg with ritonavir 100 mg once daily are limited, as this combination has only been evaluated in 119 patients in Study 045 in a regimen that also included tenofovir 300 mg once daily and a nucleoside reverse transcriptase inhibitor. Considering that tenofovir has been shown to decrease the plasma levels of atazanavir (with or without concomitant ritonavir), the safety data derived from this study may not fully reflect the safety profile of REYATAZ plus ritonavir when used in clinical practice within antiretroviral combinations that exclude tenofovir. An alteration of the safety profile of REYATAZ cannot be excluded in this context.

REYATAZ has been evaluated for safety and tolerability in combination therapy with other antiretroviral medicinal products in Phase II and III trials in 1,596 adult patients. The majority of patients (1,046) received REYATAZ 400 mg once daily without ritonavir. The median duration of treatment was 102 weeks in Phase II trials and 31 weeks in the Phase III trials. Adverse events were comparable between patients who received REYATAZ 300 mg with ritonavir 100 mg once daily and patients who received REYATAZ 400 mg once daily, except that jaundice and elevated total bilirubin levels were reported more frequently with REYATAZ plus ritonavir.

Among patients who received 400 mg once daily or 300 mg with ritonavir 100 mg once daily, the only adverse events of any severity reported very commonly with at least a possible relationship to regimens containing REYATAZ and one or more NRTIs were nausea (23%), headache (10%), and jaundice (10%). Among patients receiving REYATAZ 300 mg with ritonavir 100 mg, the frequency of jaundice was 15%. Jaundice was reported within a few days to a few months after the initiation of treatment (see 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 4.4 and 5.1).

Adult patients

The following adverse events 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, < 1/10), uncommon (≥ 1/1,000, < 1/100), rare (≥ 1/10,000, < 1/1,000), or very rare (< 1/10,000).
Immune system disorders: uncommon: allergic reaction

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

Psychiatric disorders: uncommon: anxiety, depression, sleep disorder

Nervous system disorders: common: headache, insomnia, peripheral neurologic symptoms; uncommon: abnormal dream, amnesia, confusion, dizziness, somnolence; rare: abnormal gait

Eye disorders: common: scleral icterus

Cardiac disorders and vascular disorders: uncommon: syncope; rare: hypertension, oedema, palpitation

Respiratory, thoracic and mediastinal disorders: uncommon: dyspnea

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

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

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

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

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

Reproductive system and breast disorders: uncommon: gynecomastia

General disorders and administration site conditions: common: asthenia; uncommon: chest pain, fatigue, fever, malaise
Laboratory abnormalities
The most frequently reported laboratory abnormality in patients receiving regimens containing REYATAZ and one or more NRTIs was elevated total bilirubin (82% Grade 1, 2, 3, or 4). Grade 3 or 4 elevation of total bilirubin was noted in 31% (26% Grade 3, 5% Grade 4, reported predominantly as elevated indirect [unconjugated] bilirubin). Among patients treated with REYATAZ 300 mg once daily with 100 mg ritonavir once daily, 45% had Grade 3-4 total bilirubin elevations (see 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 amylase (11%), elevated creatine kinase (7%), elevated alanine aminotransferase/serum glutamic-pyruvic transaminase (ALT/SGPT) (5%), low neutrophils (4%), elevated aspartate aminotransferase/serum glutamic-oxaloacetic transaminase (AST/SGOT) (3%), and elevated lipase (3%).

One 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 585 patients receiving atazanavir 400 mg once daily, 74 patients were co-infected with chronic hepatitis B or C, and among 119 patients receiving atazanavir 300 mg once daily with ritonavir 100 mg once daily, 20 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 4.4).

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) hyperbilirubinemia (without associated liver function test changes) or PR interval prolongations may be observed (see 4.4 and 4.8).

Treatment of overdose with REYATAZ should consist of general supportive measures, including monitoring of vital signs and 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: J05A E

Mechanism of action: atazanavir is an azapeptide HIV-1 protease inhibitor. 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 activity (EC50 of 2 to 5 nM) against a variety of HIV isolates in the absence of human serum. REYATAZ administered 300 mg once daily with ritonavir 100 mg once daily results in a mean (±SD) Cmin of 862 (±838) ng/ml. The estimated protein-adjusted (in 40% human serum) Cmin is approximately 50 to 300 fold higher than the EC50 values generated in representative HIV-infected cell lines. Combinations of atazanavir with stavudine, didanosine, lamivudine, zidovudine, nelfinavir, indinavir, ritonavir, saquinavir, or amprenavir in
HIV-infected peripheral blood mononuclear cells yielded additive antiviral effects and did not result in antagonistic anti-HIV activity or enhanced cytotoxic effects at the highest concentrations used for antiviral evaluation.

**Cross-resistance in vitro in viruses resistant to other protease inhibitors:** atazanavir susceptibility was evaluated in 943 clinical isolates from patients without prior atazanavir exposure and exhibiting a wide array of genotypic and phenotypic patterns. In vitro, there was a clear trend toward decreased susceptibility to atazanavir as isolates exhibited high resistance levels to multiple protease inhibitors. In general, susceptibility to atazanavir was retained (83% of isolates displayed < 2.5 fold change in EC_{50}) among isolates resistant to no more than 2 protease inhibitors. Eighteen percent of isolates had 4 or more of the following 6 mutations considered critical mutations for protease inhibitors: amino acid substitutions 10, 46, 54, 82, 84, and 90. These isolates expressed a median fold change in EC_{50} relative to wildtype of 12.0 for atazanavir. Therefore, viral isolates having at least 4 of these specific mutations would be considered resistant for atazanavir.

**Resistance in vivo:** in antiretroviral treatment naive patients, the I50L substitution, sometimes in combination with an A71V change, is the signature resistance mutation for atazanavir. An atazanavir resistance phenotype is expressed in all recombinant viral clones containing the I50L substitution in a variety of genetic backgrounds. Resistance levels ranged from 3.5- to 29-fold. There was no evidence of cross-resistance between atazanavir and amprenavir, with insertion of the I50L and I50V substitutions yielding selective resistance to atazanavir and amprenavir, respectively.

In antiretroviral treatment experienced patients, within the 74 isolates from patients who developed resistance to atazanavir on therapy that included either atazanavir, atazanavir + ritonavir, or atazanavir + saquinavir, only 9 isolates from patients treated with either atazanavir or atazanavir + ritonavir displayed the I50L phenotype previously described in naive patients. The resistance in antiretroviral treatment experienced patients mainly occurs by accumulation of the primary and secondary resistance substitutions described previously to be involved in protease inhibitor resistance. These isolates developed higher levels of resistance to the other protease inhibitors.

**Clinical experience:** in antiretroviral treatment experienced patients, the benefit of REYATAZ is based only on Study 045 where REYATAZ 300 mg once daily was used with ritonavir 100 mg once daily and compared with lopinavir + ritonavir. Study 045 is an ongoing, randomised, multicenter trial comparing REYATAZ (300 mg once daily) with ritonavir (100 mg once daily) to REYATAZ (400 mg once daily) with saquinavir soft gelatin capsules (1,200 mg once daily), and to lopinavir + ritonavir (400/100 mg fixed dose combination twice daily), each in combination with tenofovir (see 4.5 and 4.8) and one NRTI, in 347 (of 358 randomised) 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. Sixteen of 120 (13%) patients in the REYATAZ + ritonavir treatment arm and 18 of 123 (15%) patients in the lopinavir + ritonavir arm had four or more of the PI mutations 10, 46, 54, 82, 84, and 90. Thirty-two percent of patients in the study had a viral strain with fewer than two NRTI mutations. 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 log_{10} copies/ml (range: 2.6 to 5.9 log_{10} copies/ml). The population included in this study was moderately pretreated.

The primary endpoint was the time-averaged difference in change from baseline in HIV RNA through 24 weeks.

Through 24 weeks of treatment, the decreases from baseline in HIV RNA levels (primary endpoint) were 1.86 log_{10} copies/ml for REYATAZ + ritonavir and 1.89 log_{10} copies/ml for lopinavir + ritonavir. REYATAZ + ritonavir was similar (non-inferior) to lopinavir + ritonavir on this efficacy measure (time-averaged difference of 0.14, 97.5% confidence interval [-0.09, 0.37]). Consistent results were obtained with the last observation carried forward method of analysis (time-averaged difference of 0.10, 97.5% confidence interval [-0.13, 0.33]). The proportions of patients with HIV RNA
< 400 copies/ml in the REYATAZ + ritonavir arm and the lopinavir + ritonavir arm were 63% and 60%, respectively, by intent-to-treat analysis, with missing values considered as failures. The proportions of patients with HIV RNA < 50 copies/ml in the REYATAZ + ritonavir arm and the lopinavir + ritonavir arm were 38% and 41%, respectively. 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 68% (47%) and 68% (51%), respectively. The mean increases from baseline in CD4 cell count were 83 cells/mm³ and 90 cells/mm³ in the REYATAZ + ritonavir and lopinavir + ritonavir arms, respectively. Two subset analyses were performed based on baseline genotypic mutations. In the first, the results significantly favoured the lopinavir + ritonavir arm when considering the subset of patients with ≥ 4 mutations among the following: 10, 20, 24, 32, 33, 36, 46, 48, 50, 54, 63, 71, 73, 82, 84 and 90. In the second, for patients with < 4 of the protease gene mutations 10, 46, 54, 82, 84, and 90, the proportion with HIV RNA < 400 copies/ml was 70% for REYATAZ + ritonavir and 65% for lopinavir + ritonavir, and the proportion with HIV RNA < 50 copies/ml was 44% in each treatment arm. In patients with ≥ 4 of these mutations, the proportion with HIV RNA < 400 copies/ml was 19% for REYATAZ + ritonavir and 39% for lopinavir + ritonavir, and the proportion with HIV RNA < 50 copies/ml was respectively 0% and 22%.

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

The data available on the lipid profile are described in the following table:

<table>
<thead>
<tr>
<th>Study -045 24 weeks</th>
<th>ATV/RTV</th>
<th>LPV/RTV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total Cholesterol</td>
<td>-8%</td>
<td>3%</td>
</tr>
<tr>
<td>LDL Cholesterol</td>
<td>-10%</td>
<td>-4%</td>
</tr>
<tr>
<td>HDL Cholesterol</td>
<td>-7%</td>
<td>0%</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>-2%</td>
<td>31%</td>
</tr>
</tbody>
</table>

5.2 Pharmacokinetic properties

Limited data are available on the pharmacokinetics of atazanavir in association with low dose ritonavir. The pharmacokinetics of atazanavir were evaluated in healthy adult volunteers and in HIV-infected patients; no substantial differences were observed between the two groups. The pharmacokinetics of atazanavir exhibit a non-linear disposition and a high inter/intra-subject variability that is minimised with food. In healthy subjects, the AUC of atazanavir from the capsules and oral powder were similar. Therefore, HIV-infected patients can use the two formulations interchangeably.

Absorption: the pharmacokinetics of atazanavir boosted with ritonavir is currently supported by limited data in patients. In a pharmacokinetic study in HIV-positive patients (n= 10), multiple dosing of REYATAZ 300 mg once daily with ritonavir 100 mg once daily with a light meal for 2 weeks produced a mean steady-state C_max (SD) of 5,233 ng/ml (3,033), occurring approximately 3.0 hours (T_max) after administration, and a mean steady-state trough concentration (SD) of 862 ng/ml (838). The mean steady-state plasma AUC (SD) of atazanavir was 53,761 ng hr/ml (35,294).

Food effect: administration of atazanavir with either a light meal or a high fat meal decreased the coefficient of variation of AUC and C_max approximately one-half compared to the fasting state. A similar decrease in the coefficient of variation was noted when REYATAZ 300 mg once daily with ritonavir 100 mg once daily was administered with a light meal in healthy subjects. 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. The mean elimination half-life of atazanavir in HIV-infected adult patients (n= 10) was 8.6 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 on patients with renal insufficiency (see 4.2); however, the impact of renal impairment on atazanavir elimination is anticipated to be minimal.

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 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 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.

The cloned human cardiac potassium channel, hERG, was inhibited by 15% in an in vitro patch clamp assay at a concentration (30 µM) corresponding to 30-fold the free drug concentration at Cmax in humans. 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 2-week and 9-month oral toxicity studies in dogs showed no drug-related electrocardiographic changes. The clinical relevance of these preclinical data
is unknown. Potential cardiac effects of this product in humans cannot be ruled out (see 4.4 and 4.8). The potential for PR prolongation should be considered in cases of overdose (see 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
Indigotin (E132)
Titanium dioxide (E171)

Blue ink containing:
Shellac
Dehydrated alcohol
Butyl alcohol
Propylene glycol
Ammonia solution
Indigotine aluminium lake (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**

One high-density polyethylene (HDPE) bottle closed with child resistant polypropylene closure containing 60 capsules.
Each Alu/Alu blister card contains 6 capsules, 60 capsules per carton.
Not all pack sizes may be marketed.

6.6 **Instructions for use and handling**

No special requirements.

7. **MARKETING AUTHORISATION HOLDER**

BRISTOL-MYERS SQUIBB PHARMA EEIG
141-149 Staines Road
Hounslow TW3 3JA
United Kingdom

8. **MARKETING AUTHORISATION NUMBER(S)**

EU/0/00/000/000

9. **DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**

10. **DATE OF REVISION OF THE TEXT**
1. NAME OF THE MEDICINAL PRODUCT

REYATAZ 150 mg hard capsules

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains 150 mg of atazanavir (corresponding to 170.8 mg atazanavir sulphate).
For excipients, see 6.1.

3. PHARMACEUTICAL FORM

Capsule, hard.
The capsules are opaque blue and powder blue. They are printed with edible white and blue inks, with "BMS 150" on one half and with "3624" on the other half.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

REYATAZ is indicated for the treatment of HIV-1 infected, antiretroviral treatment experienced 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 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 should be based on individual viral resistance testing and the patient’s treatment history (see 5.1).

4.2 Posology and method of administration

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

Oral use.

Adults: the recommended dose of REYATAZ is 300 mg (REYATAZ is available as 100 mg, 150 mg and 200 mg hard capsules) once daily taken with ritonavir 100 mg once daily and with food. Ritonavir is used as a booster of atazanavir pharmacokinetics (see 4.5 and 5.1).

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

Infants, toddlers, children, and adolescents: the efficacy and safety of REYATAZ have not been established in this population (see 5.2).

Patients with renal impairment: no dosage adjustment is needed (see 5.2).

Patients with hepatic impairment: REYATAZ with ritonavir should be used with caution in patients with mild hepatic insufficiency. REYATAZ should not be used in patients with moderate to severe hepatic insufficiency (see 4.3, 4.4, and 5.2). REYATAZ with ritonavir has not been studied in patients with hepatic insufficiency.
Method of administration: for oral administration. The capsules should be swallowed whole. REYATAZ oral powder is available for patients who are unable to swallow capsules. (See Summary of Product Characteristics for REYATAZ oral powder).

4.3 Contraindications

Hypersensitivity to atazanavir or to any of the excipients (see 6.1).

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

REYATAZ with ritonavir should not be used in combination with rifampicin (see 4.5).

REYATAZ with ritonavir should 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, and ergot alkaloids, particularly, ergotamine, dihydroergotamine, ergonovine, methylergonovine) (see 4.5).

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

4.4 Special warnings and special 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.

There are insufficient data to recommend a dose in antiretroviral treatment-naive patients at present.

Co-administration of REYATAZ with ritonavir in doses greater than 100 mg once daily has not been clinically evaluated. The use of higher ritonavir doses might alter the safety profile of atazanavir (cardiac effects, hyperbilirubinemia) and therefore is not recommended.

Patients with coexisting conditions

Atazanavir is primarily hepatically metabolised and increased plasma concentrations were observed in patients with hepatic impairment (see 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 events. 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 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.

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 5.1).

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.

Consideration should be given to the measurement of fasting serum lipids and blood glucose. Lipid disorders should be managed as clinically appropriate (see 4.8).

In clinical studies, REYATAZ (with or without ritonavir) has been shown to induce dyslipidemia to a lesser extent than comparators (see 5.1). However, the clinical impact of such findings has not been demonstrated in the absence of specific studies on cardiovascular risk.

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.

Hyperbilirubinemia
Reversible elevations in indirect (unconjugated) bilirubin related to inhibition of UDP-glucuronosyl transferase (UGT) have occurred in patients receiving REYATAZ (see 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) hyperbilirubinemia 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 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.

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

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

The concomitant use of REYATAZ and oral contraceptives should be avoided (see 4.5).
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 and ergot alkaloids, particularly ergotamine and dihydroergotamine (see 4.3).

Antiretroviral agents

Nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs):

Interaction studies with stavudine, lamivudine and zidovudine have been performed with REYATAZ without ritonavir. Based on data derived from these studies and because ritonavir is not expected to have a significant impact on the pharmacokinetics of NRTIs, the co-administration of REYATAZ and ritonavir with these medicinal products is not expected to significantly alter the exposure of the co-administered drugs. The same conclusion applies to the co-administration with abacavir. Considering that REYATAZ with ritonavir should be administered with food, didanosine should be taken 2 hours after REYATAZ with ritonavir.

Tenofovir disoproxil fumarate: atazanavir concentrations (AUC and C_{min}) are decreased when tenofovir is co-administered with REYATAZ (decrease of 25% and 40% of AUC and C_{min} respectively compared to atazanavir 400 mg). When ritonavir was added to atazanavir, the negative impact of tenofovir on atazanavir C_{min} was significantly reduced, whereas the decrease of AUC was of the same magnitude (decrease of 25% and 26% of AUC and C_{min} respectively compared to atazanavir/ritonavir 300/100 mg). The efficacy of REYATAZ with ritonavir in combination with tenofovir in treatment-experienced patients has been demonstrated in the clinical study 045 (see 4.8 and 5.1).

Non-nucleoside reverse transcriptase inhibitors (NNRTIs)

Efavirenz: if REYATAZ is to be co-administered with efavirenz, which decreases atazanavir exposure, it is recommended that REYATAZ 400 mg with ritonavir 100 mg be co-administered with efavirenz 600 mg (all as a single daily dose with food), as this combination is anticipated to result in atazanavir exposure that approximates the mean exposure to atazanavir produced by 300 mg of REYATAZ given with ritonavir 100 mg. No efficacy and safety data are available to support the co-administration of efavirenz and REYATAZ at the increased dose of 400 mg with ritonavir.

Nevirapine: The effects of co-administration of REYATAZ and nevirapine have not been studied. Nevirapine is a metabolic inducer of CYP3A4 and is expected to decrease atazanavir exposure. Therefore, in the absence of data regarding the expected interaction between REYATAZ with ritonavir and nevirapine, this co-administration is not recommended.

Protease inhibitors

Indinavir: indinavir is also associated with indirect (unconjugated) hyperbilirubinemia due to inhibition of UGT. Co-administration of REYATAZ and indinavir is not recommended (see 4.4).

Ritonavir: based on data in healthy volunteers, the addition of ritonavir 100 mg to atazanavir 300 mg has been shown to significantly increase the pharmacokinetic parameters of atazanavir (approximately, 2 fold increase of AUC and 7 fold increase of C_{min} in comparison to atazanavir 400 mg without ritonavir). In patients, the limited pharmacokinetic data currently available suggest that the impact of ritonavir might be less noticeable on the C_{min} (approximately, 3 fold increase).
The co-administration of REYATAZ with 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.

Other medicinal products

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 with ritonavir. REYATAZ with ritonavir should be administered 2 hours before or 1 hour after buffered medicinal products.

Antiarrhythmics (amiodarone, systemic lidocaine, quinidine): concentrations may be increased when co-administered with REYATAZ with ritonavir. Caution is warranted and therapeutic concentration monitoring is recommended when available. The concomitant use of quinidine is contraindicated (see 4.3).

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

Calcium channel blockers: co-administration of bepridil with REYATAZ is not recommended (see 4.3). Co-administration of diltiazem (180 mg once daily) with atazanavir (400 mg once daily) in healthy subjects resulted in a 2 to 3 fold increase in diltiazem and desacetyl-diltiazem exposure and no change in the pharmacokinetics of atazanavir. There was an increase in the maximum PR interval compared to atazanavir alone. Co-administration of diltiazem and REYATAZ with ritonavir has not been studied. An initial dose reduction of diltiazem by 50% is recommended, with subsequent titration as needed and ECG monitoring. Verapamil may also have its serum concentrations increased by REYATAZ with ritonavir; therefore, caution should be exercised when verapamil is co-administered with REYATAZ with ritonavir.

HMG-CoA reductase inhibitors (simvastatin, lovastatin, atorvastatin): simvastatin and lovastatin are highly dependent on CYP3A4 for their metabolism and co-administration with REYATAZ with ritonavir may result in increased concentrations. Concomitant use of simvastatin or lovastatin is not recommended due to an increased risk of myopathy including rhabdomyolysis. The risk of myopathy including rhabdomyolysis may also be increased when protease inhibitors, including REYATAZ with ritonavir, are used in combination with atorvastatin, which is also metabolised by CYP3A4. Caution should be exercised.

H2-Receptor antagonists and proton pump inhibitors: the effects of H2-receptor antagonists, proton pump inhibitors, or other gastric acid suppressors on REYATAZ have not been studied; however, reduced plasma concentrations of atazanavir may result due to increased gastric pH if these medicinal products are administered with REYATAZ with ritonavir. Caution should be exercised.

Immunosuppressants (cyclosporin, tacrolimus, sirolimus): concentrations of cyclosporin, tacrolimus, or sirolimus may be increased when co-administered with REYATAZ with ritonavir. More frequent therapeutic concentration monitoring of these medicinal products is recommended until plasma levels have been stabilised.

Macrolide antibiotics: co-administration of clarithromycin (500 mg twice daily) with atazanavir (400 mg once daily) resulted in a 2 fold increase in exposure to clarithromycin and a 70% decrease in exposure to 14-OH clarithromycin, with a 28% increase in the AUC of atazanavir. Dose reduction of clarithromycin may result in subtherapeutic concentrations of 14-OH clarithromycin. No recommendation regarding dose reduction can be made; therefore, caution should be exercised if REYATAZ plus ritonavir is co-administered with clarithromycin.

Oral contraceptives (ethinyl estradiol, norethindrone): the mean concentration of ethinyl estradiol, when co-administered as a 35-µg dose with atazanavir 400 mg once daily, was increased to a level
between mean concentrations produced by a 35-µg and a 50-µg ethinyl estradiol dose, and the AUC of norethindrone was increased about 2 fold. In contrast, ritonavir may decrease ethinyl estradiol concentrations. The effects of co-administration of oral contraceptives and REYATAZ with ritonavir have not been studied. The concomitant use of REYATAZ and oral contraceptives should be avoided (see 4.4). Alternate reliable methods of contraception should be considered.

**Rifabutin:** simultaneous administration of 400 mg of atazanavir and 150 mg of rifabutin once daily for 14 days resulted in no clinically important change in the C_max or AUC for atazanavir. No dose adjustment is needed for REYATAZ. The rifabutin C_max for the 150-mg dose was 1.5 fold higher and the AUC was 2.3 fold higher than historical data for a standard 300-mg dose. A rifabutin dose reduction of up to 75% (e.g., 150 mg every other day or 3 times per week) is recommended when administered with REYATAZ with ritonavir.

**Rifampicin:** although the effect of rifampicin on REYATAZ has not been studied, rifampicin decreases plasma concentrations and AUC of most protease inhibitors by about 90%. This may result in loss of therapeutic effect and development of resistance. The concomitant use of REYATAZ and rifampicin is contraindicated (see 4.3).

**Sildenafil:** sildenafil is metabolised by CYP3A4. Co-administration with REYATAZ may result in increased concentrations of sildenafil and an increase in sildenafil-associated adverse events, including hypotension, visual changes, and priapism. Patients should be warned about these possible side effects.

**Triazole antifungal agents:** co-administration with ketoconazole has only been studied with REYATAZ without ritonavir. Co-administration of 200 mg of ketoconazole with 400 mg of atazanavir in healthy subjects resulted in negligible increases in atazanavir AUC and C_max (respectively 11% and 3%). Plasma levels of both atazanavir and ritonavir may be increased by ketoconazole and itraconazole. High doses of ketoconazole and itraconazole (> 200 mg/day) should be used cautiously with atazanavir and ritonavir, by assessing the risk versus the benefit of such a combination.

**Warfarin:** co-administration with REYATAZ with 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 and ritonavir, especially when commencing therapy.

**St. John’s wort (Hypericum perforatum):** REYATAZ should not be used concomitantly with products containing St. John's wort since it 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 4.3).

### 4.6 Pregnancy and lactation

There are no adequate and well-controlled studies in pregnant women. Studies in animals have not shown evidence of selective developmental toxicity or effects on reproductive function and fertility (see 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 hyperbilirubinemia 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

There are no data to suggest that atazanavir affects the ability to drive or use machines. However, patients should be informed that dizziness has been reported during treatment with regimens containing REYATAZ (see 4.8).

4.8 Undesirable effects

Data on the safety and tolerability of REYATAZ 300 mg with ritonavir 100 mg once daily are limited, as this combination has only been evaluated in 119 patients in Study 045 in a regimen that also included tenofovir 300 mg once daily and a nucleoside reverse transcriptase inhibitor. Considering that tenofovir has been shown to decrease the plasma levels of atazanavir (with or without concomitant ritonavir), the safety data derived from this study may not fully reflect the safety profile of REYATAZ plus ritonavir when used in clinical practice within antiretroviral combinations that exclude tenofovir. An alteration of the safety profile of REYATAZ cannot be excluded in this context.

REYATAZ has been evaluated for safety and tolerability in combination therapy with other antiretroviral medicinal products in Phase II and III trials in 1,596 adult patients. The majority of patients (1,046) received REYATAZ 400 mg once daily without ritonavir. The median duration of treatment was 102 weeks in Phase II trials and 31 weeks in the Phase III trials. Adverse events were comparable between patients who received REYATAZ 300 mg with ritonavir 100 mg once daily and patients who received REYATAZ 400 mg once daily, except that jaundice and elevated total bilirubin levels were reported more frequently with REYATAZ plus ritonavir.

Among patients who received 400 mg once daily or 300 mg with ritonavir 100 mg once daily, the only adverse events of any severity reported very commonly with at least a possible relationship to regimens containing REYATAZ and one or more NRTIs were nausea (23%), headache (10%), and jaundice (10%). Among patients receiving REYATAZ 300 mg with ritonavir 100 mg, the frequency of jaundice was 15%. Jaundice was reported within a few days to a few months after the initiation of treatment (see 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 4.4 and 5.1).

Adult patients

The following adverse events 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, < 1/10), uncommon (≥ 1/1,000, < 1/100), rare (≥ 1/10,000, < 1/1,000), or very rare (< 1/10,000).
Immune system disorders: uncommon: allergic reaction

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

Psychiatric disorders: uncommon: anxiety, depression, sleep disorder

Nervous system disorders: common: headache, insomnia, peripheral neurologic symptoms; uncommon: abnormal dream, amnesia, confusion, dizziness, somnolence; rare: abnormal gait

Eye disorders: common: scleral icterus

Cardiac disorders and vascular disorders: uncommon: syncope; rare: hypertension, oedema, palpitation

Respiratory, thoracic and mediastinal disorders: uncommon: dyspnea

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

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

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

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

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

Reproductive system and breast disorders: uncommon: gynecomastia

General disorders and administration site conditions: common: asthenia; uncommon: chest pain, fatigue, fever, malaise
Laboratory abnormalities

The most frequently reported laboratory abnormality in patients receiving regimens containing REYATAZ and one or more NRTIs was elevated total bilirubin (82% Grade 1, 2, 3, or 4). Grade 3 or 4 elevation of total bilirubin was noted in 31% (26% Grade 3, 5% Grade 4, reported predominantly as elevated indirect [unconjugated] bilirubin). Among patients treated with REYATAZ 300 mg once daily with 100 mg ritonavir once daily, 45% had Grade 3-4 total bilirubin elevations (see 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 amylase (11%), elevated creatine kinase (7%), elevated alanine aminotransferase/serum glutamic-pyruvic transaminase (ALT/SGPT) (5%), low neutrophils (4%), elevated aspartate aminotransferase/serum glutamic-oxaloacetic transaminase (AST/SGOT) (3%), and elevated lipase (3%).

One 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 585 patients receiving atazanavir 400 mg once daily, 74 patients were co-infected with chronic hepatitis B or C, and among 119 patients receiving atazanavir 300 mg once daily with ritonavir 100 mg once daily, 20 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 4.4).

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) hyperbilirubinemia (without associated liver function test changes) or PR interval prolongations may be observed (see 4.4 and 4.8).

Treatment of overdose with REYATAZ should consist of general supportive measures, including monitoring of vital signs and 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: J05A E

Mechanism of action: atazanavir is an azapeptide HIV-1 protease inhibitor. 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 activity (EC₅₀ of 2 to 5 nM) against a variety of HIV isolates in the absence of human serum. REYATAZ administered 300 mg once daily with ritonavir 100 mg once daily results in a mean (±SD) Cₘᵢₙ of 862 (±838) ng/ml. The estimated protein-adjusted (in 40% human serum) Cₘᵢₙ is approximately 50 to 300 fold higher than the EC₅₀ values generated in representative HIV-infected cell lines. Combinations of atazanavir with stavudine, didanosine, lamivudine, zidovudine, nelfinavir, indinavir, ritonavir, saquinavir, or amprenavir in
HIV-infected peripheral blood mononuclear cells yielded additive antiviral effects and did not result in antagonistic anti-HIV activity or enhanced cytotoxic effects at the highest concentrations used for antiviral evaluation.

Cross-resistance in vitro in viruses resistant to other protease inhibitors: atazanavir susceptibility was evaluated in 943 clinical isolates from patients without prior atazanavir exposure and exhibiting a wide array of genotypic and phenotypic patterns. In vitro, there was a clear trend toward decreased susceptibility to atazanavir as isolates exhibited high resistance levels to multiple protease inhibitors. In general, susceptibility to atazanavir was retained (83% of isolates displayed < 2.5 fold change in EC50) among isolates resistant to no more than 2 protease inhibitors. Eighteen percent of isolates had 4 or more of the following 6 mutations considered critical mutations for protease inhibitors: amino acid substitutions 10, 46, 54, 82, 84, and 90. These isolates expressed a median fold change in EC50 relative to wildtype of 12.0 for atazanavir. Therefore, viral isolates having at least 4 of these specific mutations would be considered resistant for atazanavir.

Resistance in vivo: in antiretroviral treatment naive patients, the I50L substitution, sometimes in combination with an A71V change, is the signature resistance mutation for atazanavir. An atazanavir resistance phenotype is expressed in all recombinant viral clones containing the I50L substitution in a variety of genetic backgrounds. Resistance levels ranged from 3.5- to 29-fold. There was no evidence of cross-resistance between atazanavir and amprenavir, with insertion of the I50L and I50V substitutions yielding selective resistance to atazanavir and amprenavir, respectively.

In antiretroviral treatment experienced patients, within the 74 isolates from patients who developed resistance to atazanavir on therapy that included either atazanavir, atazanavir + ritonavir, or atazanavir + saquinavir, only 9 isolates from patients treated with either atazanavir or atazanavir + ritonavir displayed the I50L phenotype previously described in naive patients. The resistance in antiretroviral treatment experienced patients mainly occurs by accumulation of the primary and secondary resistance substitutions described previously to be involved in protease inhibitor resistance. These isolates developed higher levels of resistance to the other protease inhibitors.

Clinical experience: in antiretroviral treatment experienced patients, the benefit of REYATAZ is based only on Study 045 where REYATAZ 300 mg once daily was used with ritonavir 100 mg once daily and compared with lopinavir + ritonavir. Study 045 is an ongoing, randomised, multicenter trial comparing REYATAZ (300 mg once daily) with ritonavir (100 mg once daily) to REYATAZ (400 mg once daily) with saquinavir soft gelatine capsules (1,200 mg once daily), and to lopinavir + ritonavir (400/100 mg fixed dose combination twice daily), each in combination with tenofovir (see 4.5 and 4.8) and one NRTI, in 347 (of 358 randomised) patients with virologic failure on two or more prior regimens containing at least one PI, NRTI, and NNRTI. At baseline, 34% of patients were receiving a PI and 60% were receiving an NNRTI. Sixteen of 120 (13%) patients in the REYATAZ + ritonavir treatment arm and 18 of 123 (15%) patients in the lopinavir + ritonavir arm had four or more of the PI mutations 10, 46, 54, 82, 84, and 90. Thirty-two percent of patients in the study had a viral strain with fewer than two NRTI mutations. 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 5.9 log10 copies/ml). The population included in this study was moderately pretreated.

The primary endpoint was the time-averaged difference in change from baseline in HIV RNA through 24 weeks.

Through 24 weeks of treatment, the decreases from baseline in HIV RNA levels (primary endpoint) were 1.86 log10 copies/ml for REYATAZ + ritonavir and 1.89 log10 copies/ml for lopinavir + ritonavir. REYATAZ + ritonavir was similar (non-inferior) to lopinavir + ritonavir on this efficacy measure (time-averaged difference of 0.14, 97.5% confidence interval [-0.09, 0.37]). Consistent results were obtained with the last observation carried forward method of analysis (time-averaged difference of 0.10, 97.5% confidence interval [-0.13, 0.33]). The proportions of patients with HIV RNA
< 400 copies/ml in the REYATAZ + ritonavir arm and the lopinavir + ritonavir arm were 63% and 60%, respectively, by intent-to-treat analysis, with missing values considered as failures. The proportions of patients with HIV RNA < 50 copies/ml in the REYATAZ + ritonavir arm and the lopinavir + ritonavir arm were 38% and 41%, respectively. 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 68% (47%) and 68% (51%), respectively. The mean increases from baseline in CD4 cell count were 83 cells/mm$^3$ and 90 cells/mm$^3$ in the REYATAZ + ritonavir and lopinavir + ritonavir arms, respectively. Two subset analyses were performed based on baseline genotypic mutations. In the first, the results significantly favoured the lopinavir + ritonavir arm when considering the subset of patients with $\geq$ 4 mutations among the following: 10, 20, 24, 32, 33, 36, 46, 48, 50, 54, 63, 71, 73, 82, 84 and 90. In the second, for patients with < 4 of the protease gene mutations 10, 46, 54, 82, 84, and 90, the proportion with HIV RNA < 400 copies/ml was 70% for REYATAZ + ritonavir and 65% for lopinavir + ritonavir, and the proportion with HIV RNA < 50 copies/ml was 44% in each treatment arm. In patients with $\geq$ 4 of these mutations, the proportion with HIV RNA < 400 copies/ml was 19% for REYATAZ + ritonavir and 39% for lopinavir + ritonavir, and the proportion with HIV RNA < 50 copies/ml was respectively 0% and 22%.

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

The data available on the lipid profile are described in the following table:

<table>
<thead>
<tr>
<th>Study -045 24 weeks</th>
<th>ATV/RTV</th>
<th>LPV/RTV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total Cholesterol</td>
<td>-8%</td>
<td>3%</td>
</tr>
<tr>
<td>LDL Cholesterol</td>
<td>-10%</td>
<td>-4%</td>
</tr>
<tr>
<td>HDL Cholesterol</td>
<td>-7%</td>
<td>0%</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>-2%</td>
<td>31%</td>
</tr>
</tbody>
</table>

5.2 Pharmacokinetic properties

Limited data are available on the pharmacokinetics of atazanavir in association with low dose ritonavir. The pharmacokinetics of atazanavir were evaluated in healthy adult volunteers and in HIV-infected patients; no substantial differences were observed between the two groups. The pharmacokinetics of atazanavir exhibit a non-linear disposition and a high inter/intra-subject variability that is minimised with food. In healthy subjects, the AUC of atazanavir from the capsules and oral powder were similar. Therefore, HIV-infected patients can use the two formulations interchangeably.

**Absorption:** the pharmacokinetics of atazanavir boosted with ritonavir is currently supported by limited data in patients. In a pharmacokinetic study in HIV-positive patients (n= 10), multiple dosing of REYATAZ 300 mg once daily with ritonavir 100 mg once daily with a light meal for 2 weeks produced a mean steady-state C$_{max}$ (SD) of 5,233 ng/ml (3,033), occurring approximately 3.0 hours (T$_{max}$) after administration, and a mean steady-state trough concentration (SD) of 862 ng/ml (838). The mean steady-state plasma AUC (SD) of atazanavir was 53,761 ng hr/ml (35,294).

**Food effect:** administration of atazanavir with either a light meal or a high fat meal decreased the coefficient of variation of AUC and C$_{max}$ approximately one-half compared to the fasting state. A similar decrease in the coefficient of variation was noted when REYATAZ 300 mg once daily with ritonavir 100 mg once daily was administered with a light meal in healthy subjects. 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. The mean elimination half-life of atazanavir in HIV-infected adult patients (n= 10) was 8.6 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 on patients with renal insufficiency (see 4.2); however, the impact of renal impairment on atazanavir elimination is anticipated to be minimal.

**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 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 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.

The cloned human cardiac potassium channel, hERG, was inhibited by 15% in an in vitro patch clamp assay at a concentration (30 µM) corresponding to 30-fold the free drug concentration at $C_{\text{max}}$ in humans. 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 2-week and 9-month oral toxicity studies in dogs showed no drug-related electrocardiographic changes. The clinical relevance of these preclinical data
is unknown. Potential cardiac effects of this product in humans cannot be ruled out (see 4.4 and 4.8). The potential for PR prolongation should be considered in cases of overdose (see 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
Indigotin (E132)
Titanium dioxide (E171)

Blue ink containing:
Shellac
Dehydrated alcohol
Butyl alcohol
Propylene glycol
Ammonia solution
Indigotine aluminium lake (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

One high-density polyethylene (HDPE) bottle closed with child resistant polypropylene closure containing 60 capsules.
Each Alu/Alu blister card contains 6 capsules, 60 capsules per carton.
Not all pack sizes may be marketed.

6.6 Instructions for use and handling

No special requirements.

7. MARKETING AUTHORIZATION HOLDER

BRISTOL-MYERS SQUIBB PHARMA EEIG
141-149 Staines Road
Hounslow TW3 3JA
United Kingdom

8. MARKETING AUTHORIZATION NUMBER(S)

EU/0/00/000/000

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORIZATION

10. DATE OF REVISION OF THE TEXT
1. NAME OF THE MEDICINAL PRODUCT

REYATAZ 200 mg hard capsules

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains 200 mg of atazanavir (corresponding to 227.8 mg atazanavir sulphate). For excipients, see 6.1.

3. PHARMACEUTICAL FORM

Capsule, hard. The capsules are opaque blue. They are printed with edible white ink, with "BMS 200" on one half and with "3631" on the other half.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

REYATAZ is indicated for the treatment of HIV-1 infected, antiretroviral treatment experienced 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 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 should be based on individual viral resistance testing and the patient’s treatment history (see 5.1).

4.2 Posology and method of administration

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

Oral use.

Adults: the recommended dose of REYATAZ is 300 mg (REYATAZ is available as 100 mg, 150 mg and 200 mg hard capsules) once daily taken with ritonavir 100 mg once daily and with food. Ritonavir is used as a booster of atazanavir pharmacokinetics (see 4.5 and 5.1).

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

Infants, toddlers, children, and adolescents: the efficacy and safety of REYATAZ have not been established in this population (see 5.2).

Patients with renal impairment: no dosage adjustment is needed (see 5.2).

Patients with hepatic impairment: REYATAZ with ritonavir should be used with caution in patients with mild hepatic insufficiency. REYATAZ should not be used in patients with moderate to severe hepatic insufficiency (see 4.3, 4.4, and 5.2). REYATAZ with ritonavir has not been studied in patients with hepatic insufficiency.
Method of administration: for oral administration. The capsules should be swallowed whole. REYATAZ oral powder is available for patients who are unable to swallow capsules. (See Summary of Product Characteristics for REYATAZ oral powder).

4.3 Contraindications

Hypersensitivity to atazanavir or to any of the excipients (see 6.1).

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

REYATAZ with ritonavir should not be used in combination with rifampicin (see 4.5).

REYATAZ with ritonavir should 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, and ergot alkaloids, particularly, ergotamine, dihydroergotamine, ergonovine, methylergonovine) (see 4.5).

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

4.4 Special warnings and special 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.

There are insufficient data to recommend a dose in antiretroviral treatment-naive patients at present.

Co-administration of REYATAZ with ritonavir in doses greater than 100 mg once daily has not been clinically evaluated. The use of higher ritonavir doses might alter the safety profile of atazanavir (cardiac effects, hyperbilirubinemia) and therefore is not recommended.

Patients with coexisting conditions

Atazanavir is primarily hepatically metabolised and increased plasma concentrations were observed in patients with hepatic impairment (see 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 events. 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 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.

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 5.1).

There have been reports of increased bleeding, including spontaneous skin haematomas and haemarthroses, in type A and B haemophilic 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. Haemophilic 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.

Consideration should be given to the measurement of fasting serum lipids and blood glucose. Lipid disorders should be managed as clinically appropriate (see 4.8).

In clinical studies, REYATAZ (with or without ritonavir) has been shown to induce dyslipidemia to a lesser extent than comparators (see 5.1). However, the clinical impact of such findings has not been demonstrated in the absence of specific studies on cardiovascular risk.

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.

Hyperbilirubinemia
Reversible elevations in indirect (unconjugated) bilirubin related to inhibition of UDP-glucuronosyl transferase (UGT) have occurred in patients receiving REYATAZ (see 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) hyperbilirubinemia 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 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.

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

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

The concomitant use of REYATAZ and oral contraceptives should be avoided (see 4.5).
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 and ergot alkaloids, particularly ergotamine and dihydroergotamine (see 4.3).

Antiretroviral agents

*Nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs):*

Interaction studies with stavudine, lamivudine and zidovudine have been performed with REYATAZ without ritonavir. Based on data derived from these studies and because ritonavir is not expected to have a significant impact on the pharmacokinetics of NRTIs, the co-administration of REYATAZ and ritonavir with these medicinal products is not expected to significantly alter the exposure of the co-administered drugs. The same conclusion applies to the co-administration with abacavir. Considering that REYATAZ with ritonavir should be administered with food, didanosine should be taken 2 hours after REYATAZ with ritonavir.

*Tenofovir disoproxil fumarate:*

Atazanavir concentrations (AUC and C_{min}) are decreased when tenofovir is co-administered with REYATAZ (decrease of 25% and 40% of AUC and C_{min} respectively compared to atazanavir 400 mg). When ritonavir was added to atazanavir, the negative impact of tenofovir on atazanavir C_{min} was significantly reduced, whereas the decrease of AUC was of the same magnitude (decrease of 25% and 26% of AUC and C_{min} respectively compared to atazanavir/ritonavir 300/100 mg). The efficacy of REYATAZ with ritonavir in combination with tenofovir in treatment-experienced patients has been demonstrated in the clinical study 045 (see 4.8 and 5.1).

*Non-nucleoside reverse transcriptase inhibitors (NNRTIs)*

Efavirenz: if REYATAZ is to be co-administered with efavirenz, which decreases atazanavir exposure, it is recommended that REYATAZ 400 mg with ritonavir 100 mg be co-administered with efavirenz 600 mg (all as a single daily dose with food), as this combination is anticipated to result in atazanavir exposure that approximates the mean exposure to atazanavir produced by 300 mg of REYATAZ given with ritonavir 100 mg. No efficacy and safety data are available to support the co-administration of efavirenz and REYATAZ at the increased dose of 400 mg with ritonavir.

Nevirapine: The effects of co-administration of REYATAZ and nevirapine have not been studied. Nevirapine is a metabolic inducer of CYP3A4 and is expected to decrease atazanavir exposure. Therefore, in the absence of data regarding the expected interaction between REYATAZ with ritonavir and nevirapine, this co-administration is not recommended.

*Protease inhibitors*

Indinavir: indinavir is also associated with indirect (unconjugated) hyperbilirubinemia due to inhibition of UGT. Co-administration of REYATAZ and indinavir is not recommended (see 4.4).

Ritonavir: based on data in healthy volunteers, the addition of ritonavir 100 mg to atazanavir 300 mg has been shown to significantly increase the pharmacokinetic parameters of atazanavir (approximately, 2 fold increase of AUC and 7 fold increase of C_{min} in comparison to atazanavir 400 mg without ritonavir). In patients, the limited pharmacokinetic data currently available suggest that the impact of ritonavir might be less noticeable on the C_{min} (approximately, 3 fold increase).
The co-administration of REYATAZ with 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.

**Other medicinal products**

*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 with ritonavir. REYATAZ with ritonavir should be administered 2 hours before or 1 hour after buffered medicinal products.

*Antiarrhythmics (amiodarone, systemic lidocaine, quinidine)*: concentrations may be increased when co-administered with REYATAZ with ritonavir. Caution is warranted and therapeutic concentration monitoring is recommended when available. The concomitant use of quinidine is contraindicated (see 4.3).

*Antineoplastics*: atazanavir inhibits UGT and may interfere with the metabolism of irinotecan, resulting in increased irinotecan toxicities.

*Calcium channel blockers*: co-administration of bepridil with REYATAZ is not recommended (see 4.3). Co-administration of diltiazem (180 mg once daily) with atazanavir (400 mg once daily) in healthy subjects resulted in a 2 to 3 fold increase in diltiazem and desacetyl-diltiazem exposure and no change in the pharmacokinetics of atazanavir. There was an increase in the maximum PR interval compared to atazanavir alone. Co-administration of diltiazem and REYATAZ with ritonavir has not been studied. An initial dose reduction of diltiazem by 50% is recommended, with subsequent titration as needed and ECG monitoring. Verapamil may also have its serum concentrations increased by REYATAZ with ritonavir; therefore, caution should be exercised when verapamil is co-administered with REYATAZ with ritonavir.

*HMG-CoA reductase inhibitors (simvastatin, lovastatin, atorvastatin)*: simvastatin and lovastatin are highly dependent on CYP3A4 for their metabolism and co-administration with REYATAZ with ritonavir may result in increased concentrations. Concomitant use of simvastatin or lovastatin is not recommended due to an increased risk of myopathy including rhabdomyolysis. The risk of myopathy including rhabdomyolysis may also be increased when protease inhibitors, including REYATAZ with ritonavir, are used in combination with atorvastatin, which is also metabolised by CYP3A4. Caution should be exercised.

*H₂-Receptor antagonists and proton pump inhibitors*: the effects of H₂-receptor antagonists, proton pump inhibitors, or other gastric acid suppressors on REYATAZ have not been studied; however, reduced plasma concentrations of atazanavir may result due to increased gastric pH if these medicinal products are administered with REYATAZ with ritonavir. Caution should be exercised.

*Immunosuppressants (cyclosporin, tacrolimus, sirolimus)*: concentrations of cyclosporin, tacrolimus, or sirolimus may be increased when co-administered with REYATAZ with ritonavir. More frequent therapeutic concentration monitoring of these medicinal products is recommended until plasma levels have been stabilised.

*Macrolide antibiotics*: co-administration of clarithromycin (500 mg twice daily) with atazanavir (400 mg once daily) resulted in a 2 fold increase in exposure to clarithromycin and a 70% decrease in exposure to 14-OH clarithromycin, with a 28% increase in the AUC of atazanavir. Dose reduction of clarithromycin may result in subtherapeutic concentrations of 14-OH clarithromycin. No recommendation regarding dose reduction can be made; therefore, caution should be exercised if REYATAZ plus ritonavir is co-administered with clarithromycin.

*Oral contraceptives (ethinyl estradiol, norethindrone)*: the mean concentration of ethinyl estradiol, when co-administered as a 35-µg dose with atazanavir 400 mg once daily, was increased to a level
between mean concentrations produced by a 35-µg and a 50-µg ethinyl estradiol dose, and the AUC of norethindrone was increased about 2 fold. In contrast, ritonavir may decrease ethinyl estradiol concentrations. The effects of co-administration of oral contraceptives and REYATAZ with ritonavir have not been studied. The concomitant use of REYATAZ and oral contraceptives should be avoided (see 4.4). Alternate reliable methods of contraception should be considered.

**Rifabutin:** simultaneous administration of 400 mg of atazanavir and 150 mg of rifabutin once daily for 14 days resulted in no clinically important change in the C<sub>max</sub> or AUC for atazanavir. No dose adjustment is needed for REYATAZ. The rifabutin C<sub>max</sub> for the 150-mg dose was 1.5 fold higher and the AUC was 2.3 fold higher than historical data for a standard 300-mg dose. A rifabutin dose reduction of up to 75% (e.g., 150 mg every other day or 3 times per week) is recommended when administered with REYATAZ with ritonavir.

**Rifampicin:** although the effect of rifampicin on REYATAZ has not been studied, rifampicin decreases plasma concentrations and AUC of most protease inhibitors by about 90%. This may result in loss of therapeutic effect and development of resistance. The concomitant use of REYATAZ and rifampicin is contraindicated (see 4.3).

**Sildenafil:** sildenafil is metabolised by CYP3A4. Co-administration with REYATAZ may result in increased concentrations of sildenafil and an increase in sildenafil-associated adverse events, including hypotension, visual changes, and priapism. Patients should be warned about these possible side effects.

**Triazole antifungal agents:** co-administration with ketoconazole has only been studied with REYATAZ without ritonavir. Co-administration of 200 mg of ketoconazole with 400 mg of atazanavir in healthy subjects resulted in negligible increases in atazanavir AUC and C<sub>max</sub> (respectively 11% and 3%). Plasma levels of both atazanavir and ritonavir may be increased by ketoconazole and itraconazole. High doses of ketoconazole and itraconazole (> 200 mg/day) should be used cautiously with atazanavir and ritonavir, by assessing the risk versus the benefit of such a combination.

**Warfarin:** co-administration with REYATAZ with 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 and ritonavir, especially when commencing therapy.

**St. John’s wort (Hypericum perforatum):** REYATAZ should not be used concomitantly with products containing St. John's wort since it 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 4.3).

### 4.6 Pregnancy and lactation

There are no adequate and well-controlled studies in pregnant women. Studies in animals have not shown evidence of selective developmental toxicity or effects on reproductive function and fertility (see 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 hyperbilirubinemia 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

There are no data to suggest that atazanavir affects the ability to drive or use machines. However, patients should be informed that dizziness has been reported during treatment with regimens containing REYATAZ (see 4.8).

4.8 Undesirable effects

Data on the safety and tolerability of REYATAZ 300 mg with ritonavir 100 mg once daily are limited, as this combination has only been evaluated in 119 patients in Study 045 in a regimen that also included tenofovir 300 mg once daily and a nucleoside reverse transcriptase inhibitor. Considering that tenofovir has been shown to decrease the plasma levels of atazanavir (with or without concomitant ritonavir), the safety data derived from this study may not fully reflect the safety profile of REYATAZ plus ritonavir when used in clinical practice within antiretroviral combinations that exclude tenofovir. An alteration of the safety profile of REYATAZ cannot be excluded in this context.

REYATAZ has been evaluated for safety and tolerability in combination therapy with other antiretroviral medicinal products in Phase II and III trials in 1,596 adult patients. The majority of patients (1,046) received REYATAZ 400 mg once daily without ritonavir. The median duration of treatment was 102 weeks in Phase II trials and 31 weeks in the Phase III trials. Adverse events were comparable between patients who received REYATAZ 300 mg with ritonavir 100 mg once daily and patients who received REYATAZ 400 mg once daily, except that jaundice and elevated total bilirubin levels were reported more frequently with REYATAZ plus ritonavir.

Among patients who received 400 mg once daily or 300 mg with ritonavir 100 mg once daily, the only adverse events of any severity reported very commonly with at least a possible relationship to regimens containing REYATAZ and one or more NRTIs were nausea (23%), headache (10%), and jaundice (10%). Among patients receiving REYATAZ 300 mg with ritonavir 100 mg, the frequency of jaundice was 15%. Jaundice was reported within a few days to a few months after the initiation of treatment (see 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 4.4 and 5.1).

Adult patients

The following adverse events 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, < 1/10), uncommon (≥ 1/1,000, < 1/100), rare (≥ 1/10,000, < 1/1,000), or very rare (< 1/10,000).
Immune system disorders: uncommon: allergic reaction

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

Psychiatric disorders: uncommon: anxiety, depression, sleep disorder

Nervous system disorders: common: headache, insomnia, peripheral neurologic symptoms; uncommon: abnormal dream, amnesia, confusion, dizziness, somnolence; rare: abnormal gait

Eye disorders: common: scleral icterus

Cardiac disorders and vascular disorders: uncommon: syncope; rare: hypertension, oedema, palpitation

Respiratory, thoracic and mediastinal disorders: uncommon: dyspnea

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

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

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

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

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

Reproductive system and breast disorders: uncommon: gynecomastia

General disorders and administration site conditions: common: asthenia; uncommon: chest pain, fatigue, fever, malaise
Laboratory abnormalities
The most frequently reported laboratory abnormality in patients receiving regimens containing REYATAZ and one or more NRTIs was elevated total bilirubin (82% Grade 1, 2, 3, or 4). Grade 3 or 4 elevation of total bilirubin was noted in 31% (26% Grade 3, 5% Grade 4, reported predominantly as elevated indirect [unconjugated] bilirubin). Among patients treated with REYATAZ 300 mg once daily with 100 mg ritonavir once daily, 45% had Grade 3-4 total bilirubin elevations (see 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 amylase (11%), elevated creatine kinase (7%), elevated alanine aminotransferase/serum glutamic-pyruvic transaminase (ALT/SGPT) (5%), low neutrophils (4%), elevated aspartate aminotransferase/serum glutamic-oxaloacetic transaminase (AST/SGOT) (3%), and elevated lipase (3%).

One 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 585 patients receiving atazanavir 400 mg once daily, 74 patients were co-infected with chronic hepatitis B or C, and among 119 patients receiving atazanavir 300 mg once daily with ritonavir 100 mg once daily, 20 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 4.4).

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) hyperbilirubinemia (without associated liver function test changes) or PR interval prolongations may be observed (see 4.4 and 4.8).

Treatment of overdose with REYATAZ should consist of general supportive measures, including monitoring of vital signs and 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: J05A E

Mechanism of action: atazanavir is an azapeptide HIV-1 protease inhibitor. 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 activity (EC₅₀ of 2 to 5 nM) against a variety of HIV isolates in the absence of human serum. REYATAZ administered 300 mg once daily with ritonavir 100 mg once daily results in a mean (±SD) Cₘᵟᵢₙ of 862 (±838) ng/ml. The estimated protein-adjusted (in 40% human serum) Cₘᵟᵢₙ is approximately 50 to 300 fold higher than the EC₅₀ values generated in representative HIV-infected cell lines. Combinations of atazanavir with stavudine, didanosine, lamivudine, zidovudine, nelfinavir, indinavir, ritonavir, saquinavir, or amprenavir in
HIV-infected peripheral blood mononuclear cells yielded additive antiviral effects and did not result in antagonistic anti-HIV activity or enhanced cytotoxic effects at the highest concentrations used for antiviral evaluation.

Cross-resistance in vitro in viruses resistant to other protease inhibitors: atazanavir susceptibility was evaluated in 943 clinical isolates from patients without prior atazanavir exposure and exhibiting a wide array of genotypic and phenotypic patterns. In vitro, there was a clear trend toward decreased susceptibility to atazanavir as isolates exhibited high resistance levels to multiple protease inhibitors. In general, susceptibility to atazanavir was retained (83% of isolates displayed < 2.5 fold change in EC50) among isolates resistant to no more than 2 protease inhibitors. Eighteen percent of isolates had 4 or more of the following 6 mutations considered critical mutations for protease inhibitors: amino acid substitutions 10, 46, 54, 82, 84, and 90. These isolates expressed a median fold change in EC50 relative to wildtype of 12.0 for atazanavir. Therefore, viral isolates having at least 4 of these specific mutations would be considered resistant for atazanavir.

Resistance in vivo: in antiretroviral treatment naive patients, the I50L substitution, sometimes in combination with an A71V change, is the signature resistance mutation for atazanavir. An atazanavir resistance phenotype is expressed in all recombinant viral clones containing the I50L substitution in a variety of genetic backgrounds. Resistance levels ranged from 3.5- to 29-fold. There was no evidence of cross-resistance between atazanavir and amprenavir, with insertion of the I50L and I50V substitutions yielding selective resistance to atazanavir and amprenavir, respectively.

In antiretroviral treatment experienced patients, within the 74 isolates from patients who developed resistance to atazanavir on therapy that included either atazanavir, atazanavir + ritonavir, or atazanavir + saquinavir, only 9 isolates from patients treated with either atazanavir or atazanavir + ritonavir displayed the I50L phenotype previously described in naive patients. The resistance in antiretroviral treatment experienced patients mainly occurs by accumulation of the primary and secondary resistance substitutions described previously to be involved in protease inhibitor resistance. These isolates developed higher levels of resistance to the other protease inhibitors.

Clinical experience: in antiretroviral treatment experienced patients, the benefit of REYATAZ is based only on Study 045 where REYATAZ 300 mg once daily was used with ritonavir 100 mg once daily and compared with lopinavir + ritonavir. Study 045 is an ongoing, randomised, multicenter trial comparing REYATAZ (300 mg once daily) with ritonavir (100 mg once daily) to REYATAZ (400 mg once daily) with saquinavir soft gelatine capsules (1,200 mg once daily), and to lopinavir + ritonavir (400/100 mg fixed dose combination twice daily), each in combination with tenofovir (see 4.5 and 4.8) and one NRTI, in 347 (of 358 randomised) 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. Sixteen of 120 (13%) patients in the REYATAZ + ritonavir treatment arm and 18 of 123 (15%) patients in the lopinavir + ritonavir arm had four or more of the PI mutations 10, 46, 54, 82, 84, and 90. Thirty-two percent of patients in the study had a viral strain with fewer than two NNRTI mutations. 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 5.9 log10 copies/ml). The population included in this study was moderately pretreated.

The primary endpoint was the time-averaged difference in change from baseline in HIV RNA through 24 weeks.

Through 24 weeks of treatment, the decreases from baseline in HIV RNA levels (primary endpoint) were 1.86 log10 copies/ml for REYATAZ + ritonavir and 1.89 log10 copies/ml for lopinavir + ritonavir. REYATAZ + ritonavir was similar (non-inferior) to lopinavir + ritonavir on this efficacy measure (time-averaged difference of 0.14, 97.5% confidence interval [-0.09, 0.37]). Consistent results were obtained with the last observation carried forward method of analysis (time-averaged difference of 0.10, 97.5% confidence interval [-0.13, 0.33]). The proportions of patients with HIV RNA
< 400 copies/ml in the REYATAZ + ritonavir arm and the lopinavir + ritonavir arm were 63% and 60%, respectively, by intent-to-treat analysis, with missing values considered as failures. The proportions of patients with HIV RNA < 50 copies/ml in the REYATAZ + ritonavir arm and the lopinavir + ritonavir arm were 38% and 41%, respectively. 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 68% (47%) and 68% (51%), respectively. The mean increases from baseline in CD4 cell count were 83 cells/mm³ and 90 cells/mm³ in the REYATAZ + ritonavir and lopinavir + ritonavir arms, respectively. Two subset analyses were performed based on baseline genotypic mutations. In the first, the results significantly favoured the lopinavir + ritonavir arm when considering the subset of patients with ≥ 4 mutations among the following: 10, 20, 24, 32, 33, 36, 46, 48, 50, 54, 63, 71, 73, 82, 84 and 90. In the second, for patients with < 4 of the protease gene mutations 10, 46, 54, 82, 84, and 90, the proportion with HIV RNA < 400 copies/ml was 70% for REYATAZ + ritonavir and 65% for lopinavir + ritonavir, and the proportion with HIV RNA < 50 copies/ml was 44% in each treatment arm. In patients with ≥ 4 of these mutations, the proportion with HIV RNA < 400 copies/ml was 19% for REYATAZ + ritonavir and 39% for lopinavir + ritonavir, and the proportion with HIV RNA < 50 copies/ml was respectively 0% and 22%.

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

The data available on the lipid profile are described in the following table:

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<th>Study -045 24 weeks</th>
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<tr>
<td></td>
<td>ATV/RTV</td>
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<tr>
<td>Total Cholesterol</td>
<td>-8%</td>
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<tr>
<td>LDL Cholesterol</td>
<td>-10%</td>
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<td>HDL Cholesterol</td>
<td>-7%</td>
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<tr>
<td>Triglycerides</td>
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### 5.2 Pharmacokinetic properties

Limited data are available on the pharmacokinetics of atazanavir in association with low dose ritonavir. The pharmacokinetics of atazanavir were evaluated in healthy adult volunteers and in HIV-infected patients; no substantial differences were observed between the two groups. The pharmacokinetics of atazanavir exhibit a non-linear disposition and a high inter/intra-subject variability that is minimised with food. In healthy subjects, the AUC of atazanavir from the capsules and oral powder were similar. Therefore, HIV-infected patients can use the two formulations interchangeably.

**Absorption:** the pharmacokinetics of atazanavir boosted with ritonavir is currently supported by limited data in patients. In a pharmacokinetic study in HIV-positive patients (n= 10), multiple dosing of REYATAZ 300 mg once daily with ritonavir 100 mg once daily with a light meal for 2 weeks produced a mean steady-state C\text{max} (SD) of 5,233 ng/ml (3,033), occurring approximately 3.0 hours (T\text{max}) after administration, and a mean steady-state trough concentration (SD) of 862 ng/ml (838). The mean steady-state plasma AUC (SD) of atazanavir was 53,761 ng hr/ml (35,294).

**Food effect:** administration of atazanavir with either a light meal or a high fat meal decreased the coefficient of variation of AUC and C\text{max} approximately one-half compared to the fasting state. A similar decrease in the coefficient of variation was noted when REYATAZ 300 mg once daily with ritonavir 100 mg once daily was administered with a light meal in healthy subjects. 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. The mean elimination half-life of atazanavir in HIV-infected adult patients ($n=10$) was 8.6 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 on patients with renal insufficiency (see 4.2); however, the impact of renal impairment on atazanavir elimination is anticipated to be minimal.

**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 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 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.

The cloned human cardiac potassium channel, hERG, was inhibited by 15% in an *in vitro* patch clamp assay at a concentration (30 µM) corresponding to 30-fold the free drug concentration at $C_{\text{max}}$ in humans. 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 2-week and 9-month oral toxicity studies in dogs showed no drug-related electrocardiographic changes. The clinical relevance of these preclinical data
is unknown. Potential cardiac effects of this product in humans cannot be ruled out (see 4.4 and 4.8). The potential for PR prolongation should be considered in cases of overdose (see 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
Indigotin (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

One high-density polyethylene (HDPE) bottle closed with child resistant polypropylene closure containing 60 capsules. Each Alu/Alu blister card contains 6 capsules, 60 capsules per carton. Not all pack sizes may be marketed.

6.6 Instructions for use and handling

No special requirements.

7. MARKETING AUTHORISATION HOLDER

BRISTOL-MYERS SQUIBB PHARMA EEIG
141-149 Staines Road
Hounslow TW3 3JA
United Kingdom

8. MARKETING AUTHORISATION NUMBER(S)

EU/0/00/000/000

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

10. DATE OF REVISION OF THE TEXT
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 corresponding to 56.95 mg atazanavir sulphate.
For excipients, see 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, antiretroviral treatment experienced 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 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 should be based on individual viral resistance testing and the patient’s treatment history (see 5.1).

4.2 Posology and method of administration

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

Oral use.

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 and with food. Ritonavir is used as a booster of atazanavir pharmacokinetics (see 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 taken with food (see 4.5).

Infants, toddlers, children, and adolescents: the efficacy and safety of REYATAZ have not been established in this population (see 5.2).

Patients with renal impairment: no dosage adjustment is needed (see 5.2).

Patients with hepatic impairment: REYATAZ with ritonavir should be used with caution in patients with mild hepatic insufficiency. REYATAZ should not be used in patients with moderate to severe hepatic insufficiency (see 4.3, 4.4 and 5.2). REYATAZ with ritonavir has not been studied in patients with hepatic insufficiency.
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 atazanavir or to any of the excipients (see 6.1).

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

REYATAZ with ritonavir should not be used in combination with rifampicin (see 4.5).

REYATAZ with ritonavir should 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, and ergot alkaloids, particularly, ergotamine, dihydroergotamine, ergonovine, methylergonovine) (see 4.5).

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

4.4 Special warnings and special 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.

There are insufficient data to recommend a dose in antiretroviral treatment-naive patients at present.

Co-administration of REYATAZ with ritonavir in doses greater than 100 mg once daily has not been clinically evaluated. The use of higher ritonavir doses might alter the safety profile of atazanavir (cardiac effects, hyperbilirubinemia) and therefore is not recommended.

Patients with coexisting conditions

Atazanavir is primarily hepatically metabolised and increased plasma concentrations were observed in patients with hepatic impairment (see 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 events. 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 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.

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 5.1).
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.

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.

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 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.

Consideration should be given to the measurement of fasting serum lipids and blood glucose. Lipid disorders should be managed as clinically appropriate (see 4.8).

In clinical studies, REYATAZ (with or without ritonavir) has been shown to induce dyslipidemia to a lesser extent than comparators (see 5.1). However, the clinical impact of such findings has not been demonstrated in the absence of specific studies on cardiovascular risk.

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.

Hyperbilirubinemia
Reversible elevations in indirect (unconjugated) bilirubin related to inhibition of UDP-glucuronosyl transferase (UGT) have occurred in patients receiving REYATAZ (see 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) hyperbilirubinemia 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 4.5).

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

The concomitant use of REYATAZ and oral contraceptives should be avoided (see 4.5).

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 and ergot alkaloids, particularly ergotamine and dihydroergotamine (see 4.3).

Antiretroviral agents

Nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs):

Interaction studies with stavudine, lamivudine and zidovudine have been performed with REYATAZ without ritonavir. Based on data derived from these studies and because ritonavir is not expected to have a significant impact on the pharmacokinetics of NRTIs, the co-administration of REYATAZ and ritonavir with these medicinal products is not expected to significantly alter the exposure of the co-administered drugs. The same conclusion applies to the co-administration with abacavir. Considering that REYATAZ with ritonavir should be administered with food, didanosine should be taken 2 hours after REYATAZ with ritonavir.

Tenofovir disoproxil fumarate: atazanavir concentrations (AUC and C_{min}) are decreased when tenofovir is co-administered with REYATAZ (decrease of 25% and 40% of AUC and C_{min} respectively compared to atazanavir 400 mg). When ritonavir was added to atazanavir, the negative impact of tenofovir on atazanavir C_{min} was significantly reduced, whereas the decrease of AUC was of the same magnitude (decrease of 25% and 26% of AUC and C_{min} respectively compared to atazanavir/ritonavir 300/100 mg). The efficacy of REYATAZ with ritonavir in combination with tenofovir in treatment-experienced patients has been demonstrated in the clinical study 045 (see 4.8 and 5.1).

Non-nucleoside reverse transcriptase inhibitors (NNRTIs)

Efavirenz: if REYATAZ is to be co-administered with efavirenz, which decreases atazanavir exposure, it is recommended that REYATAZ 400 mg with ritonavir 100 mg be co-administered with efavirenz 600 mg (all as a single daily dose with food), as this combination is anticipated to result in atazanavir exposure that approximates the mean exposure to atazanavir produced by 300 mg of REYATAZ given with ritonavir 100 mg. No efficacy and safety data are available to support the co-administration of efavirenz and REYATAZ at the increased dose of 400 mg with ritonavir.

Nevirapine: the effects of co-administration of REYATAZ and nevirapine have not been studied. Nevirapine is a metabolic inducer of CYP3A4 and is expected to decrease atazanavir exposure. Therefore, in the absence of data regarding the expected interaction between REYATAZ with ritonavir and nevirapine, this co-administration is not recommended.
Protease inhibitors

**Indinavir**: indinavir is also associated with indirect (unconjugated) hyperbilirubinemia due to inhibition of UGT. Co-administration of REYATAZ and indinavir is not recommended (see 4.4).

**Ritonavir**: based on data in healthy volunteers, the addition of ritonavir 100 mg to atazanavir 300 mg has been shown to significantly increase the pharmacokinetic parameters of atazanavir (approximately, 2 fold increase of AUC and 7 fold increase of C\text{min} in comparison to atazanavir 400 mg without ritonavir). In patients, the limited pharmacokinetic data currently available suggest that the impact of ritonavir might be less noticeable on the C\text{min} (approximately, 3 fold increase).

The co-administration of REYATAZ with 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.

Other medicinal products

**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 with ritonavir. REYATAZ with ritonavir should be administered 2 hours before or 1 hour after buffered medicinal products.

**Antiarrhythmics (amiodarone, systemic lidocaine, quinidine)**: concentrations may be increased when co-administered with REYATAZ with ritonavir. Caution is warranted and therapeutic concentration monitoring is recommended when available. The concomitant use of quinidine is contraindicated (see 4.3).

**Antineoplastics**: atazanavir inhibits UGT and may interfere with the metabolism of irinotecan, resulting in increased irinotecan toxicities.

**Calcium channel blockers**: co-administration of bepridil with REYATAZ is not recommended (see 4.3). Co-administration of diltiazem (180 mg once daily) with atazanavir (400 mg once daily) in healthy subjects resulted in a 2 to 3 fold increase in diltiazem and desacetyl-diltiazem exposure and no change in the pharmacokinetics of atazanavir. There was an increase in the maximum PR interval compared to atazanavir alone. Co-administration of diltiazem and REYATAZ with ritonavir has not been studied. An initial dose reduction of diltiazem by 50% is recommended, with subsequent titration as needed and ECG monitoring. Verapamil may also have its serum concentrations increased by REYATAZ with ritonavir; therefore, caution should be exercised when verapamil is co-administered with REYATAZ with ritonavir.

**HMG-CoA reductase inhibitors (simvastatin, lovastatin, atorvastatin)**: simvastatin and lovastatin are highly dependent on CYP3A4 for their metabolism and co-administration with REYATAZ with ritonavir may result in increased concentrations. Concomitant use of simvastatin or lovastatin is not recommended due to an increased risk of myopathy including rhabdomyolysis. The risk of myopathy including rhabdomyolysis may also be increased when protease inhibitors, including REYATAZ with ritonavir, are used in combination with atorvastatin, which is also metabolised by CYP3A4. Caution should be exercised.

**H\textsubscript{2}-Receptor antagonists and proton pump inhibitors**: the effects of H\textsubscript{2}-receptor antagonists, proton pump inhibitors, or other gastric acid suppressors on REYATAZ have not been studied; however, reduced plasma concentrations of atazanavir may result due to increased gastric pH if these medicinal products are administered with REYATAZ with ritonavir. Caution should be exercised.

**Immunosuppressants (cyclosporin, tacrolimus, sirolimus)**: concentrations of cyclosporin, tacrolimus, or sirolimus may be increased when co-administered with REYATAZ with ritonavir. More frequent therapeutic concentration monitoring of these medicinal products is recommended until plasma levels have been stabilised.

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Macrolide antibiotics: co-administration of clarithromycin (500 mg twice daily) with atazanavir (400 mg once daily) resulted in a 2 fold increase in exposure to clarithromycin and a 70% decrease in exposure to 14-OH clarithromycin, with a 28% increase in the AUC of atazanavir. Dose reduction of clarithromycin may result in subtherapeutic concentrations of 14-OH clarithromycin. No recommendation regarding dose reduction can be made; therefore, caution should be exercised if REYATAZ plus ritonavir is co-administered with clarithromycin.

Oral contraceptives (ethinyl estradiol, norethindrone): the mean concentration of ethinyl estradiol, when co-administered as a 35-µg dose with atazanavir 400 mg once daily, was increased to a level between mean concentrations produced by a 35-µg and a 50-µg ethinyl estradiol dose, and the AUC of norethindrone was increased about 2 fold. In contrast, ritonavir may decrease ethinyl estradiol concentrations. The effects of co-administration of oral contraceptives and REYATAZ with ritonavir have not been studied. The concomitant use of REYATAZ and oral contraceptives should be avoided (see 4.4). Alternate reliable methods of contraception should be considered.

Rifabutin: simultaneous administration of 400 mg of atazanavir and 150 mg of rifabutin once daily for 14 days resulted in no clinically important change in the C_{max} or AUC for atazanavir. No dose adjustment is needed for REYATAZ. The rifabutin C_{max} for the 150-mg dose was 1.5 fold higher and the AUC was 2.3 fold higher than historical data for a standard 300-mg dose. A rifabutin dose reduction of up to 75% (e.g., 150 mg every other day or 3 times per week) is recommended when administered with REYATAZ with ritonavir.

Rifampicin: although the effect of rifampicin on REYATAZ has not been studied, rifampicin decreases plasma concentrations and AUC of most protease inhibitors by about 90%. This may result in loss of therapeutic effect and development of resistance. The concomitant use of REYATAZ and rifampicin is contraindicated (see 4.3).

Sildenafil: sildenafil is metabolised by CYP3A4. Co-administration with REYATAZ may result in increased concentrations of sildenafil and an increase in sildenafil-associated adverse events, including hypotension, visual changes, and priapism. Patients should be warned about these possible side effects.

Triazole antifungal agents: co-administration with ketoconazole has only been studied with REYATAZ without ritonavir. Co-administration of 200 mg of ketoconazole with 400 mg of atazanavir in healthy subjects resulted in negligible increases in atazanavir AUC and C_{max} (respectively 11% and 3%). Plasma levels of both atazanavir and ritonavir may be increased by ketoconazole and itraconazole. High doses of ketoconazole and itraconazole (> 200 mg/day) should be used cautiously with atazanavir and ritonavir, by assessing the risk versus the benefit of such a combination.

Warfarin: co-administration with REYATAZ with 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 and ritonavir, especially when commencing therapy.

St. John’s wort (Hypericum perforatum): REYATAZ should not be used concomitantly with products containing St. John's wort since it 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 4.3).
4.6 Pregnancy and lactation

There are no adequate and well-controlled studies in pregnant women. Studies in animals have not shown evidence of selective developmental toxicity or effects on reproductive function and fertility (see 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 hyperbilirubinemia 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

There are no data to suggest that atazanavir affects the ability to drive or use machines. However, patients should be informed that dizziness has been reported during treatment with regimens containing REYATAZ (see 4.8).

4.8 Undesirable effects

Data on the safety and tolerability of REYATAZ 300 mg with ritonavir 100 mg once daily are limited, as this combination has only been evaluated in 119 patients in Study 045 in a regimen that also included tenofovir 300 mg once daily and a nucleoside reverse transcriptase inhibitor. Considering that tenofovir has been shown to decrease the plasma levels of atazanavir (with or without concomitant ritonavir), the safety data derived from this study may not fully reflect the safety profile of REYATAZ plus ritonavir when used in clinical practice within antiretroviral combinations that exclude tenofovir. An alteration of the safety profile of REYATAZ cannot be excluded in this context.

REYATAZ has been evaluated for safety and tolerability in combination therapy with other antiretroviral medicinal products in Phase II and III trials in 1,596 adult patients. The majority of patients (1,046) received REYATAZ 400 mg once daily without ritonavir. The median duration of treatment was 102 weeks in Phase II trials and 31 weeks in the Phase III trials. Adverse events were comparable between patients who received REYATAZ 300 mg with ritonavir 100 mg once daily and patients who received REYATAZ 400 mg once daily, except that jaundice and elevated total bilirubin levels were reported more frequently with REYATAZ plus ritonavir.

Among patients who received 400 mg once daily or 300 mg with ritonavir 100 mg once daily, the only adverse events of any severity reported very commonly with at least a possible relationship to regimens containing REYATAZ and one or more NRTIs were nausea (23%), headache (10%), and jaundice (10%). Among patients receiving REYATAZ 300 mg with ritonavir 100 mg, the frequency of jaundice was 15%. Jaundice was reported within a few days to a few months after the initiation of treatment (see 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 4.4 and 5.1).
Adult patients
The following adverse events 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, < 1/10), uncommon (≥ 1/1,000, < 1/100), rare (≥ 1/10,000, < 1/1,000), or very rare (< 1/10,000).

**Immune system disorders:** uncommon: allergic reaction

**Metabolism and nutrition disorders:**
- common: lipodystrophy;
- uncommon: anorexia, appetite increased, weight decreased, weight gain

**Psychiatric disorders:** uncommon: anxiety, depression, sleep disorder

**Nervous system disorders:**
- common: headache, insomnia, peripheral neurologic symptoms;
- uncommon: abnormal dream, amnesia, confusion, dizziness, somnolence;
- rare: abnormal gait

**Eye disorders:**
- common: scleral icterus

**Cardiac disorders and vascular disorders:**
- uncommon: syncope;
- rare: hypertension, oedema, palpitation

**Respiratory, thoracic and mediastinal disorders:**
- uncommon: dyspnea

**Gastrointestinal disorders:**
- common: abdominal pain, diarrhoea, dyspepsia, nausea, vomiting;
- uncommon: dysgeusia, flatulence, gastritis, pancreatitis, stomatitis aphthous;
- rare: abdominal distension

**Hepatobiliary disorders:**
- very common: jaundice;
- uncommon: hepatitis;
- rare: hepatosplenomegaly

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

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

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

**Reproductive system and breast disorders:**
- uncommon: gynecomastia

**General disorders and**
Laboratory abnormalities
The most frequently reported laboratory abnormality in patients receiving regimens containing REYATAZ and one or more NRTIs was elevated total bilirubin (82% Grade 1, 2, 3, or 4). Grade 3 or 4 elevation of total bilirubin was noted in 31% (26% Grade 3, 5% Grade 4), reported predominantly as elevated indirect [unconjugated] bilirubin. Among patients treated with REYATAZ 300 mg once daily with 100 mg ritonavir once daily, 45% had Grade 3-4 total bilirubin elevations (see 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 amylase (11%), elevated creatine kinase (7%), elevated alanine aminotransferase/serum glutamic-pyruvic transaminase (ALT/SGPT) (5%), low neutrophils (4%), elevated aspartate aminotransferase/serum glutamic-oxaloacetic transaminase (AST/SGOT) (3%), and elevated lipase (3%).

One 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 585 patients receiving atazanavir 400 mg once daily, 74 patients were co-infected with chronic hepatitis B or C, and among 119 patients receiving atazanavir 300 mg once daily with ritonavir 100 mg once daily, 20 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 4.4).

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) hyperbilirubinemia (without associated liver function test changes) or PR interval prolongations may be observed (see 4.4 and 4.8).

Treatment of overdose with REYATAZ should consist of general supportive measures, including monitoring of vital signs and 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: J05A E

Mechanism of action: atazanavir is an azapeptide HIV-1 protease inhibitor. 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 activity (EC50 of 2 to 5 nM) against a variety of HIV isolates in the absence of human serum. REYATAZ administered 300 mg once daily with ritonavir 100 mg once daily results in a mean (±SD) Cmin of 862 (±838) ng/ml. The estimated protein-
adjusted (in 40% human serum) C_{\text{min}} is approximately 50 to 300 fold higher than the EC_{50} values generated in representative HIV-infected cell lines. Combinations of atazanavir with stavudine, didanosine, lamivudine, zidovudine, nelfinavir, indinavir, ritonavir, saquinavir, or amprenavir in HIV-infected peripheral blood mononuclear cells yielded additive antiviral effects and did not result in antagonistic anti-HIV activity or enhanced cytotoxic effects at the highest concentrations used for antiviral evaluation.

Cross-resistance in vitro in viruses resistant to other protease inhibitors: atazanavir susceptibility was evaluated in 943 clinical isolates from patients without prior atazanavir exposure and exhibiting a wide array of genotypic and phenotypic patterns. In vitro, there was a clear trend toward decreased susceptibility to atazanavir as isolates exhibited high resistance levels to multiple protease inhibitors. In general, susceptibility to atazanavir was retained (83% of isolates displayed < 2.5 fold change in EC_{50}) among isolates resistant to no more than 2 protease inhibitors. Eighteen percent of isolates had 4 or more of the following 6 mutations considered critical mutations for protease inhibitors: amino acid substitutions 10, 46, 54, 82, 84, and 90. These isolates expressed a median fold change in EC_{50} relative to wildtype of 12.0 for atazanavir. Therefore, viral isolates having at least 4 of these specific mutations would be considered resistant for atazanavir.

Resistance in vivo: in antiretroviral treatment naive patients, the I50L substitution, sometimes in combination with an A71V change, is the signature resistance mutation for atazanavir. An atazanavir resistance phenotype is expressed in all recombinant viral clones containing the I50L substitution in a variety of genetic backgrounds. Resistance levels ranged from 3.5- to 29-fold. There was no evidence of cross-resistance between atazanavir and amprenavir, with insertion of the I50L and I50V substitutions yielding selective resistance to atazanavir and amprenavir, respectively.

In antiretroviral treatment experienced patients, within the 74 isolates from patients who developed resistance to atazanavir on therapy that included either atazanavir, atazanavir + ritonavir, or atazanavir + saquinavir, only 9 isolates from patients treated with either atazanavir or atazanavir + ritonavir displayed the I50L phenotype previously described in naive patients. The resistance in antiretroviral treatment experienced patients mainly occurs by accumulation of the primary and secondary resistance substitutions described previously to be involved in protease inhibitor resistance. These isolates developed higher levels of resistance to the other protease inhibitors.

Clinical experience: in antiretroviral treatment experienced patients, the benefit of REYATAZ is based only on Study 045 where REYATAZ 300 mg once daily was used with ritonavir 100 mg once daily and compared with lopinavir + ritonavir.

Study 045 is an ongoing, randomised, multicenter trial comparing REYATAZ (300 mg once daily) with ritonavir (100 mg once daily) to REYATAZ (400 mg once daily) with saquinavir soft gelatine capsules (1,200 mg once daily), and to lopinavir + ritonavir (400/100 mg fixed dose combination twice daily), each in combination with tenofovir (see 4.5 and 4.8) and one NRTI, in 347 (of 358 randomised) patients with virologic failure on two or more prior regimens containing at least one PI, NRTI, and NNRTI. Sixteen of 120 (13%) patients in the REYATAZ + ritonavir treatment arm and 18 of 123 (15%) patients in the lopinavir + ritonavir arm had four or more of the PI mutations 10, 46, 54, 82, 84, and 90. Thirty-two percent of patients in the study had a viral strain with fewer than two NRTI mutations. 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 log_{10} copies/ml (range: 2.6 to 5.9 log_{10} copies/ml). The population included in this study was moderately pretreated.

The primary endpoint was the time-averaged difference in change from baseline in HIV RNA through 24 weeks.

Through 24 weeks of treatment, the decreases from baseline in HIV RNA levels (primary endpoint) were 1.86 log_{10} copies/ml for REYATAZ + ritonavir and 1.89 log_{10} copies/ml for lopinavir + ritonavir.
REYATAZ + ritonavir was similar (non-inferior) to lopinavir + ritonavir on this efficacy measure (time-averaged difference of 0.14, 97.5% confidence interval [-0.09, 0.37]). Consistent results were obtained with the last observation carried forward method of analysis (time-averaged difference of 0.10, 97.5% confidence interval [-0.13, 0.33]). The proportions of patients with HIV RNA < 400 copies/ml in the REYATAZ + ritonavir arm and the lopinavir + ritonavir arm were 63% and 60%, respectively, by intent-to-treat analysis, with missing values considered as failures. The proportions of patients with HIV RNA < 50 copies/ml in the REYATAZ + ritonavir arm and the lopinavir + ritonavir arm were 38% and 41%, respectively. 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 68% (47%) and 68% (51%), respectively. The mean increases from baseline in CD4 cell count were 83 cells/mm^3 and 90 cells/mm^3 in the REYATAZ + ritonavir and lopinavir + ritonavir arms, respectively. Two subset analyses were performed based on baseline genotypic mutations. In the first, the results significantly favoured the lopinavir + ritonavir arm when considering the subset of patients with ≥ 4 mutations among the following: 10, 20, 24, 32, 33, 63, 71, 73, 82, 84 and 90. In the second, for patients with < 4 of the protease gene mutations 10, 46, 54, 82, 84, and 90, the proportion with HIV RNA < 400 copies/ml was 70% for REYATAZ + ritonavir and 65% for lopinavir + ritonavir, and the proportion with HIV RNA < 50 copies/ml was 44% in each treatment arm. In patients with ≥ 4 of these mutations, the proportion with HIV RNA < 400 copies/ml was 19% for REYATAZ + ritonavir and 39% for lopinavir + ritonavir, and the proportion with HIV RNA < 50 copies/ml was respectively 0% and 22%.

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

The data available on the lipid profile are described in the following table:

<table>
<thead>
<tr>
<th></th>
<th>ATV/RTV</th>
<th>LPV/RTV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total Cholesterol</td>
<td>-8%</td>
<td>3%</td>
</tr>
<tr>
<td>LDL Cholesterol</td>
<td>-10%</td>
<td>-4%</td>
</tr>
<tr>
<td>HDL Cholesterol</td>
<td>-7%</td>
<td>0%</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>-2%</td>
<td>31%</td>
</tr>
</tbody>
</table>

5.2 Pharmacokinetic properties

Limited data are available on the pharmacokinetics of atazanavir in association with low dose ritonavir. The pharmacokinetics of atazanavir were evaluated in healthy adult volunteers and in HIV-infected patients; no substantial differences were observed between the two groups. The pharmacokinetics of atazanavir exhibit a non-linear disposition and a high inter/intra-subject variability that is minimised with food. In healthy subjects, the AUC of atazanavir from the capsules and oral powder were similar. Therefore, HIV-infected patients can use the two formulations interchangeably.

**Absorption:** the pharmacokinetics of atazanavir boosted with ritonavir is currently supported by limited data in patients. In a pharmacokinetic study in HIV-positive patients (n= 10), multiple dosing of REYATAZ 300 mg once daily with ritonavir 100 mg once daily with a light meal for 2 weeks produced a mean steady-state Cmax (SD) of 5,233 ng/ml (3,033), occurring approximately 3.0 hours (Tmax) after administration, and a mean steady-state trough concentration (SD) of 862 ng/ml (838). The mean steady-state plasma AUC (SD) of atazanavir was 53,761 ng hr/ml (35,294).

**Food effect:** administration of atazanavir with either a light meal or a high fat meal decreased the coefficient of variation of AUC and Cmax approximately one-half compared to the fasting state. A similar decrease in the coefficient of variation was noted when REYATAZ 300 mg once daily with ritonavir 100 mg once daily was administered with a light meal in healthy subjects. 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. The mean elimination half-life of atazanavir in HIV-infected adult patients (n= 10) was 8.6 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 on patients with renal insufficiency (see 4.2); however, the impact of renal impairment on atazanavir elimination is anticipated to be minimal.

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 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 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.

The cloned human cardiac potassium channel, hERG, was inhibited by 15% in an in vitro patch clamp assay at a concentration (30 µM) corresponding to 30-fold the free drug concentration at C\(_{\text{max}}\) in humans. 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 2-week and 9-month oral toxicity studies in dogs showed no drug-related electrocardiographic changes. The clinical relevance of these preclinical data is unknown. Potential cardiac effects of this product in humans cannot be ruled out (see 4.4 and 4.8). The potential for PR prolongation should be considered in cases of overdose (see 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 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

6.2 Incompatibilities
Not applicable.
6.3 Shelf life

2 years
After opening: 2 months.

6.4 Special precautions for storage

Keep container tightly closed.

6.5 Nature and contents of container

High density polyethylene (HDPE) bottles closed with child resistant polypropylene closures. Each bottle contains 180 g of REYATAZ and is packaged in a carton with a measuring spoon.

6.6 Instructions for use and handling

No special requirements.

7. MARKETING AUTHORISATION HOLDER

BRISTOL-MYERS SQUIBB PHARMA EEIG
141-149 Staines Road
Hounslow TW3 3JA
United Kingdom

8. MARKETING AUTHORISATION NUMBER(S)

EU/0/00/000/000

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

10. DATE OF REVISION OF THE TEXT
ANNEX II

A. MANUFACTURING AUTHORISATION HOLDER RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OF THE MARKETING AUTHORISATION

C. SPECIFIC OBLIGATIONS TO BE FULFILLED BY THE MARKETING AUTHORISATION HOLDER
A. MANUFACTURING AUTHORISATION HOLDER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer responsible for batch release

Bristol-Myers Squibb, Champ “Lachaud”, La Goualle, F-19250 Meymac, France

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, 4.2)

- OTHER CONDITIONS

The holder of this marketing authorisation must inform the European Commission about the marketing plans for the medicinal product authorised by this decision.

C. SPECIFIC OBLIGATIONS TO BE FULFILLED BY THE MARKETING AUTHORISATION HOLDER

The Marketing Authorisation Holder shall complete the following programme of studies within the specified time frame, the results of which shall form the basis of the annual reassessment of the benefit/risk profile.

Clinical

1. The applicant will provide the results of ongoing studies (in particular 48 weeks of study 045, including ITT and per protocol analysis) to further support the efficacy / safety profile of atazanavir (ATV). A Clinical Study Report will be submitted by March 04 (as type II variation).
2. The applicant will provide clinical data from the use of ATV with ritonavir (ATV/r) within triple once daily combination expected to be increasingly used in clinical practice with the arrival of the once daily ATV/r association. A 24 weeks report (-089) will be submitted in June 05 and a 48 weeks report (-089) will be submitted in December 05.
3. The applicant will further assess the pharmacokinetics of atazanavir boosted with ritonavir in patients (in this field the pharmacokinetic sub-study 045 should be provided and pharmacokinetic data without tenofovir should also be provided), The PK substudy –045 report will be submitted in June 04 and the PK substudy –089 report will be submitted in June 05.
4. The applicant will provide results of the drug-drug interaction study with ATV and VIDEX EC. The Final Study Report will be submitted in December 04.
5. The applicant will provide results of the drug-drug interaction study with ATV/r and nevirapine. The Final Study Report will be submitted in December 05.
6. Considering that the currently dose adjustment of ATV/r in combination with efavirenz is based on extrapolation the applicant should provide clinical data to support the efficacy / safety of this recommendation. A 24 weeks report will be submitted in June 05 and a 48 weeks report will be submitted in December 05.
7. The applicant should commit to analyse the virological response according to the HIV subtypes in ongoing (when feasible)/planned studies. The applicant commits to do so when feasible within clinical studies and include results into Clinical Study Reports.
8. The applicant will pursue investigations to substantiate the geno- and phenotypic resistance profiles of the drug from ongoing clinical trials. This will be performed routinely throughout the clinical program.
9. The characteristic of ATV as low dyslipidemia inducer has been substantiated within the clinical development of the drug. However, in the absence of specific studies exploring the impact of
ATV in patients with dyslipidemia at baseline it is difficult to take advantage of this potential added value. It would have been of particular value to explore the switch from patients experiencing dyslipidemia induced by PIs (only poor data derived from rollover of studies 007 and 008 have been provided) The applicant should commit to perform adequate clinical studies in this field to provide reliable response in term of therapeutic management of patients.

A 48 weeks report –067 will be submitted in September 05, a 12 weeks report –100 will be submitted in January 05 and a 48 weeks report –100 will be submitted in October 05.

**Pharmacovigilance**

1. The post marketing surveillance should focus on: lipids abnormalities, hepatic events, cardiac events, lipodystrophy, hyperbilirubinemia, jaundice, icterus, rash, lactic acidosis and depression. Follow-ups will be submitted in each PSUR.

2. Complementary investigations are necessary to better appreciate the cardiotoxic potential of the drug:
   - The dose and concentration dependence prolongation of the QTc interval with ATV, and particularly when combined with low dose of ritonavir should be further discussed.
     - The in vitro HERG assay should be re-done in specific conditions (mammalian cells, with dofetilide, cisapride or E4031 as positive control).
     - The in vitro study on Purkinje fibers should be re-done in extreme conditions (frequency of stimulation <0.3 Hz).
     - Results from study AI424034 (significant difference in QTc interval >30 msec-<60 msec for males treated with ATV should be further discussed.

The applicant will submit a proposal for evaluation to the rapporteur by January 04.
ANNEX III

LABELLING AND PACKAGE LEAFLET
A. LABELLING
PARTICULARS TO APPEAR ON THE OUTER PACKAGING OR, WHERE THERE IS NO OUTER PACKAGING, ON THE IMMEDIATE PACKAGING CARTON FOR BOTTLE WITH CAPSULES

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 corresponding to 113.9 mg atazanavir sulphate.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

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

Do not store above 25°C.
Store in the original container.
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
141-149 Staines Road
Hounslow TW3 3JA
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/0/00/000/000

13. MANUFACTURER’S BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE
PARTICULARS TO APPEAR ON THE OUTER PACKAGING OR, WHERE THERE IS NO OUTER PACKAGING, ON THE IMMEDIATE PACKAGING LABEL FOR BOTTLE WITH CAPSULES

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### PARTICULARS TO APPEAR ON THE OUTER PACKAGING OR, WHERE THERE IS NO OUTER PACKAGING, ON THE IMMEDIATE PACKAGING CARTON FOR BLISTERS WITH CAPSULES

<table>
<thead>
<tr>
<th>1. NAME OF THE MEDICINAL PRODUCT</th>
</tr>
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<tbody>
<tr>
<td>REYATAZ 100 mg hard capsules</td>
</tr>
<tr>
<td>atazanavir</td>
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</table>

<table>
<thead>
<tr>
<th>2. STATEMENT OF ACTIVE SUBSTANCE(S)</th>
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<tbody>
<tr>
<td>Each capsule contains 100 mg of atazanavir corresponding to 113.9 mg atazanavir sulphate.</td>
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<th>5. METHOD AND ROUTE(S) OF ADMINISTRATION</th>
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<td>Oral use.</td>
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<th>6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN</th>
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<tr>
<th>9. SPECIAL STORAGE CONDITIONS</th>
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<tbody>
<tr>
<td>Do not store above 25°C.</td>
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</table>
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

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United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/0/00/000/000

13. MANUFACTURER’S BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE
### MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

<table>
<thead>
<tr>
<th>1. NAME OF THE MEDICINAL PRODUCT</th>
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<tbody>
<tr>
<td>REYATAZ 100 mg hard capsules</td>
<td>atazanavir</td>
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<tr>
<th>2. NAME OF THE MARKETING AUTHORISATION HOLDER</th>
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PARTICULARS TO APPEAR ON THE OUTER PACKAGING OR, WHERE THERE IS NO OUTER PACKAGING, ON THE IMMEDIATE PACKAGING CARTON FOR BOTTLE WITH CAPSULES

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 corresponding to 170.8 mg atazanavir sulphate.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

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

Do not store above 25°C.
Store in the original container.
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REYATAZ 150 mg hard capsules
atazanavir

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each capsule contains 150 mg of atazanavir corresponding to 170.8 mg atazanavir sulphate.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

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

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Do not store above 25°C.
10. **SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE**

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BRISTOL-MYERS SQUIBB PHARMA EEIG  
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<td>3.</td>
<td>EXP {MM/YYYY}</td>
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<th>BATCH NUMBER</th>
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<tr>
<td>4.</td>
<td>Lot</td>
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</table>
### PARTICULARS TO APPEAR ON THE OUTER PACKAGING OR, WHERE THERE IS NO OUTER PACKAGING, ON THE IMMEDIATE PACKAGING CARTON FOR BOTTLE WITH CAPSULES

1. NAME OF THE MEDICINAL PRODUCT

REYATAZ 200 mg hard capsules
atazanavir

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each capsule contains 200 mg of atazanavir corresponding to 227.8 mg atazanavir sulphate.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

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

Do not store above 25°C.
Store in the original container.
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  
   141-149 Staines Road  
   Hounslow TW3 3JA  
   United Kingdom

12. **MARKETING AUTHORISATION NUMBER(S)**

   EU/0/00/000/000

13. **MANUFACTURER’S BATCH NUMBER**

   Lot

14. **GENERAL CLASSIFICATION FOR SUPPLY**

   Medicinal product subject to medical prescription.

15. **INSTRUCTIONS ON USE**
PARTICULARS TO APPEAR ON THE OUTER PACKAGING OR, WHERE THERE IS NO OUTER PACKAGING, ON THE IMMEDIATE PACKAGING LABEL FOR BOTTLE WITH CAPSULES

1. NAME OF THE MEDICINAL PRODUCT

REYATAZ 200 mg hard capsules
atazanavir

2. STATEMENT OF ACTIVE SUBSTANCE(S)

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

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

Do not store above 25°C.
Store in the original container.
<table>
<thead>
<tr>
<th>10.</th>
<th><strong>SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE</strong></th>
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<td>BRISTOL-MYERS SQUIBB PHARMA EEIG</td>
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<td>Lot</td>
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<tr>
<td>14.</td>
<td><strong>GENERAL CLASSIFICATION FOR SUPPLY</strong></td>
</tr>
<tr>
<td>15.</td>
<td><strong>INSTRUCTIONS ON USE</strong></td>
</tr>
</tbody>
</table>
PARTICULARS TO APPEAR ON THE OUTER PACKAGING OR, WHERE THERE IS NO OUTER PACKAGING, ON THE IMMEDIATE PACKAGING CARTON FOR BLISTERS WITH CAPSULES

1. NAME OF THE MEDICINAL PRODUCT

REYATAZ 200 mg hard capsules
atazanavir

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each capsule contains 200 mg of atazanavir corresponding to 227.8 mg atazanavir sulphate.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

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

Do not store above 25°C.
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
141-149 Staines Road
Hounslow TW3 3JA
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/0/00/000/000

13. MANUFACTURER’S BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE
## Minimum Particulars to Appear on Blister Strips

<table>
<thead>
<tr>
<th><strong>1. Name of the Medicinal Product</strong></th>
<th>REYATAZ 200 mg hard capsules atazanavir</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>2. Name of the Marketing Authorisation Holder</strong></td>
<td>BRISTOL-MYERS SQUIBB PHARMA EEIG</td>
</tr>
<tr>
<td><strong>3. Expiry Date</strong></td>
<td>EXP {MM/YYYY}</td>
</tr>
<tr>
<td><strong>4. Batch Number</strong></td>
<td>Lot</td>
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</tbody>
</table>
**PARTICULARS TO APPEAR ON THE OUTER PACKAGING OR, WHERE THERE IS NO OUTER PACKAGING, ON THE IMMEDIATE PACKAGING CARTON 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 corresponding to 56.95 mg atazanavir sulphate.

3. **LIST OF EXCIPIENTS**

Also contains aspartame (E951) and sucrose.

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 container tightly closed.
<table>
<thead>
<tr>
<th>10.</th>
<th>SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE</th>
</tr>
</thead>
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<tr>
<td></td>
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<td></td>
<td>Hounslow TW3 3JA</td>
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<td></td>
<td>United Kingdom</td>
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<td>GENERAL CLASSIFICATION FOR SUPPLY</td>
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<tr>
<td></td>
<td>Medicinal product subject to medical prescription.</td>
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<tr>
<td>15.</td>
<td>INSTRUCTIONS ON USE</td>
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</table>
### PARTICULARS TO APPEAR ON THE OUTER PACKAGING OR, WHERE THERE IS NO OUTER PACKAGING, ON THE IMMEDIATE PACKAGING LABEL FOR BOTTLE WITH ORAL POWDER

<table>
<thead>
<tr>
<th>1. NAME OF THE MEDICINAL PRODUCT</th>
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<tbody>
<tr>
<td>REYATAZ 50 mg/1.5 g oral powder</td>
</tr>
<tr>
<td>atazanavir</td>
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<table>
<thead>
<tr>
<th>2. STATEMENT OF ACTIVE SUBSTANCE(S)</th>
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<tbody>
<tr>
<td>One measuring spoon of 1.5 g oral powder contains 50 mg of atazanavir</td>
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<table>
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<tr>
<th>3. LIST OF EXCIPIENTS</th>
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<thead>
<tr>
<th>4. PHARMACEUTICAL FORM AND CONTENTS</th>
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<tr>
<td>180 g oral powder</td>
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<tr>
<th>5. METHOD AND ROUTE(S) OF ADMINISTRATION</th>
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<tbody>
<tr>
<td>Oral use</td>
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<tr>
<td>Read the package leaflet before use.</td>
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<tr>
<th>6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN</th>
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<tbody>
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<td>Keep out of the reach and sight of children.</td>
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<tr>
<th>9. SPECIAL STORAGE CONDITIONS</th>
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<tbody>
<tr>
<td>Keep container tightly closed.</td>
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<td><strong>10.</strong></td>
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B. PACKAGE LEAFLET
 PACKAGE LEAFLET

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 further questions, please ask your doctor or your pharmacist.
- This medicine has been prescribed for you personally and you should not pass it on to others. It may harm them, even if their symptoms are the same as yours.

In this leaflet:

1. What is REYATAZ and how is it supplied?
2. Before you take REYATAZ
3. How to take REYATAZ
4. Possible side effects of REYATAZ
5. How to store REYATAZ
6. Further information

REYATAZ 100 mg hard capsules

The active substance in REYATAZ is atazanavir. Each capsule contains 100 mg of atazanavir corresponding to 113.9 mg of atazanavir 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, n-butyl alcohol, isopropyl alcohol, dehydrated alcohol, indigotin (E132), and titanium dioxide (E171).

The marketing authorisation holder of REYATAZ is:

BRISTOL-MYERS SQUIBB PHARMA EEIG
141-149 Staines Road
Hounslow TW3 3JA
United Kingdom

The manufacturer of REYATAZ is:

BRISTOL-MYERS SQUIBB
Champ “Lachaud”, La Goualle
F-19250 Meymac
France

1. WHAT IS REYATAZ AND HOW IS IT SUPPLIED?

Your doctor has prescribed REYATAZ for you because you are infected by the Human Immunodeficiency Virus (HIV) that causes Acquired Immunodeficiency Syndrome (AIDS).

REYATAZ is a treatment for HIV. It works by reducing the amount of HIV in your body and enhances your immune system. In this way REYATAZ reduces the risk of developing illnesses linked to HIV infection.

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.
What is REYATAZ?

**REYATAZ is an antiviral (or antiretroviral) medicine.** It is one of a group called *protease inhibitors*. These medicines control HIV infection by inhibiting a protein that the HIV needs for its multiplication.

REYATAZ is prescribed for use in combination with other anti-HIV medicines. Your doctor will discuss with you which combination of these medicines with REYATAZ is best for you.

How is REYATAZ supplied?

REYATAZ 100 mg hard capsules are supplied in bottles of 60 capsules or in blister strips in packs of 60 capsules. REYATAZ also comes as a powder for patients who have difficulty swallowing capsules. Not all presentations may be marketed in all countries.

2. **BEFORE YOU TAKE REYATAZ**

Do not take REYATAZ

- if you are **hypersensitive (allergic)** to atazanavir or any of the other ingredients of 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); pimozide (used to treat schizophrenia); quinidine or bepridil (used to correct heart rhythm); ergotamine, dihydroergotamine, ergonovine, methylergonovine (used to treat headaches)
  - medicines containing the herbal product St. John’s wort (*Hypericum perforatum*).

Tell your doctor at once if any of these apply to you.
Tell your doctor also if you have liver problems. Your doctor will evaluate how severe your liver disease is before deciding whether you can take REYATAZ.

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 been told by your doctor that you have an intolerance to some sugars (e.g. lactose), contact your doctor before taking this medicinal product.
- if you have hepatitis B or C
- if you have type A or B haemophilia
- if you have diabetes
- if you are taking oral contraceptives ("the Pill") to prevent pregnancy.
- if you notice changes in body fat. Redistribution, accumulation, or loss of body fat may occur in patients receiving antiretroviral therapy.

Taking REYATAZ with food

It is important that you take REYATAZ with food (a meal or a substantial snack).

Taking REYATAZ during 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.
Use in children and adolescents

The efficacy and safety of REYATAZ have not yet been established in children.

Driving or using machines

There are no data to indicate that atazanavir affects the ability to drive or use machines.

Taking other medicines with REYATAZ

There are some medicines you cannot take at all with REYATAZ. These are listed earlier in section 2, under Do not take REYATAZ.

There are other medicines that may not mix with REYATAZ. Tell your doctor if you are taking any prescription or non-prescription medicines, including herbal products, but it is especially important to mention these:

- other medicines to treat HIV infection
- sildenafil (used by men to treat impotence (erectile dysfunction))
- oral contraceptives ("the Pill")
- any medicines to reduce stomach acid
- medicines to lower blood pressure, to slow heart rate, or to correct heart rhythm
- simvastatin, lovastatin, and atorvastatin (used to lower blood cholesterol)
- cyclosporin, tacrolimus, and sirolimus (medicines to decrease the effects of body’s immune system)
- certain antibiotics (rifabutin, clarithromycin)
- ketoconazole (antifungals)
- warfarin (anticoagulant, used to reduce the blood clots)
- irinotecan (used to treat cancer).

3. HOW TO TAKE REYATAZ

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.

Take REYATAZ capsules with food (a meal or a substantial snack). Swallow the capsules whole. Do not open the capsules.

It is important to take REYATAZ as prescribed by your doctor. This way, you can be sure your medicine is fully effective and you reduce the risk of developing resistance to the treatment.

If you take too much REYATAZ

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 double the next dose.
4. **POSSIBLE SIDE EFFECTS OF REYATAZ**

REYATAZ can have side effects. 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 most common side effects** of REYATAZ when given in combination with other anti-HIV medicines are:
- feeling sick (nausea, upset stomach, vomiting)
- headache, difficulty sleeping
- a yellow colour to the skin or the white part of the eyes.
- skin rash
- abdominal pain, diarrhoea

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.

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 you notice these or any other side effects** not mentioned 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 store above 25°C.
- Bottle: Store in the original containers.
- Do not use after the expiry date stated on the bottle label, carton, or blister.

6. **FURTHER INFORMATION**

For any further information about REYATAZ, please contact the local representative of the Marketing Authorisation Holder.
This leaflet was last approved on {date}
PACKAGE LEAFLET

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 further questions, please ask your doctor or your pharmacist.
- This medicine has been prescribed for you personally and you should not pass it on to others. It may harm them, even if their symptoms are the same as yours.

In this leaflet:

1. What is REYATAZ and how is it supplied?
2. Before you take REYATAZ
3. How to take REYATAZ
4. Possible side effects of REYATAZ
5. How to store REYATAZ
6. Further information

REYATAZ 150 mg hard capsules

The active substance in REYATAZ is atazanavir. Each capsule contains 150 mg of atazanavir corresponding to 170.8 mg of atazanavir 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, n-butyl alcohol, isopropyl alcohol, dehydrated alcohol, indigotin (E132), and titanium dioxide (E171).

The marketing authorisation holder of REYATAZ is:

BRISTOL-MYERS SQUIBB PHARMA EEIG
141-149 Staines Road
Hounslow TW3 3JA
United Kingdom

The manufacturer of REYATAZ is:

BRISTOL-MYERS SQUIBB
Champ “Lachaud”, La Goualle
F-19250 Meymac
France

1. WHAT IS REYATAZ AND HOW IS IT SUPPLIED?

Your doctor has prescribed REYATAZ for you because you are infected by the Human Immunodeficiency Virus (HIV) that causes Acquired Immunodeficiency Syndrome (AIDS).

REYATAZ is a treatment for HIV. It works by reducing the amount of HIV in your body and enhances your immune system. In this way REYATAZ reduces the risk of developing illnesses linked to HIV infection.

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.
What is REYATAZ?

REYATAZ is an antiviral (or antiretroviral) medicine. It is one of a group called protease inhibitors. These medicines control HIV infection by inhibiting a protein that the HIV needs for its multiplication.

REYATAZ is prescribed for use in combination with other anti-HIV medicines. Your doctor will discuss with you which combination of these medicines with REYATAZ is best for you.

How is REYATAZ supplied?

REYATAZ 150 mg hard capsules are supplied in bottles of 60 capsules or in blister strips in packs of 60 capsules. REYATAZ also comes as a powder for patients who have difficulty swallowing capsules. Not all presentations may be marketed in all countries.

2. BEFORE YOU TAKE REYATAZ

Do not take REYATAZ

- if you are hypersensitive (allergic) to atazanavir or any of the other ingredients of 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); pimozide (used to treat schizophrenia); quinidine or bepridil (used to correct heart rhythm);
  - ergotamine, dihydroergotamine, ergonovine, methylergonovine (used to treat headaches)
  - medicines containing the herbal product St. John’s wort (Hypericum perforatum).

Tell your doctor at once if any of these apply to you.
Tell your doctor also if you have liver problems. Your doctor will evaluate how severe your liver disease is before deciding whether you can take REYATAZ.

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 been told by your doctor that you have an intolerance to some sugars (e.g. lactose), contact your doctor before taking this medicinal product.
- if you have hepatitis B or C
- if you have type A or B haemophilia
- if you have diabetes
- if you are taking oral contraceptives ("the Pill") to prevent pregnancy.
- if you notice changes in body fat. Redistribution, accumulation, or loss of body fat may occur in patients receiving antiretroviral therapy.

Taking REYATAZ with food

It is important that you take REYATAZ with food (a meal or a substantial snack).

Taking REYATAZ during 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.
Use in children and adolescents

The efficacy and safety of REYATAZ have not yet been established in children.

Driving or using machines

There are no data to indicate that atazanavir affects the ability to drive or use machines.

Taking other medicines with REYATAZ

There are some medicines you cannot take at all with REYATAZ. These are listed earlier in section 2, under Do not take REYATAZ.

There are other medicines that may not mix with REYATAZ. Tell your doctor if you are taking any prescription or non-prescription medicines, including herbal products, but it is especially important to mention these:

- other medicines to treat HIV infection
- sildenafil (used by men to treat impotence (erectile dysfunction))
- oral contraceptives ("the Pill")
- any medicines to reduce stomach acid
- medicines to lower blood pressure, to slow heart rate, or to correct heart rhythm
- simvastatin, lovastatin, and atorvastatin (used to lower blood cholesterol)
- cyclosporin, tacrolimus, and sirolimus (medicines to decrease the effects of body’s immune system)
- certain antibiotics (rifabutin, clarithromycin)
- ketoconazole (antifungals)
- warfarin (anticoagulant, used to reduce the blood clots)
- irinotecan (used to treat cancer).

3. HOW TO TAKE REYATAZ

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.

Take REYATAZ capsules with food (a meal or a substantial snack). Swallow the capsules whole. Do not open the capsules.

It is important to take REYATAZ as prescribed by your doctor. This way, you can be sure your medicine is fully effective and you reduce the risk of developing resistance to the treatment.

If you take too much REYATAZ

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 double the next dose.
4. POSSIBLE SIDE EFFECTS OF REYATAZ

REYATAZ can have side effects. 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 most common side effects of REYATAZ when given in combination with other anti-HIV medicines are:
- feeling sick (nausea, upset stomach, vomiting)
- headache, difficulty sleeping
- a yellow colour to the skin or the white part of the eyes.
- skin rash
- abdominal pain, diarrhoea

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.

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 you notice these or any other side effects not mentioned 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 store above 25°C.
- Bottle: Store in the original containers.
- Do not use after the expiry date stated on the bottle label, carton, or blister.

6. FURTHER INFORMATION

For any further information about REYATAZ, please contact the local representative of the Marketing Authorisation Holder.
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This leaflet was last approved on {date}
REYATAZ 200 mg hard capsules

The active substance in REYATAZ is atazanavir. Each capsule contains 200 mg of atazanavir corresponding to 227.8 mg of atazanavir 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, n-butyl alcohol, isopropyl alcohol, indigotin (E132), and titanium dioxide (E171).

The marketing authorisation holder of REYATAZ is:

BRISTOL-MYERS SQUIBB PHARMA EEIG
141-149 Staines Road
Hounslow TW3 3JA
United Kingdom

The manufacturer of REYATAZ is:

BRISTOL-MYERS SQUIBB
Champ “Lachaud”, La Goualle
F-19250 Meymac
France

1. WHAT IS REYATAZ AND HOW IS IT SUPPLIED?

Your doctor has prescribed REYATAZ for you because you are infected by the Human Immunodeficiency Virus (HIV) that causes Acquired Immunodeficiency Syndrome (AIDS).

REYATAZ is a treatment for HIV. It works by reducing the amount of HIV in your body and enhances your immune system. In this way REYATAZ reduces the risk of developing illnesses linked to HIV infection.

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.
What is REYATAZ?

**REYATAZ is an antiviral (or antiretroviral) medicine.** It is one of a group called **protease inhibitors**. These medicines control HIV infection by inhibiting a protein that the HIV needs for its multiplication.

REYATAZ is prescribed for use in combination with other anti-HIV medicines. Your doctor will discuss with you which combination of these medicines with REYATAZ is best for you.

How is REYATAZ supplied?

REYATAZ 200 mg hard capsules are supplied in bottles of 60 capsules or in blister strips in packs of 60 capsules. REYATAZ also comes as a powder for patients who have difficulty swallowing capsules. Not all presentations may be marketed in all countries.

2. BEFORE YOU TAKE REYATAZ

Do not take REYATAZ

- if you are hypersensitive (allergic) to atazanavir or any of the other ingredients of 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); pimozide (used to treat schizophrenia); quinidine or bepridil (used to correct heart rhythm); ergotamine, dihydroergotamine, ergonovine, methylergonovine (used to treat headaches)
  - medicines containing the herbal product St. John’s wort (*Hypericum perforatum*).

Tell your doctor at once if any of these apply to you.
Tell your doctor also if you have liver problems. Your doctor will evaluate how severe your liver disease is before deciding whether you can take REYATAZ.

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 been told by your doctor that you have an intolerance to some sugars (e.g. lactose), contact your doctor before taking this medicinal product.
- if you have hepatitis B or C
- if you have type A or B haemophilia
- if you have diabetes
- if you are taking oral contraceptives ("the Pill") to prevent pregnancy.
- if you notice changes in body fat. Redistribution, accumulation, or loss of body fat may occur in patients receiving antiretroviral therapy.

Taking REYATAZ with food

It is important that you take REYATAZ with food (a meal or a substantial snack).

Taking REYATAZ during 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.
Use in children and adolescents

The efficacy and safety of REYATAZ have not yet been established in children.

Driving or using machines

There are no data to indicate that atazanavir affects the ability to drive or use machines.

Taking other medicines with REYATAZ

There are some medicines you cannot take at all with REYATAZ. These are listed earlier in section 2, under Do not take REYATAZ.

There are other medicines that may not mix with REYATAZ. Tell your doctor if you are taking any prescription or non-prescription medicines, including herbal products, but it is especially important to mention these:
- other medicines to treat HIV infection
- sildenafil (used by men to treat impotence (erectile dysfunction))
- oral contraceptives ("the Pill")
- any medicines to reduce stomach acid
- medicines to lower blood pressure, to slow heart rate, or to correct heart rhythm
- simvastatin, lovastatin, and atorvastatin (used to lower blood cholesterol)
- cyclosporin, tacrolimus, and sirolimus (medicines to decrease the effects of body’s immune system)
- certain antibiotics (rifabutin, clarithromycin)
- ketoconazole (antifungals)
- warfarin (anticoagulant, used to reduce the blood clots)
- irinotecan (used to treat cancer).

3. HOW TO TAKE REYATAZ

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.

Take REYATAZ capsules with food (a meal or a substantial snack). Swallow the capsules whole. Do not open the capsules.

It is important to take REYATAZ as prescribed by your doctor. This way, you can be sure your medicine is fully effective and you reduce the risk of developing resistance to the treatment.

If you take too much REYATAZ

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 double the next dose.
4. POSSIBLE SIDE EFFECTS OF REYATAZ

REYATAZ can have side effects. 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 most common side effects of REYATAZ when given in combination with other anti-HIV medicines are:
- feeling sick (nausea, upset stomach, vomiting)
- headache, difficulty sleeping
- a yellow colour to the skin or the white part of the eyes.
- skin rash
- abdominal pain, diarrhoea

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.

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 you notice these or any other side effects not mentioned 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 store above 25°C.
- Bottle: Store in the original containers.
- Do not use after the expiry date stated on the bottle label, carton, or blister.

6. FURTHER INFORMATION

For any further information about REYATAZ, please contact the local representative of the Marketing Authorisation Holder.
This leaflet was last approved on {date}
In this leaflet:

1. **What is REYATAZ and how is it supplied?**
2. **Before you take REYATAZ**
3. **How to take REYATAZ**
4. **Possible side effects of REYATAZ**
5. **How to store REYATAZ**
6. **Further information**

**REYATAZ 50 mg/1.5 g oral powder**

The active substance in REYATAZ is atazanavir. One measuring spoon of 1.5 g oral powder contains 50 mg of atazanavir corresponding to 56.95 mg of atazanavir sulphate. The other ingredients are aspartame (E951), sucrose, and orange vanilla flavour.

**The marketing authorisation holder of REYATAZ is:**

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141-149 Staines Road
Hounslow TW3 3JA
United Kingdom

**The manufacturer of REYATAZ is:**

BRISTOL-MYERS SQUIBB
Champ “Lachaud”, La Goualle
F-19250 Meymac
France

1. **WHAT IS REYATAZ AND HOW IS IT SUPPLIED?**

Your doctor has prescribed REYATAZ for you because you are infected by the Human Immunodeficiency Virus (HIV) that causes Acquired Immunodeficiency Syndrome (AIDS).

**REYATAZ is a treatment for HIV.** It works by reducing the amount of HIV in your body and enhances your immune system. In this way REYATAZ reduces the risk of developing illnesses linked to HIV infection.

**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.

**What is REYATAZ?**

**REYATAZ is an antiviral (or antiretroviral) medicine.** It is one of a group called **protease inhibitors**. These medicines control HIV infection by inhibiting a protein that the HIV needs for its multiplication.
REYATAZ is prescribed for use in combination with other anti-HIV medicines. Your doctor will discuss with you which combination of these medicines with REYATAZ is best for you.

How is REYATAZ supplied?

REYATAZ oral powder is supplied in bottles containing 180 g of powder together with a plastic measuring spoon. REYATAZ also exists in capsules. However, not all presentations may be marketed in all countries.

2. BEFORE YOU TAKE REYATAZ

Do not take REYATAZ

- if you are hypersensitive (allergic) to atazanavir or any of the other ingredients of 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); pimozide (used to treat schizophrenia); quinidine or bepridil (used to correct heart rhythm);
  - ergotamine, dihydroergotamine, ergonovine, methylergonovine (used to treat headaches)
  - medicines containing the herbal product St. John’s wort (Hypericum perforatum)

Tell your doctor at once if any of these apply to you. Tell your doctor also if you have liver problems. Your doctor will evaluate how severe your liver disease is before deciding whether you can take REYATAZ.

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 are taking oral contraceptives ("the Pill") to prevent pregnancy.
- if you notice changes in body fat. Redistribution, accumulation, or loss of body fat may occur in patients receiving antiretroviral therapy.

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.

Taking REYATAZ with food

It is important that you take REYATAZ with food (a meal or a substantial snack).
Taking REYATAZ during 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.

Use in children and adolescents

The efficacy and safety of REYATAZ have not yet been established in children.

Driving or using machines

There are no data to indicate that atazanavir affects the ability to drive or use machines.

Taking other medicines with REYATAZ

There are some medicines you cannot take at all with REYATAZ. These are listed earlier in section 2, under Do not take REYATAZ.

There are other medicines that may not mix with REYATAZ. Tell your doctor if you are taking any prescription or non-prescription medicines, including herbal products, but it is especially important to mention these:

- other medicines to treat HIV infection
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- oral contraceptives ("the Pill")
- any medicines to reduce stomach acid
- medicines to lower blood pressure, to slow heart rate, or to correct heart rhythm
- simvastatin, lovastatin, and atorvastatin (used to lower blood cholesterol)
- cyclosporin, tacrolimus, and sirolimus (medicines to decrease the effects of body's immune system)
- certain antibiotics (rifabutin, clarithromycin)
- ketoconazole (antifungals)
- warfarin (anticoagulant, used to reduce the blood clots)
- irinotecan (used to treat cancer).

3. HOW TO TAKE REYATAZ

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.

It is important to take REYATAZ as prescribed by your doctor. This way, you can be sure your medicine is fully effective and you reduce the risk of developing resistance to the treatment.
If you take too much REYATAZ

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 double the next dose.

4. POSSIBLE SIDE EFFECTS OF REYATAZ

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The most common side effects of REYATAZ when given in combination with other anti-HIV medicines are:

- feeling sick (nausea, upset stomach, vomiting)
- headache, difficulty sleeping
- a yellow colour to the skin or the white part of the eyes.
- skin rash
- abdominal pain, diarrhoea

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.

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 you notice these or any other side effects not mentioned in this leaflet, please tell your HIV doctor or nurse.

5. HOW TO STORE REYATAZ

- Keep out of the reach and sight of children.
- Keep container tightly closed.
- Do not use after the expiry date stated on the package and on the bottle label.

6. FURTHER INFORMATION

For any further information about REYATAZ, please contact the local representative of the Marketing Authorisation Holder.
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