ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS
1. NAME OF THE MEDICINAL PRODUCT

Telzir 700 mg film-coated tablets.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 700 mg of fosamprenavir as fosamprenavir calcium (equivalent to approximately 600 mg of amprenavir).

For excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablets.

Pink film coated, capsule shaped, biconvex tablets, marked with GXLL7 on one side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Telzir in combination with low dose ritonavir is indicated for the treatment of Human Immunodeficiency Virus Type 1 (HIV-1) infected adults in combination with other antiretroviral medicinal products.

In moderately antiretroviral experienced patients, Telzir in combination with low dose ritonavir has not been shown to be as effective as lopinavir / ritonavir.

In heavily pretreated patients the use of Telzir in combination with low dose ritonavir has not been sufficiently studied.

In protease inhibitor (PI) experienced patients the choice of Telzir should be based on individual viral resistance testing and treatment history (see section 5.1).

4.2 Posology and method of administration

Telzir must only be given with low dose ritonavir as a pharmacokinetic enhancer of amprenavir and in combination with other antiretroviral medicinal products. The Summary of Product Characteristics of ritonavir must therefore be consulted prior to initiation of therapy with Telzir.

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

Telzir (fosamprenavir) is a pro-drug of amprenavir and must not be administered concomitantly with other medicinal products containing amprenavir.

The importance of complying with the full recommended dosing regimen should be stressed to all patients.
**Adults (greater than or equal to 18 years of age)**

For antiretroviral naïve and experienced patients the recommended dose is 700 mg fosamprenavir twice daily with 100 mg ritonavir twice daily, in combination with other antiretroviral medicinal products (see section 5.1).

Caution is advised if the recommended doses of fosamprenavir with ritonavir detailed above are exceeded (see section 4.4).

**Children (less than 12 years of age) and adolescents (12 to 17 years of age)**

The safety and efficacy of Telzir with ritonavir has not yet been established in these patient populations. Therefore, this combination must not be used in this age group until further data becomes available.

**Elderly (over 65 years of age)**

The pharmacokinetics of fosamprenavir have not been studied in this patient population (see section 5.2).

**Renal impairment**

No initial dose adjustment is considered necessary in patients with renal impairment (see section 5.2).

**Hepatic impairment**

There are limited data regarding the use of Telzir with ritonavir when co-administered to patients with hepatic impairment and therefore specific dosage recommendations cannot be made. Consequently, Telzir in combination with ritonavir should be used with caution in patients with mild or moderate hepatic impairment and is contraindicated in those with severe hepatic impairment (see sections 4.3, 4.4 and 5.2).

Telzir is administered orally. Telzir (tablets) with ritonavir can be taken with or without food.

Telzir is also available as an oral suspension for use in adults unable to swallow tablets.

### 4.3 Contraindications

Hypersensitivity to fosamprenavir, amprenavir or to any of the excipients of Telzir, or to ritonavir.

Patients with severe hepatic impairment (see sections 4.4 and 5.2).

Telzir must not be administered concurrently with medicinal products with narrow therapeutic windows that are substrates of cytochrome P450 3A4 (CYP3A4), e.g. amiodarone, astemizole, bepridil, cisapride, dihydroergotamine, ergotamine, pimozide, quinine, terfenadine (see section 4.5).

Telzir with ritonavir must not be co-administered with medicinal products with narrow therapeutic windows that are highly dependent on CYP2D6 metabolism, e.g. flecainide and propafenone (see section 4.5).

Rifampicin must not be administered concurrently with Telzir (see section 4.5).

Herbal preparations containing St John’s wort (Hypericum perforatum) must not be used while taking Telzir due to the risk of decreased plasma concentrations and reduced clinical effects of amprenavir (see section 4.5).
4.4 Special warnings and special precautions for use

Patients should be advised that treatment with Telzir, or any other current antiretroviral therapy, does not cure HIV and that they may still develop opportunistic infections and other complications of HIV infection. Current antiretroviral therapies, including Telzir, have not been proven to prevent the risk of transmission of HIV to others through sexual contact or blood contamination. Appropriate precautions should continue to be taken.

Fosamprenavir contains a sulphonamide moiety. The potential for cross-sensitivity between medicinal products in the sulphonamide class and fosamprenavir is unknown. In the pivotal studies of Telzir, in patients receiving fosamprenavir with ritonavir there was no evidence of an increased risk of rashes in patients with a history of sulphonamide allergy versus those who did not have a sulphonamide allergy. Yet, Telzir should be used with caution in patients with a known sulphonamide allergy.

Co-administration of Telzir 700 mg twice daily with ritonavir in doses greater than 100 mg twice daily has not been clinically evaluated. The use of higher ritonavir doses might alter the safety profile of the combination and therefore is not recommended.

Liver disease

The safety and efficacy of Telzir have not been established in patients with significant underlying liver disease. Telzir should be used with caution in patients with mild or moderate hepatic impairment and is contraindicated in patients with severe hepatic impairment. Patients with chronic hepatitis B or C and treated with combination antiretroviral therapy are at an increased risk of 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.

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.

Medicinal products – interactions

The use of Telzir concomitantly with midazolam or triazolam is not recommended (see section 4.5).

The use of Telzir concomitantly with halofantrine or lidocaine (systemic) is not recommended (see section 4.5).

The use of Telzir concomitantly with PDE5 inhibitors (e.g. sildenafil and vardenafil) is not recommended (see section 4.5).

Concomitant use of Telzir with simvastatin or lovastatin is not recommended due to an increased risk of myopathy, including rhabdomyolysis (see section 4.5).

A reduction in the rifabutin dosage by at least 75 % is recommended when administered with Telzir with ritonavir. Further dose reduction may be necessary (see section 4.5).

Because of the interactions with amprenavir, the efficacy of hormonal contraceptives may be impaired. Therefore, alternative reliable barrier methods of contraception are recommended for women of childbearing potential (see section 4.5).

Anticonvulsants (carbamazepine, phenobarbital, phenytoin) should be used with caution. Telzir may be less effective due to decreased amprenavir plasma concentrations in patients taking these medicinal products concomitantly (see section 4.5).
Therapeutic concentration monitoring is recommended for immunosuppressant medicinal products (cyclosporine, tacrolimus, rapamycin) when co-administered with Telzir (see section 4.5).

Therapeutic concentration monitoring is recommended for tricyclic antidepressants (e.g. desipramine and nortriptyline) when coadministered with Telzir (see section 4.5).

When methadone is coadministered with Telzir, patients should be closely monitored for opiate abstinence syndrome (see section 4.5).

When warfarin or other oral anticoagulants are coadministered with Telzir a reinforced monitoring of INR (International Normalised Ratio) is recommended (see section 4.5).

Rash / cutaneous reactions

Most patients with mild or moderate rash can continue Telzir. Appropriate antihistamines (e.g. cetirizine dihydrochloride) may reduce pruritus and hasten the resolution of rash. Severe and life-threatening skin reactions, including Stevens-Johnson syndrome, were reported in less than 1 % of patients included in the clinical development programme. Telzir should be permanently discontinued in case of severe rash, or in case of rash of moderate intensity with systemic or mucosal symptoms (see section 4.8).

Haemophiliac patients

There have been reports of increased bleeding including spontaneous skin haematomas and haemarthroses in haemophiliac patients type A and B treated with protease inhibitors (PIs). In some patients administration of factor VIII was necessary. 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 evoked, although the mechanism of action has not been elucidated. Haemophiliac patients should therefore be informed of the possibility of increased bleeding.

Hyperglycaemia

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

Lipodystrophy

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 section 4.8).

4.5 Interaction with other medicinal products and other forms of interaction

When fosamprenavir and ritonavir are co-administered, the ritonavir metabolic drug interaction profile may predominate because ritonavir is a more potent CYP3A4 inhibitor. The full prescribing information for ritonavir must therefore be consulted prior to initiation of
therapy with Telzir with ritonavir. Ritonavir also inhibits CYP2D6 but to a lesser extent than CYP3A4. Ritonavir induces CYP3A4, CYP1A2, CYP2C9 and glucuronosyl transferase.

Additionally, both amprenavir, the active metabolite of fosamprenavir, and ritonavir are primarily metabolised in the liver by CYP3A4. Therefore, any medicinal products that either share this metabolic pathway or modify CYP3A4 activity may modify the pharmacokinetics of amprenavir and ritonavir. Similarly administration of fosamprenavir with ritonavir may modify the pharmacokinetics of other active substances that share this metabolic pathway.

- Associations contraindicated (see section 4.3)

CYP3A4 substrates with narrow therapeutic index
Telzir must not be administered concurrently with medicinal products with narrow therapeutic windows containing active substances that are substrates of cytochrome P450 3A4 (CYP3A4).
Co-administration may result in competitive inhibition of the metabolism of these active substances thus increasing their plasma level and leading to serious and / or life-threatening adverse reactions such as cardiac arrhythmia (e.g. amiodarone, astemizole, bepridil, cisapride, pimozide, quinidine, terfenadine) or peripheral vasospasm or ischaemia (e.g. ergotamine, dihydroergotamine).

CYP2D6 substrates with narrow therapeutic index
Telzir with ritonavir must not be co-administered with medicinal products containing active substances that are highly dependent on CYP2D6 metabolism and for which elevated plasma concentrations are associated with serious and / or life-threatening adverse reactions. These active substances include flecainide and propafenone.

Rifampicin
Rifampicin reduces the amprenavir plasma AUC by approximately 82 %. Based on information for other protease inhibitors, it is expected that co-administration of Telzir with ritonavir with rifampicin will also result in large decreases in plasma concentrations of amprenavir. Accordingly, Telzir with ritonavir must not be co-administered with rifampicin.

St John’s wort (Hypericum perforatum)
Serum levels of amprenavir and ritonavir can be reduced by concomitant use of the herbal preparation St John’s wort (Hypericum perforatum). This is due to induction of drug metabolising enzymes by St John’s wort. Herbal preparations containing St John’s wort should therefore not be combined with Telzir with ritonavir. If a patient is already taking St John’s wort, check amprenavir, ritonavir and if possible viral levels and stop St John’s wort. Amprenavir and ritonavir levels may increase on stopping St John’s wort. The inducing effect may persist for at least 2 weeks after cessation of treatment with St John’s wort.

- Other combinations

Antiretroviral medicinal products

Non-nucleoside reverse transcriptase inhibitors

Efavirenz: there was no clinically relevant interaction when fosamprenavir 700 mg twice daily and ritonavir 100 mg twice daily was used concurrently with efavirenz (600 mg once daily).

Nevirapine: based on the effect of nevirapine on other HIV protease inhibitors, nevirapine may decrease the serum concentration of amprenavir. Appropriate doses of the combination with respect to safety and efficacy have not been established. This combination should be used with caution.
Nucleoside / Nucleotide reverse transcriptase inhibitors

Interaction studies with abacavir, lamivudine and zidovudine have been performed with amprenavir 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 fosamprenavir and ritonavir with these medicinal products is not expected to significantly alter the exposure of the co-administered active substances.

Didanosine chewable tablet: no pharmacokinetic study has been performed with fosamprenavir in combination with didanosine. Clinically significant interaction resulting from an increase in the stomach pH due to the didanosine antacid component is unlikely and no dose separation or adjustment is considered necessary when fosamprenavir and didanosine are administered concomitantly (see chapter, Antacids). No significant interaction is expected with didanosine gastro-resistant capsule.

Tenofovir: no recommendations can be drawn at this stage on the co-administration of fosamprenavir with ritonavir with tenofovir.

Protease Inhibitors

Lopinavir / ritonavir: no dose recommendation can be given for the co-administration of Telzir with ritonavir and lopinavir / ritonavir, but close monitoring is advised because the safety and efficacy of this combination is unknown. The C\textsubscript{max}, AUC and C\textsubscript{min} of lopinavir were increased by 30 %, 37 % and 52 % respectively when lopinavir 400 mg with ritonavir 100 mg twice daily was given with fosamprenavir 700 mg with ritonavir 100 mg twice daily for two weeks. The C\textsubscript{max}, AUC and C\textsubscript{min} of amprenavir were decreased by 58 %, 63 % and 65 % respectively.

When lopinavir 533 mg with ritonavir 133 mg was administered in combination with fosamprenavir 1400 mg twice daily for two weeks, the C\textsubscript{max}, AUC, and C\textsubscript{min} of lopinavir were unchanged compared to values observed for lopinavir 400 mg with ritonavir 100 mg twice daily. However, the AUC and C\textsubscript{min} of amprenavir were decreased by 26 % and 42 %, respectively; whereas, C\textsubscript{max} was not significantly altered compared to values obtained for fosamprenavir 700 mg with ritonavir 100 mg twice daily.

No interaction studies have been undertaken between fosamprenavir with ritonavir and the protease inhibitors: indinavir, saquinavir, nelfinavir and atazanavir.

Antibiotics / Antifungals

Clarithromycin: a reduction in the clarithromycin dose should be considered when co-administered with Telzir with ritonavir in patients with renal impairment as moderate increases in clarithromycin concentrations are expected when co-administered with Telzir with ritonavir.

Erythromycin: no pharmacokinetic study has been performed with fosamprenavir with ritonavir in combination with erythromycin, however, plasma levels of erythromycin may be increased when co-administered.

Ketoconazole / Itraconazole: co-administration of amprenavir with ketoconazole increased ketoconazole AUC by 44 %. When ritonavir is co-administered, a larger increase in ketoconazole concentration may occur. Itraconazole concentrations are expected to increase in the same manner as ketoconazole. In the absence of specific studies of fosamprenavir with ritonavir in combination with ketoconazole or itraconazole, no recommendations can be drawn in terms of dose adjustment.

Rifabutin: co-administration of amprenavir with rifabutin results in a 200 % increase in rifabutin plasma concentrations (AUC) which could potentially lead to an increase of rifabutin related adverse reactions, notably uveitis. When ritonavir is co-administered a larger increase in rifabutin concentrations may occur. A reduction in the rifabutin dosage by at least 75 % is recommended when administered with Telzir with ritonavir. Further dose reduction may be necessary.
Other medicinal products

Medicinal products that may reduce plasma amprenavir concentrations when co-administered with Telzir

Antacids, Histamine H₂ receptor antagonist and Proton-Pump inhibitors: no dose adjustment for any of the respective medicinal products is considered necessary when antacids, proton-pump inhibitors or histamine H₂ receptor antagonists are administered concomitantly with fosamprenavir. The AUC and Cₘₐₓ of amprenavir were decreased by 18 % and 35 % respectively, whilst the Cₘᵦᵢₙ(C₁₂₇₇) was comparable, when a single 1400 mg dose of fosamprenavir was co-administered with a single 30 ml dose of antacid suspension (equivalent to 3.6 grams aluminium hydroxide and 1.8 grams magnesium hydroxide).

Serum levels of amprenavir can be reduced by concomitant use of histamine H₂ receptor antagonists (for example ranitidine and cimetidine). Concurrent administration of ranitidine (300 mg single dose) with fosamprenavir (1400 mg single dose) decreased plasma amprenavir AUC by 30 % and Cₘₐₓ by 51 %. There was, however, no change observed in the amprenavir Cₘᵦᵢₙ (C₁₂₇₇).

Anticonvulsant active substances: concomitant administration of anticonvulsant active substances known as enzymatic inducers (phenytoin, phenobarbital, carbamazepine) with fosamprenavir may lead to a decrease in the plasma concentrations of amprenavir. These combinations should be used with caution.

Medicinal products whose plasma levels may be increased when co-administered with Telzir

Other medicinal products with a narrow therapeutic window: some substances (e.g. lidocaine (by systemic route) and halofantrine) given with Telzir may cause serious adverse reactions. Concomitant use is not recommended.

Benzodiazepines: concomitant use of Telzir with midazolam or triazolam could result in prolonged sedation or respiratory depression and thus is not recommended.

Erectile dysfunction medicinal products: concomitant use is not recommended. Based on data for ritonavir and other protease inhibitors, plasma concentrations of PDE5 inhibitors (e.g. sildenafil and vardenafil) are expected to substantially increase when co-administered with Telzir with ritonavir and may result in an increase in PDE5 inhibitor associated adverse reactions, including hypotension, visual changes and priapism.

HMG-CoA reductase inhibitors: if treatment with a HMG-CoA reductase inhibitor is indicated, pravastatin or fluvastatin is recommended because their metabolism is not dependent on CYP 3A4 and interactions are not expected with protease inhibitors. HMG-CoA reductase inhibitors which are highly dependent on CYP3A4 for metabolism, such as lovastatin and simvastatin, are expected to have markedly increased plasma concentrations when co-administered with Telzir with ritonavir. Since increased concentrations of HMG-CoA reductase inhibitors may cause myopathy, including rhabdomyolysis, the combination of lovastatin or simvastatin with Telzir with ritonavir is not recommended. No adjustment of the fosamprenavir or ritonavir dose is required when co-administered with atorvastatin.

The Cₘᵦᵢₙ, AUC and Cₘᵢₜₐₙ of atorvastatin were increased by 184 %, 153 % and 73 % respectively when atorvastatin (10 mg once daily for 4 days) was given with fosamprenavir 700 mg twice daily with ritonavir 100 mg twice daily for two weeks. The Cₘᵦᵢₙ, AUC and Cₘᵢₜₐₙ of amprenavir were unchanged. When used with Telzir with ritonavir, doses of atorvastatin no greater than 20 mg / day should be administered, with careful monitoring for atorvastatin toxicity.
**Immunosuppressants**: frequent therapeutic concentration monitoring of immunosuppressant levels is recommended until levels have stabilised as plasma concentrations of cyclosporin, rapamycin and tacrolimus may be increased when co-administered with fosamprenavir with ritonavir.

**Tricyclic antidepressants**: careful monitoring of the therapeutic and adverse reactions of tricyclic antidepressants is recommended when they (for example desipramine and nortriptyline) are concomitantly administered with Telzir.

**Medicinal products whose plasma levels may be decreased when co-administered with Telzir**

**Methadone**: no data are available on the co-administration of fosamprenavir with ritonavir and methadone. Amprenavir and ritonavir both decrease plasma concentrations of methadone. When methadone is co-administered with Telzir with ritonavir, patients should be closely monitored for opiate abstinence syndrome, with concomitant monitoring of methadone plasma levels.

**Oral anticoagulants**: a reinforced monitoring of the International Normalised Ratio is recommended in case of administration of Telzir with ritonavir with warfarin or other oral anticoagulants, due to a possible decrease or increase of their antithrombotic effect.

**Oral contraceptives**: alternative reliable barrier methods of contraception are recommended for women of childbearing potential. Oestrogens and progestogens may interact with fosamprenavir and ritonavir, thus concomitant use may impair the efficacy of hormonal contraceptives.

**4.6 Pregnancy and lactation**

**Pregnancy**

There is no clinical experience with fosamprenavir in pregnant women. In animal studies at systemic plasma exposures (AUC) to amprenavir lower than therapeutic exposure in patients treated with Telzir, some developmental toxicity was observed (see section 5.3). In view of the low exposure in reproductive toxicity studies, the potential developmental toxicity of Telzir has not been fully determined.

Telzir should be used during pregnancy only if the potential benefit justifies the potential risk to the foetus.

**Lactation**

Amprenavir-related material was found in rat milk, but it is not known whether amprenavir is excreted in human milk. Rat pups exposed pre and post-natally to amprenavir and fosamprenavir showed developmental toxicity (see section 5.3).

It is therefore recommended that mothers treated with Telzir do not breast-feed their infants. As a general rule, it is recommended that HIV-infected women must not breast-feed under any circumstances to avoid transmission of HIV.

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

No studies on the effects of Telzir in combination with ritonavir on the ability to drive and use machines have been performed. The adverse reaction profile of Telzir should be borne in mind when considering the patient’s ability to drive or operate machinery (see section 4.8).
4.8 Undesirable effects

The safety of fosamprenavir has been studied in 755 patients in Phase II and III controlled clinical trials. The safety of the co-administration of fosamprenavir with low dose ritonavir was established in two pivotal Phase III trials: APV30002 (n = 322) in antiretroviral naïve patients, fosamprenavir (1400 mg) given once daily in combination with ritonavir (200 mg) as part of a triple regimen including abacavir and lamivudine. APV30003 in protease inhibitor experienced patients, fosamprenavir given in combination with low dose ritonavir either once daily (1400 mg / 200 mg) (n = 106) or twice daily (700 mg / 100 mg) (n = 106) in combination with two active reverse transcriptase inhibitors (RTIs).

The adverse reaction profile was similar across all the respective studies: antiretroviral naïve (APV30002) and protease inhibitor experienced (twice daily dosing, APV30003) patient populations.

The adverse reactions are listed by body system, organ class and absolute frequency. Frequencies are defined as: 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), including isolated reports. The frequency of the reactions were calculated using adverse reactions that were of at least moderate intensity (Grade 2 or more) and reported by investigators as being attributable to the medicinal products used in the studies. The most frequent clinical adverse reactions (occurring in at least 1 % of patients) reported in the two large clinical studies in adults with at least a possible casual relationship to Telzir are summarised below.

<table>
<thead>
<tr>
<th>Body System</th>
<th>Adverse reaction</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nervous system disorders</td>
<td>Headache, dizziness</td>
<td>Common</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td>Diarrhoea</td>
<td>Very common</td>
</tr>
<tr>
<td></td>
<td>Loose stools, nausea, vomiting, abdominal pain</td>
<td>Common</td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td>Rash</td>
<td>Common</td>
</tr>
<tr>
<td>General disorders and administration site conditions</td>
<td>Fatigue</td>
<td>Common</td>
</tr>
</tbody>
</table>

Rash / cutaneous reactions: erythematous or maculopapular cutaneous eruptions, with or without pruritus, may occur during therapy. The rash generally will resolve spontaneously without the necessity of discontinuing treatment with the fosamprenavir with ritonavir.

Severe or life-threatening rash, including Stevens-Johnson syndrome is rare, reported in less than 1 % of patients included in the clinical development programme. Fosamprenavir with ritonavir therapy should be definitively stopped in case of severe rash or in case of rash of mild or moderate intensity associated with systemic or mucosal signs (see section 4.4).

Clinical chemistry abnormalities: clinical chemistry abnormalities (Grade 3 or 4) potentially related to treatment with fosamprenavir with ritonavir and reported in greater than or equal to 1 % of patients, included:
increased ALT (common), AST (common), serum lipase (common) and triglycerides (very common). Grade 3 or 4 elevations in total cholesterol values were observed in less than 1% of patients (<1% APV30002; 0% APV 30003).

**Lipodystrophy**: combination antiretroviral therapy has been associated with redistribution of body fat (lipodystrophy) in HIV patients including the loss of peripheral and facial subcutaneous fat, increased intra-abdominal and visceral fat, breast hypertrophy and dorsocervical fat accumulation (buffalo hump) (see section 4.4).

**Metabolic abnormalities**: combination antiretroviral therapy has been associated with metabolic abnormalities such as hypertriglyceridaemia, hypercholesterolaemia, insulin resistance, hyperglycaemia and hyperlactataemia (see section 4.4).

**Hyperglycaemia**: new onset of diabetes mellitus, hyperglycaemia or exacerbations of existing diabetes mellitus have been reported in patients receiving antiretroviral protease inhibitors (see section 4.4).

**Rhabdomyolysis**: an increase in CPK, myalgia, myositis, and rarely, rhabdomyolysis, have been reported with protease inhibitors, more specifically in association with nucleoside analogues.

**Haemophiliac patients**: there have been reports of increased spontaneous bleeding in haemophiliac patients receiving antiretroviral protease inhibitors (see section 4.4).

### 4.9 Overdose

There is no known antidote for Telzir. It is not known whether amprenavir can be removed by peritoneal dialysis or haemodialysis. If overdosage occurs, the patient should be monitored for evidence of toxicity (see section 4.8) and standard supportive treatment applied as necessary.

### 5. PHARMACOLOGICAL PROPERTIES

#### 5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antivirals for systemic use, protease inhibitor, ATC Code: J05A (pending)

**Mechanism of action**

Fosamprenavir is rapidly converted to amprenavir by cellular or serum phosphatases in vivo. Amprenavir is a competitive inhibitor of HIV-1 protease. Amprenavir binds to the active site of HIV-1 protease and thereby prevents the processing of viral gag and gag-pol polyprotein precursors, resulting in the formation of immature non-infectious viral particles.

Fosamprenavir has little or no antiviral activity in vitro. The in vitro antiviral activity observed with fosamprenavir is due to the presence of trace amounts of amprenavir. The in vitro antiviral activity of amprenavir was evaluated against HIV-1 IIIB in both acutely and chronically infected lymphoblastic cell lines (MT-4, CEM-CCRF, H9) and in peripheral blood lymphocytes. The 50% inhibitory concentration (IC₅₀) of amprenavir ranged from 0.012 to 0.08 μM in acutely infected cells and was 0.41 μM in chronically infected cells (1 μM = 0.50 μg/ml). In vitro, amprenavir exhibited synergistic anti-HIV-1 activity in combination with the nucleoside reverse transcriptase inhibitors (NRTIs) abacavir, didanosine and zidovudine and the protease inhibitor saquinavir, and additive anti-HIV-1 activity in combination with indinavir, nelfinavir and ritonavir. The relationship between in vitro anti-HIV-1 activity of amprenavir and the inhibition of HIV-1 replication in humans has not been defined.

Co-administration of ritonavir with fosamprenavir increase plasma amprenavir AUC by approximately 2-fold and plasma Cτ ss by 4- to 6-fold, compared to values obtained when fosamprenavir is
administered alone. Administration of fosamprenavir 700 mg twice daily with ritonavir 100 mg twice daily results in plasma amprenavir trough concentrations (geometric mean plasma $C_{\text{min}}$ 1.74 µg/ml, reported in study APV30003 in antiretroviral experienced patients) above the median IC50 value reported in this study (0.008 µg/ml [0.001 – 0.144]).

Resistance

HIV-1 isolates with a decreased susceptibility to amprenavir have been selected during in vitro serial passage experiments. Reduced susceptibility to amprenavir was associated with virus that had developed I50V or I84V or V32I+I47V or I54M mutations.

No development of genotypic or phenotypic amprenavir resistance was detected in virus from thirty-two anti retroviral therapy naïve patients receiving fosamprenavir 1400 mg with ritonavir 200 mg once daily (Study APV30002) and experiencing virological failure or on-going viral replication. A significantly higher proportion of nelfinavir treated patients acquired primary and / or secondary PRO mutations (nelfinavir 27/54 (50 %)) (p< 0.001).

Development of amprenavir resistance was detected in viral isolates from protease experienced patients receiving fosamprenavir 1400 mg with ritonavir 200 mg once daily or 700 mg fosamprenavir with 100 mg ritonavir twice daily (Study APV30003) and having virological failure or having on-going viral replication. 58% (19/33) versus 25% (7/28) patients acquired primary and / or secondary PRO mutations in the fosamprenavir with ritonavir arm versus the lopinavir / ritonavir arm. The following amprenavir resistance–associated mutations developed either alone or in combination: V32I, M46I/L, I47V, I50V, I54L/M and I84V.

Cross-Resistance

The data are currently too limited to determine a clinically relevant phenotypic cut-off for fosamprenavir with ritonavir.

Cross-resistance between amprenavir and reverse transcriptase inhibitors is unlikely to occur because the enzyme targets are different.

Telzir is not recommended for use as monotherapy, due to the rapid emergence of resistant virus.

Clinical experience

The clinical experience is mainly based on two open label studies performed in comparison to nelfinavir in antiretroviral naïve patients (study APV30002) and in comparison to lopinavir / ritonavir in antiretroviral experienced patients (study APV30003). In both studies fosamprenavir was used boosted with ritonavir.

Antiretroviral Naïve Patients

In antiretroviral naïve patients in APV30002, fosamprenavir (1400 mg) given once daily in combination with low dose ritonavir (200 mg) as part of a triple regimen including abacavir (300 mg twice daily) and lamivudine (150 mg twice daily) showed similar efficacy over 48 weeks compared to nelfinavir (1250 mg) given twice daily in combination with abacavir with lamivudine (300 and 150 mg twice daily).

Non-inferiority was demonstrated between fosamprenavir with ritonavir and nelfinavir based on the proportions of patients achieving plasma HIV-1 RNA levels < 400 copies/ml at 48 weeks (primary endpoint). In the ITT (Rebound or Discontinuation = Failure) analysis, 69 % (221 / 322) of patients receiving fosamprenavir with ritonavir achieved < 400 copies/ml compared to 68 % (221 / 327) of patients receiving nelfinavir.
The median plasma HIV-1 RNA had decreased by 3.1 log_{10} copies/ml and 3.0 log_{10} copies/ml at Week 48 in the fosamprenavir with ritonavir and nelfinavir arms respectively.

The median baseline CD4 cell count was low (170 cells/mm³ overall) in both groups. CD4 + cell counts increased in both the fosamprenavir with ritonavir and nelfinavir groups, with median increases above baseline being similar in magnitude at Week 48 (+ 203 and + 207 cells/mm³, respectively).

The data presented above demonstrates that the once daily regimen of fosamprenavir with ritonavir (1400 / 200 mg OD) in antiretroviral naïve patients showed similar efficacy compared to nelfinavir given twice daily. However, the demonstration of efficacy in this population is only based on one open label study versus nelfinavir. Another clinical study is planned to reinforce the efficacy demonstration of the medicinal product in this population. Therefore, as a conservative approach, based on enhanced amprenavir C_{trough} levels, the twice daily dosing regimen of fosamprenavir with ritonavir is recommended for optimal therapeutic management of this population (see section 4.2).

### Antiretroviral Experiend Patients

In a randomised open-label study (APV30003) in protease inhibitor experienced patients with virological failure (less than or equal to two PIs) the fosamprenavir with ritonavir combination (700 / 100 mg twice daily or 1400 / 200 mg once daily) did not demonstrate non-inferiority to lopinavir / ritonavir with regard to viral suppression as measured by the average area under the curve minus baseline (AAUCMB) for plasma HIV-1 RNA over 48 weeks (the primary end point). Results were in favour of the lopinavir / ritonavir arm as detailed below.

All patients in this study had failed treatment with a previous protease inhibitor regimen (defined as plasma HIV-1 RNA that never went below 1,000 copies/ml after at least 12 consecutive weeks of therapy, or initial suppression of HIV-1 RNA which subsequently rebounded to ≥ 1,000 copies/ml). However, only 65 % of patients were receiving a PI based regimen at study entry.

The population enrolled mainly consisted of moderately antiretroviral experienced patients. The median durations of prior exposure to NRTIs were 257 weeks for patients receiving fosamprenavir with ritonavir twice daily (79 % had ≥ 3 prior NRTIs) and 210 weeks for patients receiving lopinavir/ritonavir (64 % had ≥ 3 prior NRTIs). The median durations of prior exposure to protease inhibitors were 149 weeks for patients receiving fosamprenavir with ritonavir twice daily (49 % received ≥ 2 prior PIs) and 130 weeks for patients receiving lopinavir/ritonavir (40 % received ≥ 2 prior PIs).

The mean AAUCMBs (log_{10} c/ml) in the ITT (E) population (Observed analysis) at 48 weeks are described in the table below:
Plasma HIV-1 RNA Average Area Under the Curve Minus Baseline (AAUCMB) Values (log10 copies/ml) at week 48 by Randomisation Strata in APV30003 ITT (E) Population (Observed Analysis)

<table>
<thead>
<tr>
<th>Plasma HIV-1 RNA stratum</th>
<th>Observed analysis</th>
<th>Observed analysis</th>
<th>Observed analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>FOS/RTV BID</td>
<td>LPV/RTV BID</td>
<td>Mean Diff. (97.5% CI)</td>
</tr>
<tr>
<td></td>
<td>N=107 Mean (n)</td>
<td>N=103 Mean (n)</td>
<td>FOS/RTV BID vs LPV/RTV BID</td>
</tr>
<tr>
<td>1000 – 10,000 copies/ml</td>
<td>-1.53 (41)</td>
<td>-1.43 (43)</td>
<td>-0.104 (-0.550, 0.342)</td>
</tr>
<tr>
<td>&gt;10,000 – 100,000 copies/ml</td>
<td>-1.59 (45)</td>
<td>-1.81 (46)</td>
<td>0.216 (-0.213, 0.664)</td>
</tr>
<tr>
<td>&gt;100,000 copies/ml</td>
<td>-1.38 (19)</td>
<td>-2.61 (14)</td>
<td>1.232 (0.512, 1.952)</td>
</tr>
<tr>
<td>Total population</td>
<td>-1.53 (105)</td>
<td>-1.76 (103)</td>
<td>0.244 (-0.047, 0.536)</td>
</tr>
</tbody>
</table>

Key: FOS/RTV BID – Fosamprenavir with ritonavir twice daily, LPV/RTV BID – Lopinavir / ritonavir twice daily

When considering the proportion of patients with undetectable viral load in the fosamprenavir with ritonavir twice daily dosing regimens and lopinavir / ritonavir arms respectively, results showed a trend in favour of the lopinavir / ritonavir arms: 58 % versus 61 % (plasma HIV-1 RNA < 400 copies/ml) or 46 % versus 50 % (plasma HIV-1 RNA < 50 copies/ml) at Week 48 (secondary efficacy endpoint) in the intent to treat (RD=F) analysis.

In patients with high viral load at baseline (> 100,000 copies/ml) 7/14 (50 %) patients in the lopinavir / ritonavir group and 6/19 (32 %) patients in the fosamprenavir with ritonavir group had plasma HIV-1 RNA < 400 copies/ml.

The fosamprenavir with ritonavir twice daily regimen and the lopinavir / ritonavir twice daily regimen showed similar immunological improvements through 48 weeks of treatment as measured by median change from baseline in CD4 + cell count (fosamprenavir with ritonavir twice daily: 81 cells/mm³; lopinavir / ritonavir twice daily: 91 cells/mm³).

There are insufficient data to recommend the use of fosamprenavir with ritonavir in heavily pre-treated patients.

5.2 Pharmacokinetic properties

After oral administration, fosamprenavir is rapidly and almost completely hydrolysed to amprenavir and inorganic phosphate prior to reaching the systemic circulation. The conversion of fosamprenavir to amprenavir appears to primarily occur in the gut epithelium.

The pharmacokinetic properties of amprenavir following co-administration of Telzir with ritonavir have been evaluated in healthy adult subjects and HIV-infected patients and no substantial differences were observed between these two groups.

Telzir tablet and oral suspension formulations, both given fasted, delivered equivalent plasma amprenavir AUC∞ values and the Telzir oral suspension formulation delivered a 14 % higher plasma amprenavir Cmax as compared to the oral tablet formulation.
Absorption

After single dose administration of fosamprenavir, amprenavir peak plasma concentrations are observed approximately 2 hours after administration. Fosamprenavir AUC values are, in general, less than 1 % of those observed for amprenavir. The absolute bioavailability of fosamprenavir in humans has not been established.

After multiple dose oral administration of equivalent fosamprenavir and amprenavir doses, comparable amprenavir AUC values were observed; however, C_{max} values were approximately 30 % lower and C_{min} values were approximately 28 % higher with fosamprenavir.

After multiple dose oral administration of fosamprenavir 700 mg with ritonavir 100 mg twice daily, amprenavir was rapidly absorbed with a geometric mean (95 % CI) steady state peak plasma amprenavir concentration (C_{max}) of 6.08 (5.38-6.86) µg/ml occurring approximately 1.5 (0.75-5.0) hours after dosing (t_{max}). The mean steady state plasma amprenavir trough concentration (C_{min}) was 2.12 (1.77-2.54) µg/ml and AUC_{0-\infty} was 39.6 (34.5–45.3) h*µg/ml.

Administration of the fosamprenavir tablet formulation with a high fat meal did not alter plasma amprenavir pharmacokinetics (C_{max}, t_{max} or AUC_{0-\infty}) compared to the administration of this formulation in the fasted state. Telzir tablets may be taken without regard to food intake.

Co-administration of amprenavir with grapefruit juice was not associated with clinically significant changes in plasma amprenavir pharmacokinetics.

Distribution

The apparent volume of distribution of amprenavir following administration of Telzir is approximately 430 l (6 l/kg assuming a 70 kg body weight), suggesting a large volume of distribution, with penetration of amprenavir freely into tissues beyond the systemic circulation. This value is decreased by approximately 40 % when Telzir is co-administered with ritonavir, most likely due to an increase in amprenavir bioavailability.

In in vitro studies, the protein binding of amprenavir is approximately 90 %. It is bound to the alpha-1-acid glycoprotein (AAG) and albumin, but has a higher affinity for AAG. Concentrations of AAG have been shown to decrease during the course of antiretroviral therapy. This change will decrease the total active substance concentration in the plasma, however the amount of unbound amprenavir, which is the active moiety, is likely to be unchanged.

CSF penetration of amprenavir is negligible in humans. Amprenavir appears to penetrate into semen, though semen concentrations are lower than plasma concentrations.

Metabolism

Fosamprenavir is rapidly and almost completely hydrolysed to amprenavir and inorganic phosphate as it is absorbed through the gut epithelium, following oral administration. Amprenavir is primarily metabolised by the liver with less than 1 % excreted unchanged in the urine. The primary route of metabolism is via the cytochrome P450 3A4 enzyme. Amprenavir metabolism is inhibited by ritonavir, via inhibition of CYP3A4, resulting in increased plasma concentrations of amprenavir. Amprenavir in addition is also an inhibitor of the CYP3A4 enzyme, although to a lesser extent than ritonavir. Therefore medicinal products that are inducers, inhibitors or substrates of CYP3A4 must be used with caution when administered concurrently with Telzir with ritonavir (see sections 4.3 and 4.5).
Elimination

Following administration of Telzir, the half-life of amprenavir is 7.7 hours. When Telzir is co-administered with ritonavir, the half-life of amprenavir is increased to 15 – 23 hours. The primary route of elimination of amprenavir is via hepatic metabolism with less than 1 % excreted unchanged in the urine and no detectable amprenavir in faeces. Metabolites account for approximately 14 % of the administered amprenavir dose in the urine, and approximately 75 % in the faeces.

Special populations

Paediatrics

The pharmacokinetics of fosamprenavir in combination with ritonavir has not been studied in paediatric patients.

Elderly

The pharmacokinetics of fosamprenavir in combination with ritonavir has not been studied in patients over 65 years of age.

Renal impairment

Patients with renal impairment have not been specifically studied. Less than 1 % of the therapeutic dose of amprenavir is excreted unchanged in the urine. Renal clearance of ritonavir is also negligible, therefore the impact of renal impairment on amprenavir and ritonavir elimination should be minimal.

Hepatic impairment

Fosamprenavir is converted in man to amprenavir. The principal route of amprenavir and ritonavir elimination is hepatic metabolism. There are limited data regarding the use of this combination in patients with hepatic impairment and therefore specific dosage recommendations cannot be made (see sections 4.3 and 4.4).

5.3 Preclinical safety data

Toxicity was similar to that of amprenavir and occurred at amprenavir plasma exposure levels below human exposure after treatment with fosamprenavir in combination with ritonavir at the recommended dose.

In repeated dose toxicity studies in adult rats and dogs, fosamprenavir produced evidence of gastrointestinal disturbances (salivation, vomiting and soft to liquid faeces), and hepatic changes (increased liver weights, raised serum liver enzyme activities and microscopic changes, including hepatocyte necrosis).

In reproductive toxicity studies with fosamprenavir in rats, male fertility was not affected, but in females gravid uterine weights, numbers of ovarian corpora lutea and uterine implantation sites were reduced. In pregnant rats and rabbits there were no major effects on embryo-foetal development. However, the number of abortions increased. In rabbits, systemic exposure at the high dose level was only 0.3 times human exposure at the maximum clinical dose and thus the developmental toxicity of fosamprenavir has not been fully determined. In rats exposed pre- and post-natally to fosamprenavir, pups showed impaired physical and functional development and reduced growth. Pup survival was decreased. In addition, decreased number of implantation sites per litter and a prolongation of gestation were seen when pups were mated after reaching maturity.
Fosamprenavir was not mutagenic or genotoxic in a standard battery of in vitro and in vivo assays. Carcinogenicity studies of fosamprenavir in rats and mice have not yet been completed; however, in long-term carcinogenicity studies with amprenavir in mice and rats, there were benign hepatocellular adenomas in males at exposure levels equivalent to 2.0-fold (mice) or 3.8-fold (rats) those in humans given 1200 mg twice daily of amprenavir alone. In male mice altered hepatocellular foci were seen at doses that were at least 2.0 times human therapeutic exposure.

A higher incidence of hepatocellular carcinoma was seen in all amprenavir male mouse treatment groups. However, this increase was not statistically significantly different from male control mice by appropriate tests. The mechanism for the hepatocellular adenomas and carcinomas found in these studies has not been elucidated and the significance of the observed effects for humans is uncertain. However, there is little evidence from the exposure data in humans, both in clinical trials and from marketed use, to suggest that these findings are of clinical significance.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core:

Microcrystalline cellulose
Croscarmellose sodium
Povidone K30
Magnesium stearate
Colloidal anhydrous silica

Tablet film-coat:

Hypermellose
Titanium dioxide (E171)
Glycerol triacetate
Iron oxide red (E172)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

HDPE bottles with a child resistant polypropylene closure containing 60 tablets.

6.6 Instructions for use and handling

No special requirements.
7. MARKETING AUTHORISATION HOLDER

Glaxo Group Ltd
Greenford Road
Greenford
Middlesex UB6 0NN
United Kingdom

8. MARKETING AUTHORISATION NUMBER

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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

Telzir 50 mg/ml oral suspension.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml of oral suspension contains 50 mg fosamprenavir as fosamprenavir calcium (equivalent to approximately 43 mg amprenavir).

For excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Oral suspension.

The suspension is white to off-white in colour.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Telzir in combination with low dose ritonavir is indicated for the treatment of Human Immunodeficiency Virus Type 1 (HIV-1) infected adults in combination with other antiretroviral medicinal products.

In moderately antiretroviral experienced patients, Telzir in combination with low dose ritonavir has not been shown to be as effective as lopinavir / ritonavir.

In heavily pretreated patients the use of Telzir in combination with low dose ritonavir has not been sufficiently studied.

In protease inhibitor (PI) experienced patients, the choice of Telzir should be based on individual viral resistance testing and treatment history (see section 5.1).

4.2 Posology and method of administration

Telzir must only be given with low dose ritonavir as a pharmacokinetic enhancer of amprenavir and in combination with other antiretroviral medicinal products. The Summary of Product Characteristics of ritonavir must therefore be consulted prior to initiation of therapy with Telzir.

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

Telzir (fosamprenavir) is a pro-drug of amprenavir and must not be administered concomitantly with other medicinal products containing amprenavir.

The importance of complying with the full recommended dosing regimen should be stressed to all patients.
Adults (greater than or equal to 18 years of age)

For antiretroviral naïve and experienced patients the recommended dose is 700 mg fosamprenavir twice daily with 100 mg ritonavir twice daily, in combination with other antiretroviral medicinal products (see section 5.1).

Caution is advised if the recommended doses of fosamprenavir with ritonavir detailed above are exceeded (see section 4.4).

Children (less than 12 years of age) and adolescents (12 to 17 years of age)

The safety and efficacy of Telzir with ritonavir has not yet been established in these patient populations. Therefore, this combination must not be used in this age group until further data becomes available.

Elderly (over 65 years of age)

The pharmacokinetics of fosamprenavir have not been studied in this patient population (see section 5.2).

Renal impairment

No initial dose adjustment is considered necessary in patients with renal impairment (see section 5.2).

Hepatic impairment

There are limited data regarding the use of Telzir with ritonavir when co-administered to patients with hepatic impairment and therefore specific dosage recommendations cannot be made. Consequently, Telzir in combination with ritonavir should be used with caution in patients with mild or moderate hepatic impairment and is contraindicated in those with severe hepatic impairment (see sections 4.3, 4.4 and 5.2).

Telzir is administered orally. Telzir is also available as 700 mg film-coated tablets. The oral suspension should be taken without food and on an empty stomach.

Shake the bottle vigorously for 20 seconds before first dose is removed and 5 seconds before each subsequent dose.

4.3 Contraindications

Hypersensitivity to fosamprenavir, amprenavir or to any of the excipients of Telzir, or to ritonavir.

Patients with severe hepatic impairment (see sections 4.4 and 5.2).

Telzir must not be administered concurrently with medicinal products with narrow therapeutic windows that are substrates of cytochrome P450 3A4 (CYP3A4), e.g. amiodarone, astemizole, bepridil, cisapride, dihydroergotamine, ergotamine, pimozide, quinidine, terfenadine (see section 4.5).

Telzir with ritonavir must not be co-administered with medicinal products with narrow therapeutic windows that are highly dependent on CYP2D6 metabolism e.g. flecainide and propafenone (see section 4.5).

Rifampicin must not be administered concurrently with Telzir (see section 4.5).
Herbal preparations containing St John’s wort (Hypericum perforatum) must not be used while taking Telzir due to the risk of decreased plasma concentrations and reduced clinical effects of amprenavir (see section 4.5).

4.4 Special warnings and special precautions for use

Patients should be advised that treatment with the Telzir, or any other current antiretroviral therapy, does not cure HIV and that they may still develop opportunistic infections and other complications of HIV infection. Current antiretroviral therapies, including Telzir, have not been proven to prevent the risk of transmission of HIV to others through sexual contact or blood contamination. Appropriate precautions should continue to be taken.

Fosamprenavir contains a sulphonamide moiety. The potential for cross-sensitivity between medicinal products in the sulphonamide class and fosamprenavir is unknown. In the pivotal studies of Telzir, in patients receiving fosamprenavir with ritonavir there was no evidence of an increased risk of rashes in patients with a history of sulphonamide allergy versus those who did not have a sulphonamide allergy. Yet, Telzir should be used with caution in patients with a known sulphonamide allergy.

The Telzir oral suspension contains propyl and methyl parahydroxybenzoate. These products may cause an allergic reaction in some individuals. This reaction may be delayed.

Co-administration of Telzir 700 mg twice daily with ritonavir in doses greater than 100 mg twice daily has not been clinically evaluated. The use of higher ritonavir doses might alter the safety profile of the combination and therefore is not recommended.

Liver disease

The safety and efficacy of Telzir have not been established in patients with significant underlying liver disease. Telzir should be used with caution in patients with mild or moderate hepatic impairment and is contraindicated in patients with severe hepatic impairment. Patients with chronic hepatitis B or C and treated with combination antiretroviral therapy are at an increased risk of 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.

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.

Medicinal products – interactions

The use of Telzir concomitantly with midazolam or triazolam is not recommended (see section 4.5).

The use of Telzir concomitantly with halofantrine or lidocaine (systemic) is not recommended.

The use of Telzir concomitantly with PDE5 inhibitors (e.g. sildenafil and vardenafil) is not recommended (see section 4.5).

Concomitant use of Telzir with simvastatin or lovastatin is not recommended due to an increased risk of myopathy, including rhabdomyolysis (see section 4.5).

A reduction in the rifabutin dosage by at least 75 % is recommended when administered with Telzir with ritonavir. Further dose reduction may be necessary (see section 4.5).
Because of the interactions with amprenavir, the efficacy of hormonal contraceptives may be impaired. Therefore, alternative reliable barrier methods of contraception are recommended for women of childbearing potential (see section 4.5).

Anticonvulsants (carbamazepine, phenobarbital, phenytoin) should be used with caution. Telzir may be less effective due to decreased amprenavir plasma concentrations in patients taking these medicinal products concomitantly (see section 4.5).

Therapeutic concentration monitoring is recommended for immunosuppressant medicinal products (cyclosporine, tacrolimus, rapamycin) when co-administered with Telzir (see section 4.5).

Therapeutic concentration monitoring is recommended for tricyclic antidepressants (e.g. desipramine and nortriptyline) when co-administered with Telzir (see section 4.5).

When methadone is co-administered with Telzir, patients should be closely monitored for opiate abstinence syndrome (see section 4.5).

When warfarin or other oral anticoagulants are co-administered with Telzir a reinforced monitoring of INR (International normalised ratio) is recommended (see section 4.5).

**Rash / cutaneous reactions**

Most patients with mild or moderate rash can continue Telzir. Appropriate antihistamines (e.g. cetirizine dihydrochloride) may reduce pruritus and hasten the resolution of rash. Severe and life-threatening skin reactions, including Stevens-Johnson syndrome, were reported in less than 1% of patients included in the clinical development programme. Telzir should be permanently discontinued in case of severe rash, or in case of rash of moderate intensity with systemic or mucosal symptoms (see section 4.8).

**Haemophiliac patients**

There have been reports of increased bleeding including spontaneous skin haematomas and haemarthroses in haemophiliac patients type A and B treated with protease inhibitors (PIs). In some patients administration of factor VIII was necessary. 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 evoked, although the mechanism of action has not been elucidated. Haemophiliac patients should therefore be informed of the possibility of increased bleeding.

**Hyperglycaemia**

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

**Lipodystrophy**

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 section 4.8).

4.5 Interaction with other medicinal products and other forms of interaction

When fosamprenavir and ritonavir are co-administered, the ritonavir metabolic drug interaction profile may predominate because ritonavir is a more potent CYP3A4 inhibitor. The full prescribing information for ritonavir must therefore be consulted prior to initiation of therapy with Telzir with ritonavir. Ritonavir also inhibits CYP2D6 but to a lesser extent than CYP3A4. Ritonavir induces CYP3A4, CYP1A2, CYP2C9 and glucuronosyl transferase. Additionally, both amprenavir, the active metabolite of fosamprenavir, and ritonavir are primarily metabolised in the liver by CYP3A4. Therefore, any medicinal products that either share this metabolic pathway or modify CYP3A4 activity may modify the pharmacokinetics of amprenavir and ritonavir. Similarly, administration of fosamprenavir with ritonavir may modify the pharmacokinetics of other active substances that share this metabolic pathway.

- Associations contraindicated (see section 4.3)

CYP3A4 substrates with narrow therapeutic index
Telzir must not be administered concurrently with medicinal products with narrow therapeutic windows containing active substances that are substrates of cytochrome P450 3A4 (CYP3A4). Co-administration may result in competitive inhibition of the metabolism of these active substances thus increasing their plasma levels and leading to serious and/or life-threatening adverse reactions such as cardiac arrhythmia (e.g. amiodarone, astemizole, bepridil, cisapride, pimozide, quinidine, terfenadine) or peripheral vasospasm or ischaemia (e.g. ergotamine, dihydroergotamine).

CYP2D6 substrates with narrow therapeutic index
Telzir with ritonavir must not be co-administered with medicinal products containing active substances that are highly dependent on CYP2D6 metabolism and for which elevated plasma concentrations are associated with serious and/or life-threatening adverse reactions. These active substances include flecainide and propafenone.

Rifampicin
Rifampicin reduces the amprenavir plasma AUC by approximately 82 %. Based on information for other protease inhibitors, it is expected that co-administration of Telzir with ritonavir with rifampicin will also result in large decreases in plasma concentrations of amprenavir. Accordingly, Telzir with ritonavir must not be co-administered with rifampicin.

St John’s wort (*Hypericum perforatum*)
Serum levels of amprenavir and ritonavir can be reduced by concomitant use of the herbal preparation St John’s wort (*Hypericum perforatum*). This is due to induction of drug metabolising enzymes by St John’s wort. Herbal preparations containing St John’s wort should therefore not be combined with Telzir with ritonavir. If a patient is already taking St John’s wort, check amprenavir, ritonavir and if possible viral levels and stop St John’s wort. Amprenavir and ritonavir levels may increase on stopping St John’s wort. The inducing effect may persist for at least 2 weeks after cessation of treatment with St John’s wort.
• Other combinations

Antiretroviral medicinal products

Non-nucleoside reverse transcriptase inhibitors

Efavirenz: there was no clinically relevant interaction when fosamprenavir 700 mg twice daily and ritonavir 100 mg twice daily was used concurrently with efavirenz (600 mg once daily).

Nevirapine: based on the effect of nevirapine on other HIV protease inhibitors, nevirapine may decrease the serum concentration of amprenavir. Appropriate doses of the combination with respect to safety and efficacy have not been established. This combination should be used with caution.

Nucleoside / Nucleotide reverse transcriptase inhibitors

Interaction studies with abacavir, lamivudine and zidovudine have been performed with amprenavir 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 fosamprenavir and ritonavir with these medicinal products is not expected to significantly alter the exposure of the co-administered active substances.

Didanosine chewable tablet: no pharmacokinetic study has been performed with fosamprenavir in combination with didanosine. Clinically significant interaction resulting from an increase in the stomach pH due to the didanosine antacid component is unlikely and no dose separation or adjustment is considered necessary when fosamprenavir and didanosine are administered concomitantly (see chapter, Antacids). No significant interaction is expected with didanosine gastro-resistant capsule

Tenofovir: no recommendations can be drawn at this stage on the co-administration of fosamprenavir with ritonavir with tenofovir.

Protease Inhibitors

Lopinavir / ritonavir: no dose recommendation can be given for the co-administration of Telzir with ritonavir and lopinavir / ritonavir, but close monitoring is advised because the safety and efficacy of this combination is unknown. The \(C_{max}\), \(AUC\) and \(C_{min}\) of lopinavir were increased by 30 %, 37 % and 52 % respectively when lopinavir 400 mg with ritonavir 100 mg was given with fosamprenavir 700 mg with ritonavir 100 mg twice daily for two weeks. The \(C_{max}\), \(AUC\) and \(C_{min}\) of amprenavir were decreased by 58 %, 63 % and 65 % respectively.

When lopinavir 533 mg with ritonavir 133 mg was administered in combination with fosamprenavir 1400 mg twice daily for two weeks, the \(C_{max}\), \(AUC\), and \(C_{min}\) of lopinavir were unchanged compared to values observed for lopinavir 400 mg with ritonavir 100 mg twice daily. However, the \(AUC\) and \(C_{min}\) of amprenavir were decreased by 26 % and 42 %, respectively; whereas, \(C_{max}\) was not significantly altered compared to values obtained for fosamprenavir 700 mg with ritonavir 100 mg twice daily.

No interaction studies have been undertaken between fosamprenavir with ritonavir and the following protease inhibitors: indinavir, saquinavir, nelfinavir and atazanavir.

Antibiotics / Antifungals

Clarithromycin: a reduction in the clarithromycin dose should be considered when co-administered with Telzir with ritonavir in patients with renal impairment as moderate increases in clarithromycin concentrations are expected when coadministered with Telzir with ritonavir.
**Erythromycin**: no pharmacokinetic study has been performed with fosamprenavir with ritonavir in combination with erythromycin, however, plasma levels of erythromycin may be increased when co-administered.

**Ketoconazole / Itraconazole**: co-administration of amprenavir with ketoconazole increased ketoconazole AUC by 44%. When ritonavir is co-administered, a larger increase in ketoconazole concentration may occur. Itraconazole concentrations are expected to increase in the same manner as ketoconazole. In the absence of specific studies of fosamprenavir with ritonavir in combination with ketoconazole or itraconazole, no recommendations can be drawn in terms of dose adjustment.

**Rifabutin**: co-administration of amprenavir with rifabutin results in a 200% increase in rifabutin plasma concentrations (AUC) which could potentially lead to an increase of rifabutin related adverse reactions, notably uveitis. When ritonavir is co-administered a larger increase in rifabutin concentrations may occur. A reduction in the rifabutin dosage by at least 75% is recommended when administered with Telzir with ritonavir. Further dose reduction may be necessary.

**Other medicinal products**

**Medicinal products that may reduce plasma amprenavir concentrations when co-administered with Telzir**

Antacids, Histamine H₂ receptor antagonist and Proton-Pump inhibitors: no dose adjustment for any of the respective medicinal products is considered necessary when antacids, proton-pump inhibitors or histamine H₂ receptor antagonists are administered concomitantly with fosamprenavir. The AUC and Cₘₐₓ of amprenavir were decreased by 18% and 35% respectively, whilst the Cₐₘᵢₙ (C₁₂h) was comparable, when a single 1400 mg dose of fosamprenavir was co-administered with a single 30 ml dose of antacid suspension (equivalent to 3.6 grams aluminium hydroxide and 1.8 grams magnesium hydroxide).

Serum levels of amprenavir can be reduced by concomitant use of histamine H₂ receptor antagonists (for example ranitidine and cimetidine). Concurrent administration of ranitidine (300 mg single dose) with fosamprenavir (1400 mg single dose) decreased plasma amprenavir AUC by 30% and Cₘₐₓ by 51%. There was, however, no change observed in the amprenavir Cₐₘᵢₙ (C₁₂h).

**Anticonvulsant active substances**: concomitant administration of anticonvulsant active substances known as enzymatic inducers (phenytoin, phenobarbital, carbamazepine) with fosamprenavir may lead to a decrease in the plasma concentrations of amprenavir. These combinations should be used with caution.

**Medicinal products whose plasma levels may be increased when co-administered with Telzir**

**Other medicinal products with a narrow therapeutic window**: some substances (e.g. lidocaine (by systemic route) and halofantrine) given with Telzir may cause serious adverse reactions. Concomitant use is not recommended.

**Benzodiazepines**: concomitant use of Telzir with midazolam or triazolam could result in prolonged sedation or respiratory depression and thus is not recommended.

**Erectile dysfunction medicinal products**: concomitant use is not recommended. Based on data for ritonavir and other protease inhibitors, plasma concentrations of PDE5 inhibitors (e.g. sildenafil and vardenafil) are expected to substantially increase when co-administered with Telzir with ritonavir and may result in an increase in PDE5 inhibitor associated adverse reactions, including hypotension, visual changes and priapism.

**HMG-CoA reductase inhibitors**: if treatment with a HMG-CoA reductase inhibitor is indicated, pravastatin or fluvastatin is recommended because their metabolism is not dependent on CYP3A4 and...
interactions are not expected with protease inhibitors. HMG-CoA reductase inhibitors which are highly dependent on CYP3A4 for metabolism, such as lovastatin and simvastatin, are expected to have markedly increased plasma concentrations when co-administered with Telzir with ritonavir. Since increased concentrations of HMG-CoA reductase inhibitors may cause myopathy, including rhabdomyolysis, the combination of lovastatin or simvastatin with Telzir with ritonavir is not recommended. No adjustment of the fosamprenavir or ritonavir dose is required when co-administered with atorvastatin.

The $C_{\text{max}}$, AUC and $C_{\text{min}}$ of atorvastatin were increased by 184 %, 153 % and 73 % respectively when atorvastatin (10 mg once daily for 4 days) was given with fosamprenavir 700 mg twice daily with ritonavir 100 mg twice daily for two weeks. The $C_{\text{max}}$, AUC and $C_{\text{min}}$ of amprenavir were unchanged. When used with Telzir with ritonavir, doses of atorvastatin no greater than 20 mg/day should be administered, with careful monitoring for atorvastatin toxicity.

**Immunosuppressants:** frequent therapeutic concentration monitoring of immunosuppressant levels is recommended until levels have stabilised as plasma concentrations of cyclosporin, rapamycin and tacrolimus may be increased when co-administered with fosamprenavir with ritonavir.

**Tricyclic antidepressants:** careful monitoring of the therapeutic and adverse reactions of tricyclic antidepressants is recommended when they (for example desipramine and nortriptyline) are concomitantly administered with Telzir.

**Medicinal products whose plasma levels may be decreased when co-administered with Telzir**

**Methadone:** no data are available on the co-administration of fosamprenavir with ritonavir and methadone. Amprenavir and ritonavir both decrease plasma concentrations of methadone. When methadone is co-administered with Telzir with ritonavir, patients should be closely monitored for opiate abstinence syndrome, with concomitant monitoring of methadone plasma levels.

**Oral anticoagulants:** a reinforced monitoring of the International Normalised Ratio is recommended in case of administration of Telzir with ritonavir with warfarin or other oral anticoagulants, due to a possible decrease or increase of their antithrombotic effect.

**Oral contraceptives:** alternative reliable barrier methods of contraception are recommended for women of childbearing potential. Oestrogens and progestogens may interact with fosamprenavir and ritonavir, thus concomitant use may impair the efficacy of hormonal contraceptives.

### 4.6 Pregnancy and lactation

#### Pregnancy

There is no clinical experience with fosamprenavir in pregnant women. In animal studies at systemic plasma exposures (AUC) to amprenavir lower than therapeutic exposure in patients treated with Telzir, some developmental toxicity was observed (see section 5.3). In view of the low exposure in reproductive toxicity studies, the potential developmental toxicity of Telzir has not been fully determined.

Telzir should be used during pregnancy only if the potential benefit justifies the potential risk to the foetus.

#### Lactation

Amprenavir-related material was found in rat milk, but it is not known whether amprenavir is excreted in human milk. Rat pups exposed pre and post-natally to amprenavir and fosamprenavir showed developmental toxicity (see section 5.3).
It is therefore recommended that mothers treated with Telzir do not breast-feed their infants. As a general rule, it is recommended that HIV-infected women must not breast-feed under any circumstances to avoid transmission of HIV.

4.7 Effects on ability to drive and use machines

No studies on the effects of Telzir in combination with ritonavir on the ability to drive and use machines have been performed. The adverse reaction profile of Telzir should be borne in mind when considering the patient’s ability to drive or operate machinery (see section 4.8).

4.8 Undesirable effects

It should be noted that the Telzir oral suspension has not been evaluated clinically and that the adverse reaction profile detailed in this section is based on the experience with the Telzir film coated tablets.

The safety of fosamprenavir has been studied in 755 patients in Phase II and III controlled clinical trials. The safety of the co-administration of fosamprenavir with low dose ritonavir was established in two pivotal Phase III trials: APV30002 (n = 322) in antiretroviral naïve patients, fosamprenavir (1400 mg) given once daily in combination with ritonavir (200 mg) as part of a triple regimen including abacavir and lamivudine. APV30003 in protease inhibitor experienced patients, fosamprenavir given in combination with low dose ritonavir either once daily (1400 mg / 200 mg) (n = 106) or twice daily (700 mg / 100 mg) (n = 106) in combination with two active reverse transcriptase inhibitors (RTIs).

The adverse reaction profile was similar across all the respective studies: antiretroviral naïve (APV30002) and protease inhibitor experienced (twice daily dosing, APV30003) patient populations.

The adverse reactions are listed by body system, organ class and absolute frequency. Frequencies are defined as: 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), including isolated reports. The frequency of the reactions were calculated using adverse reactions that were of at least moderate intensity (Grade 2 or more) and reported by investigators as being attributable to the medicinal products used in the studies. The most frequent clinical adverse reactions (occurring in at least 1 % of patients) reported in the two large clinical studies in adults with at least a possible casual relationship to Telzir are summarised below.

<table>
<thead>
<tr>
<th>Body System</th>
<th>Adverse reaction</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nervous system disorders</td>
<td>Headache, dizziness</td>
<td>Common</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td>Diarrhoea</td>
<td>Very common</td>
</tr>
<tr>
<td></td>
<td>Loose stools, nausea, vomiting, abdominal pain</td>
<td>Common</td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td>Rash</td>
<td>Common</td>
</tr>
<tr>
<td>General disorders and administration site conditions</td>
<td>Fatigue</td>
<td>Common</td>
</tr>
</tbody>
</table>
Rash / cutaneous reactions: erythematous or maculopapular cutaneous eruptions, with or without pruritus, may occur during therapy. The rash generally will resolve spontaneously without the necessity of discontinuing treatment with the fosamprenavir with ritonavir.

Severe or life-threatening rash, including Stevens-Johnson syndrome is rare, reported in less than 1 % of patients included in the clinical development programme. Fosamprenavir with ritonavir therapy should be definitively stopped in case of severe rash or in case of rash of mild or moderate intensity associated with systemic or mucosal signs (see section 4.4).

Clinical chemistry abnormalities: clinical chemistry abnormalities (Grade 3 or 4) potentially related to treatment with fosamprenavir with ritonavir and reported in greater than or equal to 1 % of patients, included:
increased ALT (common), AST (common), serum lipase (common) and triglycerides (very common). Grade 3 or 4 elevations in total cholesterol values were observed in less than 1 % of patients (< 1 % APV30002 ; 0 % APV 30003).

Lipodystrophy: combination antiretroviral therapy has been associated with redistribution of body fat (lipodystrophy) in HIV patients including the loss of peripheral and facial subcutaneous fat, increased intra-abdominal and visceral fat, breast hypertrophy and dorsocervical fat accumulation (buffalo hump) (see section 4.4).

Metabolic abnormalities: combination antiretroviral therapy has been associated with metabolic abnormalities such as hypertriglyceridaemia, hypercholesterolaemia, insulin resistance, hyperglycaemia and hyperlactataemia (see section 4.4).

Hyperglycaemia: new onset of diabetes mellitus, hyperglycaemia or exacerbations of existing diabetes mellitus have been reported in patients receiving antiretroviral protease inhibitors (see section 4.4).

Rhabdomyolysis: an increase in CPK, myalgia, myositis, and rarely, rhabdomyolysis, have been reported with protease inhibitors, more specifically in association with nucleoside analogues.

Haemophiliac patients: there have been reports of increased spontaneous bleeding in haemophiliac patients receiving antiretroviral protease inhibitors (see section 4.4).

4.9 Overdose

There is no known antidote for Telzir. It is not known whether amprenavir can be removed by peritoneal dialysis or haemodialysis. If overdosage occurs, the patient should be monitored for evidence of toxicity (see section 4.8) and standard supportive treatment applied as necessary.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antivirals for systemic use, protease inhibitor, ATC Code: J05A (pending)

Mechanism of action

Fosamprenavir is rapidly converted to amprenavir by cellular or serum phosphatases in vivo. Amprenavir is a competitive inhibitor of HIV-1 protease. Amprenavir binds to the active site of HIV-1 protease and thereby prevents the processing of viral gag and gag-pol polyprotein precursors, resulting in the formation of immature non-infectious viral particles.
Fosamprenavir has little or no antiviral activity in vitro. The in vitro antiviral activity observed with fosamprenavir is due to the presence of trace amounts of amprenavir. The in vitro antiviral activity of amprenavir was evaluated against HIV-1 IIIB in both acutely and chronically infected lymphoblastic cell lines (MT-4, CEM-CCRF, H9) and in peripheral blood lymphocytes. The 50% inhibitory concentration (IC50) of amprenavir ranged from 0.012 to 0.08 µM in acutely infected cells and was 0.41 µM in chronically infected cells (1 µM = 0.50 µg/ml). In vitro, amprenavir exhibited synergistic anti-HIV-1 activity in combination with the nucleoside reverse transcriptase inhibitors (NRTIs) abacavir, didanosine and zidovudine and the protease inhibitor saquinavir, and additive anti-HIV-1 activity in combination with indinavir, nelfinavir and ritonavir. The relationship between in vitro anti-HIV-1 activity of amprenavir and the inhibition of HIV-1 replication in humans has not been defined.

Co-administration of ritonavir with fosamprenavir increase plasma amprenavir AUC by approximately 2-fold and plasma Cτ,ss by 4- to 6-fold, compared to values obtained when fosamprenavir is administered alone. Administration of fosamprenavir 700 mg twice daily with ritonavir 100 mg twice daily results in plasma amprenavir trough concentrations (geometric mean plasma Cmin 1.74 µg/ml, reported in study APV30003 in antiretroviral experienced patients) above the median IC50 value reported in this study (0.008 µg/ml [0.001 – 0.144]).

Resistance

HIV-1 isolates with a decreased susceptibility to amprenavir have been selected during in vitro serial passage experiments. Reduced susceptibility to amprenavir was associated with virus that had developed I50V or I84V or V32I+I47V or I54M mutations.

No development of genotypic or phenotypic amprenavir resistance was detected in virus from thirty-two antiretroviral therapy naïve patients receiving fosamprenavir 1400 mg with ritonavir 200 mg once daily (Study APV30002) and experiencing virological failure or on-going viral replication. A significantly higher proportion of nelfinavir treated patients acquired primary and /or secondary PRO mutations (nelfinavir 27/54 (50 %)) (p < 0.001).

Development of amprenavir resistance was detected in viral isolates from protease experienced patients receiving fosamprenavir 1400 mg with ritonavir 200 mg once daily or 700 mg fosamprenavir with 100 mg ritonavir twice daily (Study APV30003) and having virological failure or having on-going viral replication. 58% (19/33) versus 25% (7/28) patients acquired primary and / or secondary PRO mutations in the fosamprenavir with ritonavir arm versus the lopinavir / ritonavir arm. The following amprenavir resistance–associated mutations developed either alone or in combination: V32I, M46I/L, I47V, I50V, I54L/M and I84V.

Cross-Resistance

The data are currently too limited to determine a clinically relevant phenotypic cut-off for fosamprenavir with ritonavir.

Cross-resistance between amprenavir and reverse transcriptase inhibitors is unlikely to occur because the enzyme targets are different.

Telzir is not recommended for use as monotherapy, due to the rapid emergence of resistant virus.

Clinical experience

The clinical experience is mainly based on two open label studies performed in comparison to nelfinavir in antiretroviral naïve patients (study APV30002) and in comparison to lopinavir / ritonavir in antiretroviral experienced patients (study APV30003). In both studies fosamprenavir was used boosted with ritonavir.
Antiretroviral Naïve Patients

In antiretroviral naïve patients in APV30002, fosamprenavir (1400 mg) given once daily in combination with low dose ritonavir (200 mg) as part of a triple regimen including abacavir (300 mg twice daily) and lamivudine (150 mg twice daily) showed similar efficacy over 48 weeks compared to nelfinavir (1250 mg) given twice daily in combination with abacavir plus lamivudine (300 and 150 mg twice daily).

Non-inferiority was demonstrated between fosamprenavir with ritonavir and nelfinavir based on the proportions of patients achieving plasma HIV-1 RNA levels < 400 copies/ml at 48 weeks (primary endpoint). In the ITT (Rebound or Discontinuation = Failure) analysis, 69 % (221 / 322) of patients receiving fosamprenavir with ritonavir achieved < 400 copies/ml compared to 68 % (221 / 327) of patients receiving nelfinavir.

The median plasma HIV-1 RNA had decreased by 3.1 log10 copies/ml and 3.0 log10 copies/ml at Week 48 in the fosamprenavir with ritonavir and nelfinavir arms respectively.

The median baseline CD4 cell count was low (170 cells/mm³ overall) in both groups. CD4+ cell counts increased in both the fosamprenavir with ritonavir and nelfinavir groups, with median increases above baseline being similar in magnitude at Week 48 (+203 and +207 cells/mm³, respectively).

The data presented above demonstrates that the once daily regimen of fosamprenavir with ritonavir (1400/200 mg OD) in antiretroviral naïve patients showed similar efficacy compared to nelfinavir given twice daily. However, the demonstration of efficacy in this population is only based on one open label study versus nelfinavir. Another clinical study is planned to reinforce the efficacy demonstration of the medicinal product in this population. Therefore, as a conservative approach, based on enhanced amprenavir C_{trough} levels, the twice daily dosing regimen of fosamprenavir with ritonavir is recommended for optimal therapeutic management of this population (see section 4.2).

Antiretroviral Experienced Patients

In a randomised open-label study (APV30003) in protease inhibitor experienced patients with virological failure (less than or equal to two PIs) the fosamprenavir with ritonavir (700 / 100 mg twice daily or 1400 / 200 mg once daily) did not demonstrate non-inferiority to lopinavir / ritonavir with regard to viral suppression as measured by the average area under the curve minus baseline (AAUCMB) for plasma HIV-1 RNA over 48 weeks (the primary end point). Results were in favour of the lopinavir / ritonavir arm as detailed below.

All patients in this study had failed treatment with a previous protease inhibitor regimen (defined as plasma HIV-1 RNA that never went below 1,000 copies/ml after at least 12 consecutive weeks of therapy, or initial suppression of HIV-1 RNA which subsequently rebounded to ≥ 1,000 copies/ml). However, only 65 % of patients were receiving a PI based regimen at study entry.

The population enrolled mainly consisted of moderately antiretroviral experienced patients. The median durations of prior exposure to NRTIs were 257 weeks for patients receiving fosamprenavir with ritonavir twice daily (79 % had ≥ 3 prior NRTIs) and 210 weeks for patients receiving lopinavir/ritonavir (64 % had ≥ 3 prior NRTIs). The median durations of prior exposure to protease inhibitors were 149 weeks for patients receiving fosamprenavir with ritonavir twice daily (49 % received ≥ 2 prior PIs) and 130 weeks for patients receiving lopinavir/ritonavir (40 % received ≥2 prior PIs).

The mean AAUCMBs (log_{10} c/ml) in the ITT (E) population (Observed analysis) at 48 weeks are described in the table below:
## Plasma HIV-1 RNA Average Area Under the Curve Minus Baseline (AAUCMB) Values (log10 copies/ml) at week 48 by Randomisation Strata in APV30003 ITT (E) Population (Observed Analysis)

<table>
<thead>
<tr>
<th>Plasma HIV-1 RNA stratum</th>
<th>Observed analysis FOS/RTV BID N=107 Mean (n)</th>
<th>Observed analysis LPV/RTV BID N=103 Mean (n)</th>
<th>Observed analysis Mean Diff. (97.5% CI) FOS/RTV BID vs LPV/RTV BID</th>
</tr>
</thead>
<tbody>
<tr>
<td>1000 – 10,000 copies/ml</td>
<td>-1.53 (41)</td>
<td>-1.43 (43)</td>
<td>-0.104 (-0.550, 0.342)</td>
</tr>
<tr>
<td>&gt;10,000 – 100,000 copies/ml</td>
<td>-1.59 (45)</td>
<td>-1.81 (46)</td>
<td>0.216 (-0.213, 0.664)</td>
</tr>
<tr>
<td>&gt;100,000 copies/ml</td>
<td>-1.38 (19)</td>
<td>-2.61 (14)</td>
<td>1.232 (0.512, 1.952)</td>
</tr>
<tr>
<td>Total population</td>
<td>-1.53 (105)</td>
<td>-1.76 (103)</td>
<td>0.244 (-0.047, 0.536)</td>
</tr>
</tbody>
</table>

Key: FOS/RTV BID – Fosamprenavir with ritonavir twice daily, LPV/RTV BID – Lopinavir / ritonavir twice daily

When considering the proportion of patients with undetectable viral load in the fosamprenavir with ritonavir twice daily dosing regimens and lopinavir / ritonavir arms respectively, results showed a trend in favour of the lopinavir / ritonavir arms: 58 % versus 61 % (plasma HIV-1 RNA < 400 copies/ml) or 46 % versus 50 % (plasma HIV-1 RNA < 50 copies/ml) at Week 48 (secondary efficacy endpoint) in the intent to treat (RD=F) analysis.

In patients with high viral load at baseline (> 100,000 copies/ml) 7/14 (50 %) patients in the lopinavir / ritonavir group and 6/19 (32 %) patients in the fosamprenavir with ritonavir group had plasma HIV-1 RNA < 400 copies/ml.

The fosamprenavir with ritonavir twice daily regimen and the lopinavir / ritonavir twice daily regimen showed similar immunological improvements through 48 weeks of treatment as measured by median change from baseline in CD4+ cell count (fosamprenavir with ritonavir twice daily: 81 cells/mm³, lopinavir / ritonavir twice daily: 91 cells/mm³).

There are insufficient data to recommend the use of fosamprenavir with ritonavir in heavily pre-treated patients.

### 5.2 Pharmacokinetic properties

After oral administration, fosamprenavir is rapidly and almost completely hydrolysed to amprenavir and inorganic phosphate prior to reaching the systemic circulation. The conversion of fosamprenavir to amprenavir appears to primarily occur in the gut epithelium.

The pharmacokinetic properties of amprenavir following co-administration of Telzir with ritonavir have been evaluated in healthy adult subjects and HIV-infected patients and no substantial differences were observed between these two groups.

Telzir tablet and oral suspension formulations, both given fasted, delivered equivalent plasma amprenavir AUCₐ values and the Telzir oral suspension formulation delivered a 14 % higher plasma amprenavir Cₘₐₓ as compared to the oral tablet formulation. However, the bioequivalence could not be demonstrated when the oral suspension was given with food. Therefore the Telzir oral suspension should be taken without food and on an empty stomach (see section 4.2).
Absorption

After single dose administration of fosamprenavir, amprenavir peak plasma concentrations are observed approximately 2 hours after administration. Fosamprenavir AUC values are, in general, less than 1 % of those observed for amprenavir. The absolute bioavailability of fosamprenavir in humans has not been established.

After multiple dose oral administration of equivalent fosamprenavir and amprenavir doses, comparable amprenavir AUC values were observed; however, C\text{max} values were approximately 30 % lower and C\text{min} values were approximately 28 % higher with fosamprenavir.

After multiple dose oral administration of fosamprenavir 700 mg with ritonavir 100 mg twice daily, amprenavir was rapidly absorbed with a geometric mean (95 % CI) steady state peak plasma amprenavir concentration (C\text{max}) of 6.08 (5.38-6.86) \mu g/ml occurring approximately 1.5 (0.75-5.0) hours after dosing (t_{\text{max}}). The mean steady state plasma amprenavir trough concentration (C\text{min}) was 2.12 (1.77-2.54) \mu g/ml and AUC_{0-tau} was 39.6 (34.5–45.3) h*\mu g/ml.

Administration of the fosamprenavir oral suspension formulation with a high fat meal reduced plasma amprenavir AUC by approximately 25 % and C\text{max} by approximately 40 % as compared to the administration of this formulation in the fasted state.

Co-administration of amprenavir with grapefruit juice was not associated with clinically significant changes in plasma amprenavir pharmacokinetics.

Distribution

The apparent volume of distribution of amprenavir following administration of Telzir is approximately 430 l (6 l/kg assuming a 70 kg body weight), suggesting a large volume of distribution, with penetration of amprenavir freely into tissues beyond the systemic circulation. This value is decreased by approximately 40 % when Telzir is co-administered with ritonavir, most likely due to an increase in amprenavir bioavailability.

In \textit{in vitro} studies, the protein binding of amprenavir is approximately 90 %. It is bound to the alpha-1-acid glycoprotein (AAG) and albumin, but has a higher affinity for AAG. Concentrations of AAG have been shown to decrease during the course of antiretroviral therapy. This change will decrease the total active substance concentration in the plasma, however the amount of unbound amprenavir, which is the active moiety, is likely to be unchanged.

CSF penetration of amprenavir is negligible in humans. Amprenavir appears to penetrate into semen, though semen concentrations are lower than plasma concentrations.

Metabolism

Fosamprenavir is rapidly and almost completely hydrolysed to amprenavir and inorganic phosphate as it is absorbed through the gut epithelium, following oral administration. Amprenavir is primarily metabolised by the liver with less than 1 % excreted unchanged in the urine. The primary route of metabolism is via the cytochrome P450 3A4 enzyme. Amprenavir metabolism is inhibited by ritonavir, via inhibition of CYP3A4, resulting in increased plasma concentrations of amprenavir. Amprenavir in addition is also an inhibitor of the CYP3A4 enzyme, although to a lesser extent than ritonavir. Therefore medicinal products that are inducers, inhibitors or substrates of CYP3A4 must be used with caution when administered concurrently with Telzir with ritonavir (see sections 4.3 and 4.5).
Elimination

Following administration of Telzir, the half-life of amprenavir is 7.7 hours. When Telzir is co-administered with ritonavir, the half-life of amprenavir is increased to 15 – 23 hours. The primary route of elimination of amprenavir is via hepatic metabolism with less than 1 % excreted unchanged in the urine and no detectable amprenavir in faeces. Metabolites account for approximately 14 % of the administered amprenavir dose in the urine, and approximately 75 % in the faeces.

Special populations

Paediatrics

The pharmacokinetics of fosamprenavir in combination with ritonavir has not been studied in paediatric patients.

Elderly

The pharmacokinetics of fosamprenavir in combination with ritonavir has not been studied in patients over 65 years of age.

Renal impairment

Patients with renal impairment have not been specifically studied. Less than 1 % of the therapeutic dose of amprenavir is excreted unchanged in the urine. Renal clearance of ritonavir is also negligible, therefore the impact of renal impairment on amprenavir and ritonavir elimination should be minimal.

Hepatic impairment

Fosamprenavir is converted in man to amprenavir. The principal route of amprenavir and ritonavir elimination is hepatic metabolism. There are limited data regarding the use of this combination in patients with hepatic impairment and therefore specific dosage recommendations cannot be made (see sections 4.3 and 4.4).

5.3 Preclinical safety data

Toxicity was similar to that of amprenavir and occurred at amprenavir plasma exposure levels below human exposure after treatment with fosamprenavir in combination with ritonavir at the recommended dose.

In repeated dose toxicity studies in adult rats and dogs, fosamprenavir produced evidence of gastrointestinal disturbances (salivation, vomiting and soft to liquid faeces), and hepatic changes (increased liver weights, raised serum liver enzyme activities and microscopic changes, including hepatocyte necrosis).

In reproductive toxicity studies with fosamprenavir in rats, male fertility was not affected, but in females gravid uterine weights, numbers of ovarian corpora lutea and uterine implantation sites were reduced. In pregnant rats and rabbits there were no major effects on embryo-foetal development. However, the number of abortions increased. In rats exposed pre- and post-natally to fosamprenavir, pups showed impaired physical and functional development and reduced growth. Pup survival was decreased. In addition, decreased number of implantation sites per litter and a prolongation of gestation were seen when pups were mated after reaching maturity.

Fosamprenavir was not mutagenic or genotoxic in a standard battery of in vitro and in vivo assays. Carcinogenicity studies of fosamprenavir in rats and mice have not yet been completed; however, in
long-term carcinogenicity studies with amprenavir in mice and rats, there were benign hepatocellular adenomas in males at exposure levels equivalent to 2.0-fold (mice) or 3.8-fold (rats) those in humans given 1200 mg twice daily of amprenavir alone. In male mice altered hepatocellular foci were seen at doses that were at least 2.0 times human therapeutic exposure.

A higher incidence of hepatocellular carcinoma was seen in all amprenavir male mouse treatment groups. However, this increase was not statistically significantly different from male control mice by appropriate tests. The mechanism for the hepatocellular adenomas and carcinomas found in these studies has not been elucidated and the significance of the observed effects for humans is uncertain. However, there is little evidence from the exposure data in humans, both in clinical trials and from marketed use, to suggest that these findings are of clinical significance.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Hypromellose
Sucralose
Propylene glycol
Methyl parahydroxybenzoate (E218)
Propyl parahydroxybenzoate (E216)
Polysorbate 80
Calcium chloride dihydrate
Artificial grape bubblegum flavour
Natural peppermint flavour
Purified water

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

6.3 Shelf life

2 years.
Discard 28 days after first opening.

6.4 Special precautions for storage

Do not freeze.

6.5 Nature and contents of container

HDPE bottle with a child resistant polypropylene closure containing 225 millilitres oral suspension. A 10 ml graduated polypropylene dosing syringe and polyethylene adapter are provided in the pack.

6.6 Instructions for use and handling

No special requirements.
7. MARKETING AUTHORISATION HOLDER

Glaxo Group Ltd
Greenford Road
Greenford
Middlesex UB6 0NN
United Kingdom

8. MARKETING AUTHORISATION NUMBER

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
A  MANUFACTURING AUTHORISATION HOLDERS RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturers responsible for batch release

Film-coated tablets
Glaxo Wellcome Operations, Priory Street, Ware, Hertfordshire SG12 0DJ, United Kingdom

Oral suspension
Glaxo Wellcome GmbH & Co, Industriestrasse 32-36, D-23843, Bad Oldesloe, Germany

The printed package leaflet of the medicinal product must state the name and address of the manufacturer responsible for the release of the concerned batch.

B  CONDITIONS OF THE MARKETING AUTHORISATION

•  CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE IMPOSED ON THE MARKETING AUTHORISATION HOLDER

Medicinal product subject to restricted medical prescription (See Annex I: Summary of Product Characteristics, 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.
A. LABELLING
PARTICULARS TO APPEAR ON THE OUTER PACKAGING OR, WHERE THERE IS NO OUTER PACKAGING, ON THE IMMEDIATE PACKAGING

OUTER CARTON FOR TABLETS

1. NAME OF THE MEDICINAL PRODUCT

Telzir 700 mg film-coated tablets
Fosamprenavir

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains 700 mg fosamprenavir as fosamprenavir calcium (equivalent to approximately 600 mg of amprenavir)

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

60 film-coated tablets

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

9. SPECIAL STORAGE CONDITIONS

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**

Glaxo Group Ltd  
Greenford  
Middlesex UB6 0NN  
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 |
| BOTTLE LABEL FOR TABLETS |

1. **NAME OF THE MEDICINAL PRODUCT**

Telzir 700 mg film-coated tablets
Fosamprenavir

2. **STATEMENT OF ACTIVE SUBSTANCE(S)**

Each film-coated tablet contains 700 mg fosamprenavir as fosamprenavir calcium (equivalent to approximately 600 mg of amprenavir)

3. **LIST OF EXCIPIENTS**

4. **PHARMACEUTICAL FORM AND CONTENTS**

60 film-coated tablets

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

9. **SPECIAL STORAGE CONDITIONS**

10. **SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE**
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PARTICULARS TO APPEAR ON THE OUTER PACKAGING OR, WHERE THERE IS NO OUTER PACKAGING, ON THE IMMEDIATE PACKAGING

OUTER CARTON FOR ORAL SUSPENSION

1. NAME OF THE MEDICINAL PRODUCT

Telzir 50 mg/ml oral suspension
Fosamprenavir

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each ml of oral suspension contains 50 mg fosamprenavir as fosamprenavir calcium (equivalent to approximately 43 mg of amprenavir)

3. LIST OF EXCIPIENTS

This product also contains preservatives: methyl parahydroxybenzoate (E218) and propyl parahydroxybenzoate (E216), see leaflet for further information

4. PHARMACEUTICAL FORM AND CONTENTS

Bottle with 225 ml oral suspension
A 10 ml graduated dosing syringe and adapter are also provided in the pack

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use

Read the package leaflet before use

Shake bottle vigorously 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

Discard 28 days after first opening
9. **SPECIAL STORAGE CONDITIONS**

Do not freeze

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**

Glaxo Group Ltd
Greenford
Middlesex UB6 0NN
United Kingdom

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

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13. **MANUFACTURER’S BATCH NUMBER**

LOT

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Medicinal product subject to medical prescription.

15. **INSTRUCTIONS ON USE**
1. **NAME OF THE MEDICINAL PRODUCT**

Telzir 50 mg/ml oral suspension
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2. **STATEMENT OF ACTIVE SUBSTANCE(S)**

Each ml of oral suspension contains 50 mg fosamprenavir as fosamprenavir calcium (equivalent to approximately 43 mg of amprenavir)

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This product also contains preservatives: methyl parahydroxybenzoate (E218) and propyl parahydroxybenzoate (E216), see leaflet for further information

4. **PHARMACEUTICAL FORM AND CONTENTS**

225 ml oral suspension
A 10 ml graduated dosing syringe and adapter are also provided in the pack

5. **METHOD AND ROUTE(S) OF ADMINISTRATION**

Oral use

*Read the package leaflet before use*

Shake bottle vigorously 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

Discard 28 days after first opening
9. **SPECIAL STORAGE CONDITIONS**

Do not freeze

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 AUTHORIZATION HOLDER**

Glaxo Group Ltd
Greenford
Middlesex UB6 0NN
United Kingdom

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

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LOT

14. **GENERAL CLASSIFICATION FOR SUPPLY**

Medicinal product subject to medical prescription.

15. **INSTRUCTIONS ON USE**
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 any further questions, please ask your doctor or 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 Telzir is and what it is used for
2. Before you take Telzir
3. How to take Telzir
4. Possible side effects
5. Storing Telzir
6. Further information

Telzir 700 mg film-coated tablets
Fosamprenavir

- The active substance is fosamprenavir. Each tablet contains 700 mg of fosamprenavir as fosamprenavir calcium (equivalent to approximately 600 mg amprenavir).

- The other ingredients are: microcrystalline cellulose, croscarmellose sodium, povidone K30, magnesium stearate, colloidal anhydrous silica, hypromellose, titanium dioxide (E171), glycerol triacetate, iron oxide red (E172).

Manufacturer Marketing Authorisation Holder
Glaxo Wellcome Operations Glaxo Group Ltd
Priory Street Greenford Road
Ware Greenford
Hertfordshire SG12 0DJ Middlesex UB6 0NN
United Kingdom United Kingdom

1. WHAT TELZIR IS AND WHAT IT IS USED FOR

Telzir is supplied in plastic bottles containing 60 film-coated tablets. The tablets are capsule shaped, biconvex, pink coloured and marked with GXLL7 on one side.

Telzir is an antiviral medicine. Telzir is an inhibitor of the Human Immunodeficiency Virus (HIV) protease enzyme. It helps control HIV infection by inhibiting or interfering with the protease enzyme that HIV needs to infect new cells.

Telzir in combination with low dose ritonavir is indicated for the treatment of Human Immunodeficiency Virus (HIV) infected adults for use in combination with other anti-HIV medicines. Your doctor will determine which combination of anti-HIV medicines is best for you.

Telzir is also available as an oral suspension for those patients unable to swallow the tablets.
2. BEFORE YOU TAKE TELZIR

Telzir is to be taken in combination with ritonavir and other antiretroviral medicines. It is therefore important that you carefully read the Package Leaflet that is provided with these medicines. If you have any further questions about ritonavir or the other medicines prescribed, please ask your doctor or pharmacist.

Do not take Telzir:
- if you are hypersensitive (allergic) to fosamprenavir, amprenavir or any of the other ingredients in Telzir or to ritonavir.
- if you have severe liver disease (see ‘Take special care with Telzir’).
- if you are currently taking any of the following medicines:
  - astemizole or terfenadine (commonly used to treat allergy symptoms – these medicines may be available without prescription)
  - pimozide (used to treat schizophrenia)
  - cisapride (used to relieve certain stomach problems)
  - ergot derivatives (used to treat headaches)
  - rifampicin (used to treat tuberculosis)
  - amiodarone, quinidine (used to treat abnormal heart beat)
  - flecainide and propafenone (heart medicines)
  - bepridil (used to treat hypertension).

You must not take Telzir with products containing St John’s wort (Hypericum perforatum) as this may stop Telzir from working properly (see ‘Taking other medicines’).

Tell your doctor if you have any of these listed conditions, or are taking any of the medicines detailed above.

Take special care with Telzir

Telzir and other antiretroviral medicines help to control your condition, but they are not a cure for HIV infection. You can still continue to develop other infections and other illnesses associated with HIV disease. You should keep in regular contact with your doctor.

Telzir should not be used by patients under 18 years of age.

Treatment with Telzir has not been shown to reduce the risk of passing HIV infection on to others by sexual contact or by blood transfer. You should therefore continue to use appropriate precautions to prevent this.

You will be taking Telzir and ritonavir in combination with other antiretroviral medicines. Please read the package leaflet for these medicines carefully.

You should tell your doctor about any medical conditions that you have or have had.
- If you have a known allergy to sulphonamide containing medicines as you may have a cross sensitivity to Telzir.
- If you have a history of liver disease. Patients with chronic hepatitis B or C and treated with antiretroviral agents are at increased risk for severe and potentially fatal liver adverse effects and may require blood tests for control of liver function.
- If you have skin rash, as this has been reported in some patients treated with Telzir. Occasionally, the skin rash may be severe and you may have to stop taking this medicine. If
your doctor considers that this reaction means that you are allergic to Telzir, you must not take this medicine again.

- If you have haemophilia. There have been reports of increased bleeding in patients with haemophilia taking protease inhibitors. The reason for this is not known. You may need additional factor VIII to control any bleeding.
- If you have diabetes. In some patients taking protease inhibitors, there have been reports of increased sugar in the blood and worsening or development of diabetes mellitus.
- If you have redistribution, accumulation or loss of body fat as this may occur in patients receiving combination antiretroviral therapy. Contact your doctor if you notice changes in body fat (see 4. Possible side effects).
- If you have any other health concerns, discuss these with your doctor.

Pregnancy
Inform your doctor if you are pregnant or planning to become pregnant soon. Ask your doctor or pharmacist for advice before taking any medication. The safe use of Telzir in pregnancy has not been established.

Breast-feeding
Ask your doctor or pharmacist for advice before taking any medication. Do not breast-feed your baby while you are taking Telzir. It is recommended that HIV positive women must not breast-feed their infants in order to avoid transmission of HIV. Talk with your doctor about the best way to feed your baby.

Driving and using machines
No studies on the effects of Telzir on the ability to drive and use machines have been performed. If Telzir makes you dizzy, do not drive or operate any tools or machines.

Taking other medicines
Before starting treatment with Telzir, please inform your doctor or pharmacist if you are taking or have recently taken any other medicines, even those not prescribed. This is very important, as taking some types of medicines at the same time with Telzir and ritonavir can strengthen or weaken the effect of the medicines. This can sometimes lead to serious medical conditions.

There are some medicines that you must not take with Telzir (please see ‘Do not take Telzir’ for further information).

Telzir and ritonavir may interact with certain other medicines. The use of the following medicines, together with Telzir, should only take place on the basis of medical advice: anaesthetics (i.e. lidocaine), antibiotics (i.e. rifabutin, clarithromycin, dapsone and erythromycin), antifungals (i.e. ketoconazole, itraconazole), antimalariais (i.e. halofantrine), anticonvulsant medicines (i.e. carbamazepine, phenytoin and phenobarbital), cholesterol lowering medicines (i.e. atorvastatin, lovastatin and simvastatin), erectile dysfunction medicines (sildenafil and vardenafil), non-nucleoside reverse transcriptase inhibitors (i.e. efavirenz and nevirapine), opioids (i.e. methadone), steroids (i.e. oestrogens, progestogens and some glucocorticoids), tricyclic antidepressants (i.e. desipramine and nortriptyline), benzodiazepines (i.e. midazolam, triazolam), and others (i.e. clozapine and loratadine).

If you are taking certain medicines that can cause serious side effects, such as warfarin or other oral anticoagulants, at the same time as you are taking Telzir, your doctor may carry out additional blood tests to minimise any potential safety problems.

If you are taking the contraceptive pill, it is recommended that you use an alternative method (e.g. a condom) to prevent pregnancy while you are taking Telzir. The concomitant use of Telzir and contraceptive pill may result in a decrease of the therapeutic effect of the oral contraceptive.
The active substance in Telzir is fosamprenavir, the pro-drug of amprenavir. It is important that you do not take Telzir at the same time as any anti-HIV medicines containing amprenavir.

3. HOW TO TAKE TELZIR

Always take Telzir exactly as your doctor has instructed you. You should check with your doctor or pharmacist if you are unsure.

Do not stop taking your medicine without first talking to your doctor.

Swallow the tablets whole with water or another drink. They can be taken with or without food.

All regimens must be administered in combination with other anti-HIV medicines.

Adults (greater than or equal to 18 years of age)

The recommended dose is one Telzir tablet (700 mg fosamprenavir) with 100 mg ritonavir twice daily in combination with other anti-HIV agents.

In some cases, your doctor may adapt the dose of the Telzir or ritonavir when other medicines are administered together with this combination. Please follow the advice of your doctor carefully should they recommend a change to how you should take Telzir or ritonavir.

To get the full benefit from Telzir and avoid the emergence of resistance, it is very important that you take the full daily dose of Telzir and ritonavir prescribed by your doctor. Do not take more than the recommended dose.

If you take more Telzir than you should

If you have taken more than the prescribed dose of Telzir you should contact your doctor or pharmacist immediately for advice.

If you forget to take Telzir

If you forget to take a dose of Telzir take it as soon as you remember and then continue as before. Do not take a double dose to make up for forgotten individual doses.

4. POSSIBLE SIDE EFFECTS

Like all medicines, Telzir can have side effects. When treating HIV infection, it is not always possible to tell whether some of the undesirable effects that occur are caused by Telzir, by other medicines taken at the same time or by the HIV disease. For this reason, it is very important that you inform your doctor about any changes in your health.

A very common side effect that may occur while taking Telzir is diarrhoea. Other side effects associated with the digestive system that may be commonly observed are the following: abdominal pain, loose stools, nausea and vomiting. Other common side effects that may occur while taking Telzir are dizziness, fatigue, headache and rash.

Some people have changes in blood tests while taking Telzir. These include increases in liver and pancreatic enzyme levels and blood fat levels. Your doctor may do regular blood tests to see if Telzir is affecting your body.

In patients with haemophilia Type A and B, there have been reports of increased bleeding while taking protease inhibitors. Should this happen to you, seek immediate advice from your doctor.
There have been reports of muscle pain, tenderness or weakness, particularly with antiretroviral therapy including protease inhibitors and nucleoside analogues. On rare occasions, these muscle disorders have been serious (rhabdomyolysis).

Combination antiretroviral therapy may cause changes in body shape due to changes in fat distribution. These may include loss of fat from legs, arms and face, increased fat in the abdomen (belly) and other internal organs, breast enlargement and fatty lumps on the back of the neck (‘buffalo hump’). The cause and long-term health effects of these conditions are not known at this time. Combination antiretroviral therapy may also cause raised lactic acid and sugar in the blood, hyperlipaemia (increased fats in the blood) and resistance to insulin.

If you notice any side effects not mentioned in this leaflet, please inform your doctor or pharmacist.

5. STORING TELZIR

Keep out of the reach and sight of children.
This medicinal product does not require any special storage conditions.
Do not use after the expiry date stated on the container and the carton.

6. FURTHER INFORMATION

For any information about this medicinal product please contact the local representative of the Marketing Authorisation Holder.
<table>
<thead>
<tr>
<th>Country</th>
<th>Company Name</th>
<th>Telephone</th>
<th>Email</th>
</tr>
</thead>
<tbody>
<tr>
<td>España</td>
<td>GlaxoSmithKline, S.A.</td>
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<td>+ 370 5 264 90 00</td>
<td><a href="mailto:info.lt@gsk.com">info.lt@gsk.com</a></td>
</tr>
</tbody>
</table>

This leaflet was last approved on
Read all of this leaflet carefully before you start taking this medicine.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, please ask your doctor or 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 Telzir is and what it is used for
2. Before you take Telzir
3. How to take Telzir
4. Possible side effects
5. Storing Telzir
6. Further information

Telzir 50 mg/ml oral suspension
Fosamprenavir

- The active substance is fosamprenavir. Each ml of suspension contains 50 mg of fosamprenavir as fosamprenavir calcium salt (equivalent to approximately 43 mg of amprenavir).

- The other ingredients are: hypromellose, sucralose, polysorbate 80, calcium chloride dihydrate, artificial grape bubblegum flavour, natural peppermint flavour, purified water, propylene glycol, methyl parahydroxybenzoate (E218), propyl parahydroxybenzoate (E216).

Manufacturer
Glaxo Wellcome GmbH & Co.
Industriestrasse 32-36
D-23843 Bad Oldesloe
Germany

Marketing Authorisation Holder
Glaxo Group Ltd
Greenford Road
Greenford
Middlesex UB6 0NN
United Kingdom

1. WHAT TELZIR IS AND WHAT IT IS USED FOR

Telzir is supplied in plastic bottles containing 225 mls oral suspension. A 10 ml graduated dosing syringe and an adapter are also included in the pack. The suspension is white to off-white.

Telzir is an antiviral medicine. Telzir is an inhibitor of the Human Immunodeficiency Virus (HIV) protease enzyme. It helps control HIV infection by inhibiting or interfering with the protease enzyme that HIV needs to infect new cells.

Telzir in combination with low dose ritonavir is indicated for the treatment of Human Immunodeficiency Virus (HIV) infected adults for use in combination with other anti-HIV medicines. Your doctor will determine which combination of anti-HIV medicines is best for you.

Telzir is also available as 700 mg film-coated tablets.
2. BEFORE YOU TAKE TELZIR

Telzir is to be taken in combination with ritonavir and other antiretroviral medicines. It is therefore important that you carefully read the Package Leaflet that is provided with these medicines. If you have any further questions about ritonavir or the other medicines prescribed, please ask your doctor or pharmacist.

Do not take Telzir:
- if you are hypersensitive (allergic) to fosamprenavir, amprenavir or any of the other ingredients in Telzir or to ritonavir.
- if you have severe liver disease (see ‘Take special care with Telzir’).
- if you are currently taking any of the following medicines:
  - astemizole or terfenadine (commonly used to treat allergy symptoms – these medicines may be available without prescription)
  - pimozide (used to treat schizophrenia)
  - cisapride (used to relieve certain stomach problems)
  - ergot derivatives (used to treat headaches)
  - rifampicin (used to treat tuberculosis)
  - amiodarone, quinidine (used to treat abnormal heart beat)
  - flecainide and propafenone (heart medicines)
  - bepridil (used to treat hypertension).

You must not take Telzir with products containing St John’s wort (Hypericum perforatum) as this may stop Telzir from working properly (see ‘Taking other medicines’).

Tell your doctor if you have any of these listed conditions, or are taking any of the medicines detailed above.

Take special care with Telzir
Telzir and other antiretroviral medicines help to control your condition, but they are not a cure for HIV infection. You can still continue to develop other infections and other illnesses associated with HIV disease. You should keep in regular contact with your doctor.

Telzir should not be used by patients under 18 years of age.

Treatment with Telzir has not been shown to reduce the risk of passing HIV infection on to others by sexual contact or by blood transfer. You should therefore continue to use appropriate precautions to prevent this.

You will be taking Telzir and ritonavir in combination with other antiretroviral medicines. Please read the package leaflet for these medicines carefully.

You should tell your doctor about any medical conditions that you have or have had.
- If you have a known allergy to sulphonamide containing medicines as you may have a cross sensitivity to Telzir.
- If you have a history of liver disease. Patients with chronic hepatitis B or C and treated with antiretroviral agents are at increased risk for severe and potentially fatal liver adverse effects and may require blood tests for control of liver function.
- If you have skin rash, as this has been reported in some patients treated with Telzir. Occasionally, the skin rash may be severe and you may have to stop taking this medicine. If your doctor considers that this reaction means that you are allergic to Telzir, you must not take this medicine again.
- If you have haemophilia. There have been reports of increased bleeding in patients with haemophilia taking protease inhibitors. The reason for this is not known. You may need additional factor VIII to control any bleeding.
- If you have diabetes. In some patients taking protease inhibitors, there have been reports of increased sugar in the blood and worsening or development of diabetes mellitus.
- If you have redistribution, accumulation or loss of body fat as this may occur in patients receiving combination antiretroviral therapy. Contact your doctor if you notice changes in body fat (see 4. Possible side effects).
- If you have any other health concerns, discuss these with your doctor.

Pregnancy
Inform your doctor if you are pregnant or planning to become pregnant soon. Ask your doctor or pharmacist for advice before taking any medication. The safe use of Telzir in pregnancy has not been established.

Breast-feeding
Ask your doctor or pharmacist for advice before taking any medication. Do not breast-feed your baby while you are taking Telzir. It is recommended that HIV positive women must not breast-feed their infants in order to avoid transmission of HIV. Talk to your doctor about the best way to feed your baby.

Driving and using machines
No studies on the effects of Telzir on the ability to drive and use machines have been performed. If Telzir makes you dizzy, do not drive or operate any tools or machines.

Important information about ingredients of Telzir oral suspension
The Telzir oral suspension contains propyl and methyl parahydroxybenzoate. These ingredients may cause allergic reactions (possibly delayed).

Taking other medicines
Before starting treatment with Telzir, please inform your doctor or pharmacist if you are taking or have recently taken any other medicines, even those not prescribed. This is very important, as taking some types of medicines at the same time with Telzir and ritonavir can strengthen or weaken the effect of the medicines. This can sometimes lead to serious medical conditions.

There are some medicines that you must not take with Telzir (please see ‘Do not take Telzir’ for further information.)

Telzir and ritonavir may interact with certain other medicines. The use of the following medicines, together with Telzir, should only take place on the basis of medical advice: anaesthetics (i.e. lidocaine), antibiotics (i.e. rifabutin, clarithromycin, dapsone and erythromycin), antifungals (i.e. ketoconazole, itraconazole), antimalarials (i.e. halofantrine), anticonvulsant medicines (i.e. carbamazepine, phenytoin and phenobarbital), cholesterol lowering medicines (i.e. atorvastatin, lovastatin and simvastatin), erectile dysfunction medicines (sildenafil and vardenafil), non-nucleoside reverse transcriptase inhibitors (i.e. efavirenz and nevirapine), opioids (i.e. methadone), steroids (i.e. oestrogens, progestogens and some glucocorticoids), tricyclic antidepressants (i.e. desipramine and nortriptyline), benzodiazepines (i.e. midazolam, triazolam), and other substances (i.e. clozapine and loratadine).

If you are taking certain medicines that can cause serious side effects, such as warfarin or other oral anticoagulants, at the same time as you are taking Telzir, your doctor may carry out additional blood tests to minimise any potential safety problems.
If you are taking the contraceptive pill, it is recommended that you use an alternative method (e.g. a condom) to prevent pregnancy while you are taking Telzir. The concomitant use of Telzir and contraceptive pill may result in a decrease of the therapeutic effect of the oral contraceptive.

The active substance in Telzir is fosamprenavir, the pro-drug of amprenavir. It is important that you do not take Telzir at the same time as any anti-HIV medicines containing amprenavir.

3. HOW TO TAKE TELZIR

Always take Telzir exactly as your doctor has instructed you. You should check with your doctor or pharmacist if you are unsure.

Do not stop taking your medicine without first talking to your doctor.

Telzir oral suspension should be taken **without** food and on an empty stomach.

Shake the bottle for 20 seconds before first use. Shake the bottle for 5 seconds before subsequent uses.

All regimens must be administered in combination with other anti-HIV medicines.

A dosing syringe with a 10 ml graduation is supplied with the pack to measure your dose accurately.

**Adults (greater than or equal to 18 years of age)**

The recommended dose is 14 mls Telzir suspension (700 mg fosamprenavir) with 100 mg ritonavir twice daily in combination with other anti-HIV agents.

In some cases, your doctor may adapt the dose of Telzir or ritonavir when other medicines are administered together with this combination. Please follow the advice of your doctor carefully should they recommend a change to how you should take Telzir or ritonavir.

To get the full benefit from Telzir and avoid the emergence of resistance, it is very important that you take the **full** daily dose of Telzir and ritonavir prescribed by your doctor. Do not take **more** than the recommended dose.

Do not mix Telzir with any other medicines in the bottle or the syringe.

1. Shake the bottle vigorously before use.
2. Remove the bottle cap. Keep the cap.
3. Push the plastic adapter into the neck of the bottle, while holding the bottle firmly.
4. Insert the syringe firmly into the adapter.
5. Invert bottle.
6. Pull out the syringe plunger until the first portion of your full dose is withdrawn.
7. Turn the bottle the correct way up and remove the syringe from the adapter.
8. Administer the dose into the mouth by placing the tip of the syringe against the inside of the cheek. Slowly depress the plunger, allowing time to swallow. Forceful squirting to the back of the throat may cause choking.
9. **Repeat** steps 4 to 8 in the same way **until you have taken the whole dose**.
10. After use the syringe must not be left in the bottle. Take off the syringe and the adapter and wash them thoroughly in clean water. Let them dry completely before you use them again.
11. Tightly close the bottle with the cap again.

**If you take more Telzir than you should**

If you have taken more than the prescribed dose of Telzir you should contact your doctor or pharmacist immediately for advice.
If you forget to take Telzir
If you forget to take a dose of Telzir take it as soon as you remember and then continue as before. Do not take a double dose to make up for forgotten individual doses.

4. POSSIBLE SIDE EFFECTS

Like all medicines, Telzir can have side effects. When treating HIV infection, it is not always possible to tell whether some of the undesirable effects that occur are caused by Telzir, by other medicines taken at the same time or by the HIV disease. For this reason, it is very important that you inform your doctor about any changes in your health.

A very common side effect that may occur while taking Telzir is diarrhoea. Other side effects associated with the digestive system that may be commonly observed are the following: abdominal pain, loose stools, nausea and vomiting. Other common side effects that may occur while taking Telzir are dizziness, fatigue, headache and rash.

Some people have changes in blood tests while taking Telzir. These include increases in liver and pancreatic enzyme levels and blood fat levels. Your doctor may do regular blood tests to see if Telzir is affecting your body.

In patients with haemophilia Type A and B, there have been reports of increased bleeding while taking protease inhibitors. Should this happen to you, seek immediate advice from your doctor.

There have been reports of muscle pain, tenderness or weakness, particularly with antiretroviral therapy including protease inhibitors and nucleoside analogues. On rare occasions, these muscle disorders have been serious (rhabdomyolysis).

Combination antiretroviral therapy may cause changes in body shape due to changes in fat distribution. These may include loss of fat from legs, arms and face, increased fat in the abdomen (belly) and other internal organs, breast enlargement and fatty lumps on the back of the neck (‘buffalo hump’). The cause and long-term health effects of these conditions are not known at this time. Combination antiretroviral therapy may also cause raised lactic acid and sugar in the blood, hyperlipaemia (increased fats in the blood) and resistance to insulin.

If you notice any side effects not mentioned in this leaflet, please inform your doctor or pharmacist.

5. STORING TELZIR

Keep out of the reach and sight of children.
Do not freeze.
This medicinal product does not require any other special storage conditions.
Discard the bottle 28 days after first opening.
Do not use after the expiry date stated on the container and the carton.
6. FURTHER INFORMATION

For any information about this medicinal product please contact the local representative of the Marketing Authorisation Holder.

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