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 the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet

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, adolescents and children of 6 years and above in combination with other antiretroviral medicinal products.

In moderately antiretroviral experienced adults, Telzir in combination with low dose ritonavir has not been shown to be as effective as lopinavir / ritonavir. No comparative studies have been undertaken in children or adolescents.

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.

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.

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

Telzir tablet is administered orally.
Telzir tablet can be taken with or without food.

Telzir is also available as an oral suspension for use in patients unable to swallow tablets, and in paediatric patients less than 39 kg (please refer to the Summary of Product Characteristics for Telzir oral suspension).

Adults

The recommended dose is 700 mg fosamprenavir twice daily with 100 mg ritonavir twice daily.

Paediatric patients from 6 years of age

The adult dose of Telzir tablet 700 mg twice daily with ritonavir 100 mg twice daily may be used in children weighing at least 39 kg and able to swallow tablets.
For children weighing less than 39 kg, Telzir oral suspension is the recommended option for the most accurate dosing in children based on body weight (please refer to the Summary of Product Characteristics for Telzir oral suspension).

Children less than 6 years of age

Telzir with ritonavir is not recommended in children below 6 years due to insufficient data on pharmacokinetics, safety and antiviral response (see section 5.2).

Elderly (over 65 years of age)

The pharmacokinetics of fosamprenavir have not been studied in this patient population (see section 5.2). Therefore, no recommendations can be made in this patient population.

Renal impairment

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

Hepatic impairment

For adults with mild hepatic impairment (Child-Pugh score: 5-6) the recommended dose is 700 mg fosamprenavir twice daily with 100 mg ritonavir **once** daily.

For adults with moderate hepatic impairment (Child-Pugh score: 7-9) the recommended dose is 450 mg fosamprenavir twice daily with 100 mg ritonavir **once** daily. This adjusted dose has not been evaluated in a clinical study and has been derived from extrapolation (see section 5.2). As it is not possible to achieve this fosamprenavir dose using the tablet formulation, these patients should be treated with fosamprenavir oral suspension.

For adults with severe hepatic impairment (Child-Pugh score: 10-15): fosamprenavir should be used with caution and at a reduced dose of 300 mg fosamprenavir twice daily with 100 mg ritonavir **once** daily. As it is not possible to achieve this fosamprenavir dose using the tablet formulation, these patients should be treated with fosamprenavir oral suspension.

Overall, even with these dose adjustments for adults with hepatic impairment, some patients may have higher or lower than anticipated amprenavir and/or ritonavir plasma concentrations as compared to patients with normal hepatic function, due to increased inter-patient variability (see section 5.2), therefore close monitoring of safety and virologic response is warranted.

No dose recommendation can be made for children and adolescents with hepatic impairment as no studies have been conducted in these age groups.

4.3 Contraindications

Hypersensitivity to fosamprenavir, amprenavir, or ritonavir, or to any of the excipients listed in section 6.1.

Telzir must not be administered concurrently with medicinal products with narrow therapeutic windows that are substrates of cytochrome P450 3A4 (CYP3A4), e.g. alfuzosin, amiodarone, astemizole, bepridil, cisapride, dihydroergotamine, ergotamine, pimozide, quetiapine, quinidine, terfenadine, oral midazolam (for caution on parenterally administered midazolam, see section 4.5), oral triazolam, sildenafil used for the treatment of pulmonary arterial hypertension (for use of sildenafil in patients with erectile dysfunction, see sections 4.4 and 4.5).

Co-administration of paritaprevir and fosamprenavir/ritonavir is contraindicated due to the expected increase of paritaprevir exposure and the lack of clinical data assessing the magnitude of this increase (see section 4.5).

Concomitant use of Telzir with simvastatin or lovastatin is contraindicated because of increased plasma concentrations of lovastatin and simvastatin which can increase the risk of myopathy, including rhabdomyolysis (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).

Combination of rifampicin with Telzir with concomitant low-dose ritonavir is contraindicated (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 precautions for use

While effective viral suppression with antiretroviral therapy has been proven to substantially reduce the risk of sexual transmission, a residual risk cannot be excluded. Precautions to prevent transmission should be taken in accordance with national guidelines.

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.

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.

<u>Liver disease</u>

Telzir with ritonavir should be used with caution and at reduced doses in adults with mild, moderate, or severe hepatic impairment (see section 4.2).

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 reactions. In case of concomitant antiviral therapy for hepatitis B or C, please refer also to the relevant Summary of Product Characteristics for these medicinal products.

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 halofantrine or lidocaine (systemic) is not recommended (see section 4.5).

PDE5 inhibitors used for the treatment of erectile dysfunction: The use of Telzir concomitantly with PDE5 inhibitors (e.g. sildenafil, tadalafil, vardenafil) is not recommended (see section 4.5). Co-administration of Telzir with low dose ritonavir and these medicinal products is expected to substantially increase their concentrations and may result in PDE5 inhibitor-associated adverse events such as hypotension, visual changes and priapism (see section 4.5). Note that co-administration of Telzir with low dose ritonavir with sildenafil used for the treatment of pulmonary arterial hypertension is contraindicated (see section 4.3).

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 there may be an increased risk of hepatic transaminase elevations and hormonal levels may be altered with co-administration of fosamprenavir, ritonavir and oral contraceptives, alternative non-hormonal methods of contraception are recommended for women of childbearing potential (see section 4.5).
No data are available on the co-administration of fosamprenavir and ritonavir with oestrogens and/or progestogens when used as hormonal replacement therapies. The efficacy and safety of these therapies with fosamprenavir and ritonavir has not been established.

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

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

Hepatitis C virus (HCV) Direct-Acting Antivirals: When hepatitis C virus direct-acting antiviral (DAA) drugs, which are metabolised by CYP3A4 or are inducers/inhibitors of CYP3A4, are co-administered with fosamprenavir/ritonavir, altered plasma concentrations of medications are expected due to inhibition or induction of CYP3A4 enzyme activity (see sections 4.3 and 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.

Weight and metabolic parameters

An increase in weight and in levels of blood lipids and glucose may occur during antiretroviral therapy. Such changes may in part be linked to disease control and life style. For lipids, there is in some cases evidence for a treatment effect, while for weight gain there is no strong evidence relating this to any particular treatment. For monitoring of blood lipids and glucose reference is made to established HIV treatment guidelines. Lipid disorders should be managed as clinically appropriate.

Immune Reactivation Syndrome

In HIV-infected patients with severe immune deficiency at the time of institution of combination antiretroviral therapy (CART), an inflammatory reaction to asymptomatic or residual opportunistic pathogens may arise and cause serious clinical conditions, or aggravation of symptoms. Typically, such reactions have been observed within the first few weeks or months of initiation of CART. Relevant examples are cytomegalovirus retinitis, generalised and/or focal mycobacterium infections, and *Pneumocystis carinii* pneumonia. Any inflammatory symptoms should be evaluated and treatment instituted when necessary. Autoimmune disorders (such as Graves' disease) have also been reported to occur in the setting of immune reactivation; however, the reported time to onset is more variable and can occur many months after initiation of treatment.

Osteonecrosis

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

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.

Interaction studies have only been performed in adults.

Unless otherwise stated, studies detailed below have been performed with the recommended dosage of fosamprenavir/ritonavir (i.e. 700/100 mg twice daily), and the interaction was assessed under steady-state conditions where drugs were administered for 10 to 21 days.

Drugs by Therapeutic Area	**Interaction** **Geometric mean change (%)** **(Possible mechanism)**	**Recommendation concerning co-administration**
ANTIRETROVIRAL MEDICINAL PRODUCTS *Non-nucleoside reverse transcriptase inhibitors:*		
Efavirenz 600 mg once daily	No clinically significant interaction is observed.	No dosage adjustment necessary.
Nevirapine 200 mg twice daily	No clinically significant interaction is observed.	No dosage adjustment necessary.
Etravirine (Study conducted in 8 patients)	Amprenavir AUC ↑ 69% Amprenavir C_{min} ↑ 77% Amprenavir C_{max} ↑ 62% Etravirine AUC ↔[a] Etravirine C_{min}↔[a] Etravirine C_{max}↔[a] [a] Comparison based on historic control.	Telzir may require dose reduction (using oral suspension).
Nucleoside / Nucleotide reverse transcriptase inhibitors:		
Abacavir **Lamivudine** **Zidovudine** Study performed with amprenavir. No FPV/RTV drug interaction studies.	No clinically significant interaction is expected.	No dosage adjustment necessary.

Didanosine chewable tablet No drug interaction studies.	No clinically significant interaction is expected.	No dose separation or dosage adjustment necessary (see Antacids).
Didanosine gastro-resistant capsule No drug interaction studies.	No clinically significant interaction is expected.	No dosage adjustment necessary.
Tenofovir 300 mg once daily	No clinically significant interaction observed.	No dosage adjustment necessary.

Protease Inhibitors: According to current treatment guidelines, dual therapy with protease inhibitors is generally not recommended.		
Lopinavir / ritonavir 400 mg/100 mg twice daily **Lopinavir / ritonavir** 533 mg/133 mg twice daily (Telzir 1400 mg twice daily)	Lopinavir: C_{max}↑ 30% Lopinavir: AUC ↑ 37% Lopinavir: C_{min} ↑ 52% Amprenavir: C_{max} ↓ 58% Amprenavir: AUC ↓ 63% Amprenavir: C_{min} ↓ 65% Lopinavir: C_{max} ↔* Lopinavir: AUC ↔* Lopinavir: C_{min} ↔* * compared to lopinavir / ritonavir 400 mg/100 mg twice daily Amprenavir: C_{max} ↓ 13%* Amprenavir: AUC ↓ 26%* Amprenavir: C_{min} ↓ 42 %* * compared to fosamprenavir / ritonavir 700 mg/100 mg twice daily (Mixed CYP3A4 induction/inhibition, Pgp induction)	Concomitant use is not recommended.
Indinavir **Saquinavir** **Nelfinavir** No drug interaction studies.		No dose recommendations can be given.

Atazanavir 300 mg once daily	Atazanavir: C_{max} ↓ 24%* Atazanavir: AUC↓ 22%* Atazanavir: C_{min}↔* *compared to atazanavir/ ritonavir 300 mg/ 100 mg once daily Amprenavir: C_{max} ↔ Amprenavir: AUC ↔ Amprenavir: C_{min} ↔	No dosage adjustment necessary.
Integrase inhibitors		
Raltegravir 400 mg twice daily	<u>Fasting state</u> Amprenavir : C_{max} ↓ 14% (-36%; +15%) AUC ↓ 16% (-36%; +8%) C_{min} ↓ 19% (-42%; +13%) Raltegravir: C_{max} ↓ 51% (-75%; -3%) AUC ↓ 55% (-76%; -16%) C_{min} ↓ 36 % (-57%; -3%) <u>Fed state</u> Amprenavir: C_{max} ↓ 25% (-41%; -4%) AUC ↓ 25% (-42%; -3%) C_{min} ↓ 33% (-50%; -10%) Raltegravir: C_{max} ↓ 56% (-70%; -34%) AUC ↓ 54% (-66%; -37%) C_{min} ↓ 54 % (-74%; -18%)	Concomitant use is not recommended. Significant reductions in exposure and Cmin observed for both amprenavir and raltegravir (especially in fed conditions) may result in virological failure in patients.
Dolutegravir 50 mg once daily	<u>Dolutegravir</u> C_{max} ↓ 24% AUC ↓ 35% Cτ ↓ 49% Amprenavir: C_{max} ↔ Amprenavir: AUC ↔ Amprenavir: C_{min} ↔	No dosage adjustment of fosamprenavir or dolutegravir is recommended based on observed exposure-response relationships of clinical data. Caution is warranted and close monitoring is recommended when this combination is given in integrase inhibitor-resistant patients.
CCR5-receptor antagonists		

Maraviroc 300 mg twice daily	Maraviroc: AUC_{12} ↑ 2.49 Maraviroc: C_{max} ↑ 1.52 Maraviroc: C_{12} ↑ 4.74 Amprenavir: AUC_{12} ↓ 0.65 Amprenavir: C_{max} ↓ 0.66 Amprenavir: C_{12} ↓ 0.64 Ritonavir AUC_{12} ↓ 0.66 Ritonavir C_{max} ↓ 0.61 Ritonavir C_{12} ↔ 0.86	Concomitant use is not recommended. Significant reductions in amprenavir C_{min} observed may result in virological failure in patients.

Anti-hepatitis C virus medicinal products		
Telaprevir (*PK data from telaprevir prescribing information)*	Amprenavir ↓ AUC 0.53 (0.49-0.58) C_{max} 0.65 (0.59-0.70) C_{min} 0.44 (0.40-0.50) Telaprevir ↓ AUC 0.68 (0.63-0.72) C_{max} 0.67 (0.63-0.71) C_{min} 0.70 (0.64-0.77) Mechanism unknown.	Not recommended.
Boceprevir	Not studied. Results from studies with other HIV protease inhibitors and boceprevir suggest that co-administration of fosamprenavir/ritonavir with boceprevir is likely to lead to subtherapeutic levels of fosamprenavir and boceprevir.	Not recommended.
Simeprevir **Daclatasvir**	Not studied. Results from studies with other HIV protease inhibitors and simeprevir or daclatasvir, suggest that co-administration with fosamprenavir/ritonavir is likely to lead to increased plasma exposures of simeprevir or daclatasvir due to CYP3A4 enzyme inhibition.	Not recommended.
Paritaprevir (co-formulated with ritonavir and ombitasvir and co-administered with dasabuvir)	Not studied. Results from studies with other HIV protease inhibitors and paritaprevir/ritonavir/ ombitasvir +/- dasabuvir suggest that co-	Contraindicated (see section 4.3).

	administration of fosamprenavir/ritonavir with paritaprevir/ritonavir/ ombitasvir+/-dasabuvir is likely to lead to increased plasma exposures of paritaprevir due to CYP3A4 enzyme inhibition and higher ritonavir dose.	
ANTIARRHYTHMICS		
Amiodarone **Bepridil** **Quinidine** **Flecainide** **Propafenone**	Amiodarone: ↑ expected Bepridil: ↑ expected Quinidine: ↑ expected (CYP3A4 inhibition by FPV/RTV) Flecainide: ↑ expected Propafenone: ↑ expected (CYP2D6 inhibition by RTV)	Contraindicated (see section 4.3). Potential for serious and/or life-threatening reactions such as cardiac arrhythmias.
ERGOT DERIVATIVES		
Dihydroergotamine **Ergotamine** **Ergonovine** **Methylergonovine**	Dihydroergotamine: ↑ expected Ergonovine: ↑ expected Ergotamine: ↑ expected Methylergonovine: ↑ expected (CYP3A4 inhibition by FPV/RTV)	Contraindicated (see section 4.3). Potential for serious and/or life-threatening reactions such as acute ergot toxicity characterized by peripheral vasospasm and ischemia of the extremities and other tissues.
GASTROINTESTINAL MOTILITY AGENTS		
Cisapride	Cisapride: ↑ expected (CYP3A4 inhibition by FPV/RTV)	Contraindicated (see section 4.3). Potential for serious and/or life-threatening reactions such as cardiac arrhythmias.
ANTIHISTAMINES (HISTAMINE H1 RECEPTOR ANTAGONISTS)		
Astemizole **Terfenadine**	Astemizole: ↑ expected Terfenadine: ↑ expected (CYP3A4 inhibition by FPV/RTV)	Contraindicated (see section 4.3). Potential for serious and/or life-threatening reactions such as cardiac arrhythmias.
NEUROLEPTIC		
Pimozide	Pimozide: ↑ expected	Contraindicated (see section 4.3). Potential for serious

	(CYP3A4 inhibition by FPV/RTV)	and/or life-threatening reactions such as cardiac arrhythmias.
ANTIPSYCHOTICS		
Quetiapine	Due to CYP3A inhibition by Telzir, concentrations of quetiapine are expected to increase.	Concomitant administration of Telzir and quetiapine is contra-indicated as it may increase quetiapine-related toxicity. Increased plasma concentrations of quetiapine may lead to coma.
INFECTION *Antibacterials:*		
Clarithromycin Study performed with amprenavir. No FPV/RTV drug interaction studies.	Clarithromycin: moderate ↑ expected (CYP3A4 inhibition)	Use with caution.
Erythromycin No drug interaction studies.	Erythromycin: ↑ expected (CYP3A4 inhibition by FPV/RTV)	Use with caution.
Anti-mycobacterial:		
Rifabutin 150 mg every other day	Rifabutin: C_{max} ↓ 14%* Rifabutin: AUC(0-48) ↔* 25-O-desacetylrifabutin: C_{max} ↑ 6-fold* 25-O-desacetylrifabutin: AUC(0-48) ↑ 11-fold* *compared to rifabutin 300 mg once daily Amprenavir exposure unchanged when compared to historical data. (Mixed CYP3A4 induction/inhibition)	The increase of 25-O-desacetylrifabutin (active metabolite) could potentially lead to an increase of rifabutin related adverse events, notably uveitis. A 75 % reduction of the standard rifabutin dose (i.e. to 150 mg every other day) is recommended. Further dose reduction may be necessary (see section 4.4).
Rifampicin 600 mg once daily (Amprenavir without ritonavir) No FPV/RTV drug interaction studies	Amprenavir: AUC ↓ 82% Significant ↓ APV expected (CYP3A4 induction by rifampicin)	Contraindicated (see section 4.3). The decrease in amprenavir AUC can result in virological failure and resistance development. During attempts to overcome the decreased exposure by

		increasing the dose of other protease inhibitors with ritonavir, a high frequency of liver reactions was seen.

Anti-fungals:		
Ketoconazole 200 mg once daily for four days **Itraconazole** No drug interaction studies.	Ketoconazole: C_{max} ↑ 25% Ketoconazole: AUC ↑ 2.69-fold. Amprenavir: C_{max} ↔ Amprenavir: AUC ↔ Amprenavir: C_{min} ↔ Itraconazole: ↑ expected (CYP3A4 inhibition by FPV/RTV)	High doses (> 200 mg/day) of ketoconazole or itraconazole are not recommended.
ANTACIDS, HISTAMINE H_2 RECEPTOR ANTAGONIST AND PROTON-PUMP INHIBITORS		
Single 30 ml dose of antacid suspension (equivalent to 3.6 grams aluminium hydroxide and 1.8 grams magnesium hydroxide (Telzir 1400 mg single dose) **Ranitidine** 300 mg single dose (Telzir 1400 mg single dose) **Esomeprazole** 20 mg once daily	Amprenavir: C_{max} ↓ 35% Amprenavir: AUC ↓ 18% Amprenavir: C_{min} (C_{12h}) ↔ Amprenavir: C_{max} ↓ 51% Amprenavir: AUC ↓ 30% Amprenavir: C_{min} (C_{12h}) ↔ Amprenavir C_{max} ↔ Amprenavir AUC ↔ Amprenavir C_{min} (C_{12h}) ↔ (Increase in gastric pH)	No dosage adjustment necessary with antacids, proton-pump inhibitors or histamine H_2 receptor antagonists.
ANTICONVULSANTS		
Phenytoin 300 mg once daily	Phenytoin: C_{max} ↓ 20% Phenytoin: AUC ↓ 22% Phenytoin: C_{min} ↓ 29% (Modest induction of CYP3A4 by FPV/RTV)	It is recommended that phenytoin plasma concentrations be monitored and phenytoin dose increased as appropriate.

	Amprenavir: C_{max} ↔ Amprenavir: AUC ↑ 20% Amprenavir: C_{min} ↑ 19%	

Phenobarbital **Carbamazepine** No drug interaction studies.	Amprenavir: ↓ expected (Modest CYP3A4 induction)	Use with caution (see section 4.4).
Lidocaine (by systemic route) No drug interaction studies.	Lidocaine: ↑ expected (CYP3A4 inhibition by FPV/RTV)	Concomitant use is not recommended. It may cause serious adverse reactions (see section 4.4).
Halofantrine No drug interaction studies.	Halofantrine: ↑ expected (CYP3A4 inhibition by FPV/RTV)	Concomitant use is not recommended. It may cause serious adverse reactions (see section 4.4).
PDE5 INHIBITORS		
Sildenafil **Vardenafil** **Tadalafil** No drug interaction studies.	PDE5 inhibitors: ↑ expected (CYP3A4 inhibition by FPV/RTV)	Concomitant use is not recommended. It may result in an increase in PDE5 inhibitor-associated adverse reactions, including hypotension, visual changes and priapism (refer to PDE5 inhibitor prescribing information). Patients should be warned about these possible side effects when using PDE5 inhibitors with Telzir/ritonavir (see section 4.4). Note that co-administration of Telzir with low dose ritonavir with sildenafil used for the treatment of pulmonary arterial hypertension is contraindicated (see section 4.3).
INHALED/NASAL STEROIDS		
Fluticasone propionate 50 µg intranasal 4 times daily) for 7 days (Ritonavir 100 mg capsules twice daily for 7 days)	Fluticasone propionate: ↑ Intrinsic cortisol levels: ↓ 86 %. The effects of high fluticasone systemic exposure on ritonavir plasma levels are unknown.	Concomitant use is not recommended unless the potential benefit of treatment outweighs the risk of systemic corticosteroid effects (see section 4.4). A dose reduction of the glucocorticoid with close monitoring of local and

	Greater effects may be expected when fluticasone propionate is inhaled. (CYP3A4 inhibition by FPV/RTV)	systemic effects or a switch to a glucocorticoid, which is not a substrate for CYP3A4 (e.g. beclomethasone) should be considered. In case of withdrawal of glucocorticoids, progressive dose reduction may have to be performed over a longer period (see section 4.4).
ALPHA 1-ADRENORECEPTOR ANTAGONIST		
Alfuzosin,	Potential for increased alfuzosin concentrations which can result in hypotension. The mechanism of interaction is CYP3A4 inhibition by fosamprenavir/ritonavir.	Co-administration of TELZIR/ritonavir with alfuzosin is contraindicated (see section 4.3)

HERBAL PRODUCTS		
St. John's wort *(Hypericum perforatum)*	Amprenavir ↓ expected (CYP3A4 induction by St. John's wort)	Herbal preparations containing St John's wort must not be combined with Telzir (see section 4.3). If a patient is already taking St John's wort, check amprenavir, ritonavir and HIV RNA 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.
HMG-COA REDUCTASE INHIBITORS		
Lovastatin **Simvastatin** No drug interaction studies.	Lovastatin: ↑ expected Simvastatin: ↑ expected (CYP3A4 inhibition by FPV/RTV)	Contraindicated (see section 4.3). Increased concentrations of HMG-CoA reductase inhibitors may cause myopathy, including rhabdomyolysis. Pravastatin or fluvastatin are recommended because their metabolism is not dependent

		on CYP 3A4 and interactions are not expected with protease inhibitors.
Atorvastatin 10 mg once daily for 4 days	Atorvastatin: C_{max} ↑ 184% Atorvastatin: AUC ↑ 153% Atorvastatin: C_{min} ↑ 73% Amprenavir: C_{max} ↔ Amprenavir: AUC ↔ Amprenavir: C_{min} ↔ (CYP3A4 inhibition by FPV/RTV)	Doses of atorvastatin no greater than 20 mg/day should be administered, with careful monitoring for atorvastatin toxicity.
IMMUNOSUPPRESSANTS		
Cyclosporin **Rapamycin** **Tacrolimus** No drug interaction studies.	Cyclosporin: ↑ expected Rapamycin: ↑ expected Tacrolimus: ↑ expected (CYP3A4 inhibition by FPV/RTV)	Frequent therapeutic concentration monitoring of immunosuppressant levels is recommended until levels have stabilised (see section 4.4).

BENZODIAZEPINES		
Midazolam No drug interaction studies.	Midazolam: ↑ expected (3-4 fold for parenteral midazolam) Based on data with other protease inhibitors plasma concentrations of midazolam are expected to be significantly higher when midazolam is given orally. (CYP3A4 inhibition by FPV/RTV)	Telzir/ritonavir should not be co-administered with orally administered midazolam (see section 4.3), whereas caution should be used with co-administration of Telzir/ritonavir and parenteral midazolam. If Telzir/ritonavir is co-administered with parenteral midazolam, it should be done in an intensive care unit (ICU) or similar setting which ensures close clinical monitoring and appropriate medical management in case of respiratory depression and/or prolonged sedation. Dosage adjustment for midazolam should be considered, especially if more than a single dose of midazolam is administered.
TRICYCLIC ANTIDEPRESSANTS		
Desipramine **Nortriptyline**	Tricyclic antidepressant: ↑ expected	Careful monitoring of the therapeutic and adverse

No drug interaction studies.	(Mild CYP2D6 inhibition by RTV)	reactions of tricyclic antidepressants is recommended (see section 4.4).
OPIOIDS		
Methadone ≤ 200 mg once daily	(R-) methadone: C_{max} ↓ 21% (R-) methadone: AUC ↓ 18% (CYP induction by FPV/RTV)	The decrease of (R-) methadone (active enantiomer) is not expected to be clinically significant. As a precaution, patients should be monitored for withdrawal syndrome.

ORAL ANTICOAGULANTS		
Warfarin **Other oral anticoagulants** No drug interaction studies.	Possible ↓ or ↑ of antithrombotic effect. (Induction and/or inhibition of CYP2C9 by RTV)	Reinforced monitoring of the International Normalised Ratio is recommended (see section 4.4).
ORAL CONTRACEPTIVES		
Ethinyl estradiol 0.035 mg/norethisterone 0.5 mg once daily	Ethinyl estradiol: C_{max} ↓28% Ethinyl estradiol: AUC ↓37% Norethisterone: C_{max} ↓38% Norethisterone: AUC ↓34% Norethisterone: C_{min} ↓ 26 (CYP3A4 induction by FPV/RTV) Amprenavir: C_{max} ↔* Amprenavir: AUC ↔* Amprenavir: C_{min} ↔* * compared to historical data Ritonavir: C_{max} ↑ 63%* Ritonavir: AUC ↑ 45%* * compared to historical data Clinically significant hepatic transaminase elevations occurred in some subjects.	Alternative non-hormonal methods of contraception are recommended for women of childbearing potential (see section 4.4).
SELECTIVE SEROTONIN REUPTAKE INHIBITORS (SSRIS)		

Paroxetine 20 mg once daily	Paroxetine: C_{max} ↓ 51% Paroxetine: AUC ↓55% Amprenavir: C_{max} ↔* Amprenavir: AUC ↔* Amprenavir: C_{min} ↔* * compared to historical data Mechanism unknown.	Dose titration of paroxetine based on a clinical assessment of antidepressant response is recommended. Patients on stable dose of paroxetine who start treatment with Telzir and ritonavir should be monitored for antidepressant response.

4.6 Fertility, 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.

Breast-feeding

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 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

Summary of safety profile

The adverse reaction profile was similar across all the respective adult studies: antiretroviral naïve patients (APV30002, ESS100732), protease inhibitor experienced (twice daily dosing, APV30003) patients. This is based on safety data from a total of 864 patients exposed to fosamprenavir/ritonavir in these three studies.

The most frequently (> 5% of adult subjects treated) reported adverse reactions with fosamprenavir/ritonavir combination were gastrointestinal reactions (nausea, diarrhoea, abdominal pain and vomiting) and headache. Most adverse reactions associated with fosamprenavir/ritonavir combination therapies were mild to moderate in severity, early in onset and rarely treatment limiting. More serious adverse reactions such as serious skin rashes and hepatic transaminase elevations have also been reported (cf paragraph Description of selected adverse reactions).

Tabulated summary of adverse reactions

Adverse reactions are listed by MedDRA system organ class and absolute frequency. Frequencies are defined as: Very common (≥ 1/10), Common (≥ 1/100 to < 1/10), Uncommon (≥ 1/1,000 to < 1/100), Rare (≥ 1/10,000 to < 1/1,000) or Very rare (< 1/10,000), or Not known.

Frequency categories for the reactions below have been based on clinical trials and postmarketing data.

Most of the adverse reactions below were reported from three large clinical studies in adults, where the adverse events were of at least moderate intensity (Grade 2 or more) occurring in at least 1% of patients and reported by investigators as being attributable to the medicinal products used in the studies.

Body System	Adverse reaction	Frequency
Nervous system disorders	Headache, dizziness, oral paraesthesia	Common
Gastrointestinal disorders	Diarrhoea Loose stools, nausea, vomiting, abdominal pain	Very common Common
Skin and subcutaneous tissue disorders	Stevens Johnson syndrome Angioedema Rash (see text below “rash/cutaneous reactions”)	Rare Uncommon Common
General disorders and administration site conditions	Fatigue	Common
Investigations	Blood cholesterol increased Blood triglycerides increased Alanine aminotransferase increased Aspartate aminotransferase increased Lipase increased	Very common Common Common Common Common

Description of selected adverse reactions

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 cases of rash, including Stevens-Johnson syndrome are rare. 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 adult patients, included: increased ALT (*common*), AST (*common*), serum lipase (*common*) and triglycerides (*common*).

Metabolic parameters: Weight and levels of blood lipids and glucose may increase during antiretroviral therapy (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.

Immune Reactivation Syndrome: in HIV-infected patients with severe immune deficiency at the time of initiation of combination antiretroviral therapy (CART), an inflammatory reaction to asymptomatic or residual opportunistic infections may arise. Autoimmune disorders (such as Graves' disease) have also been reported to occur in the setting of immune reactivation; however, the reported time to onset is more variable and these events can occur many months after initiation of treatment (see section 4.4).

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

Paediatric / other populations

Children and adolescents: The adverse reaction profile in children and adolescents is based on integrated safety data from two studies (APV29005 Week 24 data and APV20003 Week 168 data [final data]) in which 158 HIV-1 infected subjects 2 to 18 years of age received fosamprenavir with ritonavir with background nucleoside reverse transcriptase inhibitor therapy (see section 5.1 for information on dosing regimens applied for each age group). 79 % of subjects received greater than 48 weeks of exposure.
Overall the safety profile in these 158 children and adolescents was similar to that observed in the adult population. Vomiting occurred more frequently amongst paediatric patients. Drug-related adverse reactions were more common in APV20003 (57%) where subjects received once daily fosamprenavir / ritonavir when compared to APV29005 (33%) where subjects received twice daily fosamprenavir / ritonavir.
No new safety concerns were identified from analyses of 48 week data from studies APV29005 or APV20002, in which 54 subjects 4 weeks to <2 years of age received twice daily fosamprenavir / ritonavir with background nucleoside reverse transcriptase inhibitor therapy and 5 subjects received only single doses of fosamprenavir with or without ritonavir.

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

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

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 overdose 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: J05AE07

Mechanism of action

The *in vitro* antiviral activity observed with fosamprenavir is due to the presence of trace amounts of amprenavir. Amprenavir is a competitive inhibitor of the 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.

Administration of fosamprenavir 700 mg twice daily with ritonavir 100 mg twice daily results in plasma amprenavir concentrations (data from study APV30003 in antiretroviral experienced patients) which results in protein adjusted median ratios of C_{min}/IC_{50} and C_{min}/IC_{95} of 21.7 (range 1.19-240) and 3.21 (range 0.26-30.0), respectively.

Antiviral activity *in vitro*

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 (IC_{50}) 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). The relationship between *in vitro* anti-HIV-1 activity of amprenavir and the inhibition of HIV-1 replication in humans has not been defined.

Resistance

In vivo

a) ART-naïve or PI-naïve patients

Various regimens have been assessed in the amprenavir/fosamprenavir development programs with and without co-administration of ritonavir. Analysis of the virological failure samples across these regimens defined four main resistance pathways: V32I+I47V, I50V, I54L/M and I84V. Additional mutations observed which may contribute to resistance were: L10V/F/R, I13V, K20R/T, L33F/V, M36I, M46I/L, I47V/L Q58E, I62V, L63P, V77I, I85V, and I93L.

When ART naïve adult patients were treated with the currently approved doses of fosamprenavir/ritonavir, as for other ritonavir boosted PI regimens, the mutations described were infrequently observed. Sixteen of 434 ART-naïve patients who received fosamprenavir 700 mg/ritonavir 100 mg twice daily in ESS100732 experienced virological failure by Week 48 with 14 isolates genotyped. Three of 14 isolates had protease resistance mutations. One resistance mutation was observed in each of 3 isolates: K20K/R, I54I/L and I93I/L respectively

Among the 81 PI-naïve paediatric patients treated with fosamprenavir / ritonavir, 15 patients met protocol-defined virological failure through 48 weeks in APV29005 and up to 108 weeks in APV20003. Treatment-emergent major or APV-associated protease mutations were observed in virus isolated from 2 patients. Resistance patterns were similar to those observed in adults.

b) PI-experienced patients

Amprenavir

In the studies of PI-experienced adult patients, PRO30017 (amprenavir 600 mg / ritonavir 100 mg twice daily in sub-study A and B with 80 and 37 patients respectively), the following mutations emerged in patients with virological failure: L10F/I/V, V11I, I13V, K20R, V32I, L33F, E34Q, M36I, M46I/L, I47V, G48V, I50V, I54L/M/T/V, Q58E, D60E, I62V, A71V, V77I, V82A/I, I84V, I85V, L90M and I93L/M.

Fosamprenavir

In the studies of PI-experienced adult patients, APV30003 and its extension, APV30005 (fosamprenavir 700 mg / ritonavir 100 mg twice daily: n=107), the following mutations emerged in patients experiencing virological failure through 96 weeks: L10F/I, L24I, V32I, L33F, M36I, M46I/L, I47V, I50V, I54L/M/S, A71I/T/V, G73S, V82A, I84V, and L90M.

In the paediatric studies APV20003 and APV29005, 77 PI-experienced patients were treated with fosamprenavir / ritonavir-based regimens and 43 patients met study-defined virologic failure criteria through 48 weeks in APV29005 and up to 108 weeks in APV20003. Treatment-emergent major protease or APV-associated mutations were observed in virus isolated from 1 patient in APV29005 and 6 patients from APV20003. The mutational profiles were similar to those described for PI-experienced adults treated with fosamprenavir / ritonavir.

Antiviral activity according to genotypic/phenotypic resistance

Genotypic resistance testing

Genotypic interpretation systems may be used to estimate the activity of amprenavir / ritonavir or fosamprenavir / ritonavir in subjects with PI-resistant isolates. The current (July 2006) ANRS AC-11 algorithm for fosamprenavir / ritonavir defines resistance as the presence of the mutations V32I+I47A/V, or I50V, or at least four mutations among: L10F/I/V, L33F, M36I, I54A/L/M/S/T/V, I62V, V82A/C/F/G, I84V and L90M and is associated with increased phenotypic resistance to fosamprenavir with ritonavir as well as reduced likelihood of virological response (resistance). Conclusions regarding the relevance of particular mutations or mutational patterns are subject to change with additional data, and it is recommended to always consult current interpretation systems for analysing resistance test results.

Phenotypic resistance testing

Clinically validated phenotypic interpretation systems may be used in association with the genotypic data to estimate the activity of amprenavir / ritonavir or fosamprenavir / ritonavir in patients with PI-resistant isolates. Resistance testing diagnostic companies have developed clinical phenotypic cut-offs for FPV/RTV that can be used to interpret resistance test results.

Clinical experience

Clinical experience with fosamprenavir boosted with ritonavir is mainly based on two open label studies one in antiretroviral naïve patients (study ESS100732), and one study in antiretroviral experienced patients (study APV30003). Both of these studies compared fosamprenavir/ritonavir with lopinavir / ritonavir.

Antiretroviral Naïve Adult Patients

In a randomised open-label study (ESS100732 - KLEAN) in antiretroviral naïve patients, fosamprenavir (700 mg) co-administered with low dose ritonavir (100 mg) in a twice daily regimen

including abacavir / lamivudine (600 mg / 300 mg) fixed dose combination tablet once daily showed comparable efficacy over 48 weeks to lopinavir / ritonavir (400 mg / 100 mg) given twice daily in combination with abacavir / lamivudine (600 mg / 300 mg once daily).

Non-inferiority was demonstrated between fosamprenavir co-administered with ritonavir and lopinavir / ritonavir based on the proportions of patients achieving plasma HIV-1 RNA levels < 400 copies/ml at 48 weeks (primary endpoint). In the Time to loss of virological response (TLOVR) analysis for the ITT(E) population, the proportion of patients achieving <400 copies/ml was 73 % (315 / 434) in the fosamprenavir with ritonavir group compared to 71 % (317 / 444) of patients receiving lopinavir / ritonavir, with a 95 % confidence interval of the difference of [-4,84%; 7;05%].

Efficacy outcomes by subgroups are described in the table below.

Table 1 Efficacy Outcome at Week 48 in ESS100732 (ART-Naïve Patients)

	FPV/RTV 700 mg/100 mg BID (n= 434)	**LPV/RTV 400 mg/100 mg BID (n=444)**
ITT-E Population TLOVR analysis	Proportion with HIV-1 RNA < 400 copies/ml	
All Subjects	72.5 %	71.4%
Baseline HIV-1 RNA < 100,000 copies/ml	69.5 % (n=197)	69.4% (n=209)
Baseline HIV-1 RNA ≥ 100,000 copies/ml	75.1% (n=237)	73.2% (n=235)
	Proportion with HIV-1 RNA < 50 copies/ml	
All Subjects	66%	65%
Baseline HIV-1 RNA < 100,000 copies/ml	67% (n=197)	64% (n=209)
Baseline HIV-1 RNA ≥ 100,000 copies/ml	65% (n=237)	66% (n=235)
	Median Change from baseline in CD4 cells (cells/µl)	
ITT-E observed analysis	176 (n=323)	191 (n=336)

Following completion of the 48 week treatment period, subjects at European and Canadian sites were eligible to participate in a study extension to Week 144 maintaining their treatment regimen as per the original randomisation. Only 22% of the original population of the KLEAN study was enrolled in the study extension.

Efficacy outcomes are described in the table below.

Table 2 Efficacy Outcome at Weeks 96 and 144 in ESS100732 Extension (ART-Naïve Patients)

	FPV/RTV 700 mg/100 mg BID (n= 105)	**LPV/RTV 400 mg/100 mg BID (n=91)**
ITT (Ext) Population TLOVR analysis	Proportion with HIV-1 RNA < 400 copies/ml	
Week 96	93%	87%
Week 144	83%	70%
	Proportion with HIV-1 RNA < 50 copies/ml	
Week 96	85%	75%
Week 144	73%	60%
ITT (Ext) Observed analysis	Median Change from baseline in CD4 cells (cells/μl)	
Week 96	292 (n=100)	286 (n=84)
Week 144	300 (n=87)	335 (n=66)

Antiretroviral Experienced Adult 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 (primary end-point) and other efficacy outcomes by subgroup are described in the tables below:

Table 3 Efficacy at Week 48 Outcomes in APV30003 ITT(E) Population (ART-experienced Patients)

	FPV/RTV BID (N=107)	**LPV/RTV BID (N=103)**
AAUCMB Observed Analysis	Mean (n)	Mean (n)
All Patients	-1.53 (105)	-1.76 (103)
1000 – 10,000 copies/ml	-1.53 (41)	-1.43 (43)
>10,000 – 100,000 copies/ml	-1.59 (45)	-1.81 (46)
>100,000 copies/ml	-1.38 (19)	-2.61 (14)
FPV/RTV BID vs LPV/RTV BID	AAUCMB Mean Diff (97.5% CI)	
All Patients	0.244 (-0.047, 0.536)	
1000 – 10,000 copies/ml	-0.104 (-0.550, 0.342)	
>10,000 – 100,000 copies/ml	0.216 (-0.213, 0.664)	
>100,000 copies/ml	1.232 (0.512, 1.952)	
AAUCMB Observed Analysis	Mean (n)	Mean (n)
All Patients	-1.53 (105)	-1.76 (103)
CD4-count <50	-1.28 (7)	-2.45 (8)
≥50	-1.55 (98)	-1.70 (95)
<200	-1.68 (32)	-2.07 (38)
≥ 200	-1.46 (73)	-1.58 (65)
GSS to OBT[1] 0	-1.42 (8)	-1.91 (4)
1	-1.30 (35)	-1.59 (23)
≥ 2	-1.68 (62)	-1.80 (76)
All Patients, RD=F Analysis[2]	n (%)	n(%)
Subjects (%) with plasma HIV-1 RNA <50 copies/ml	49 (46%)	52 (50%)
Subjects (%) with plasma HIV-1 RNA <400 copies/ml	62 (58%)	63 (61%)
Subjects with >1 $\log_{10}$ change from baseline in plasma HIV-1 RNA	62 (58%)	71 (69%)

Change from baseline in CD4 cells (cells/µl)	Median (n)	Median (n)
All Patients	81 (79)	91 (85)

Key: [1]GSS to OBT: Genotypic Sensitivity Score to Optimised Background. GSS was derived using ANRS 2007 guidelines. [2]RD=F: Rebound or discontinuation equal failure analysis which is equivalent to TLOVR. FPV/RTV BID – Fosamprenavir with ritonavir twice daily, LPV/RTV BID – Lopinavir / ritonavir twice daily

Table 4 AAUCMB at Week 48 by genotypic sensitivity score in OBT and baseline resistance to FPV/RTV

	Week 48 AAUCMB (n)		
Genotypic Sensitivity Score in OBT	**All Subjects**	**Susceptiple to FPV/RTV < 4 mutations from score**	**Resistant to FPV/RTV ≥ 4 mutations from score**
0	-1.42 (8)	-1.83 (4)	-1.01 (4)
1	-1.30 (35)	-1.42 (29)	-0.69 (6)
≥ 2	-1.68 (62)	-1.76 (56)	-0.89 (6)
All patients	-1.53 (105)	-1.65 (89)	-0.85 (16)

As shown in the above table, there were only 16 patients harbouring baseline virus with resistance to FPV/RTV according to the ANRS score. Data from this small number further analysed by GSS subgroups need to be interpreted with caution.

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

Children and adolescent patients above the age of six

Fosamprenavir tablets and oral suspension with ritonavir in combination with NRTIs have been evaluated in protease inhibitor naïve and experienced children and adolescent patients. The benefit in this age group has mainly been derived from study APV29005, an open label 48 week study evaluating the pharmacokinetic profiles, safety, and antiviral activity of fosamprenavir with ritonavir administered twice daily to HIV 1 protease inhibitor experienced and naive patients 2 to 18 years of age. Results through 48 weeks of treatment are provided below.

APV29005 enrolled 30 patients aged 6 to 11 (the majority of whom were treated with fosamprenavir / ritonavir 18/3 mg/kg twice daily or the adult tablet regimen), and 40 patients aged 12 to 18 (the majority of whom were treated with the adult tablet regimen).

Table 5 Baseline Characteristics and Efficacy Outcomes at Week 48 in APV29005 ITT(E) Population

	Patients aged 6 to 11 N=30	Patients aged 12 to 18 N=40
Baseline Characteristics		

ART/PI status, n (%)		
ART-naïve	2 (7)	14 (35)
ART-experienced, PI-naïve	8 (27)	12 (30)
PI-experienced	20 (67)	14 (35)
Median duration of prior ART exposure, weeks		
NRTI	386	409
PI	253	209
Median plasma HIV-1 RNA log10 copies/mL	4.6 (n=29)	4.7
>100,000 copies/ml, n (%)	9 (31)	13 (33)
Median CD4 cells/µl	470	250
CD4 count < 350 cells/µl, n (%)	10 (33)	27 (68)
Efficacy Outcomes		
Patients with plasma HIV-1 RNA <400 copies/ml, Snapshot analysis	16 (53%)	25 (63%)
Median change from baseline in CD4 cells (cells/µl), observed analysis	210 (n=21)	140 (n=35)

These data were further substantiated by the supportive study APV20003; however, a different dosage regimen than that of study APV29005 was used.

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 C_{max} 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.

Co-administration of ritonavir with fosamprenavir increase plasma amprenavir AUC by approximately 2-fold and plasma $C_{\tau,ss}$ by 4- to 6-fold, compared to values obtained when fosamprenavir is administered alone.

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 $AUC_{0\text{-}tau}$ was 39.6 (34.5–45.3) h*µg/ml.

Administration of the fosamprenavir tablet formulation in the fed state (standardised high fat meal: 967 kcal, 67 grams fat, 33 grams protein, 58 grams carbohydrate) 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.

Biotransformation

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

In a clinical study on pharmacokinetics of fosamprenavir in paediatric patients, eight subjects 12 to 18 years of age received the standard fosamprenavir adult tablet dose of 700 mg twice daily (with ritonavir 100 mg twice daily). Compared to the historical adult population receiving fosamprenavir / ritonavir 700 / 100 mg twice daily, 12 to 18 year old subjects had 20 % lower plasma APV AUC(0-24), 23 % lower C_{max}, and 20 % lower C_{min} values. Children 6 to 11 years of age (n=9) receiving fosamprenavir / ritonavir 18 / 3 mg/kg twice daily had 26 % higher AUC(0-24) and similar C_{max} and C_{min} values when compared to the historical adult population receiving fosamprenavir / ritonavir 700 / 100 mg twice daily.

APV20002 is a 48 week, Phase II, open label study designed to evaluate the pharmacokinetics, safety, tolerability and antiviral activity of fosamprenavir with and without ritonavir in paediatric subjects 4 weeks to < 2 years of age. Compared to the historical adult population receiving fosamprenavir with ritonavir 700 mg / 100 mg twice daily, a subset of five pediatric subjects ages 6 to < 24-months receiving fosamprenavir / ritonavir 45/7 mg/kg twice daily demonstrated that despite an approximate 5-fold increase in fosamprenavir and ritonavir doses on a mg/kg basis, plasma amprenavir AUC(0-τ) was approximately 48 % lower, C_{max} 26 % lower, and Cτ 29 % lower in the paediatric subjects. No dosing recommendations can be made for the very young (children < 2 years of age) and Telzir with ritonavir is not recommended for this patient population (see section 4.2).

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.

The plasma amprenavir pharmacokinetics were evaluated in a 14 day repeat-dose study in HIV-1 infected adult subjects with mild, moderate, or severe hepatic impairment receiving fosamprenavir with ritonavir compared to matched control subjects with normal hepatic function.

In subjects with mild hepatic impairment (Child-Pugh score of 5-6), the dosage regimen of fosamprenavir 700 mg twice daily with a reduced dosing frequency of ritonavir 100 mg once daily provided slightly higher plasma amprenavir C_{max} (17 %), slightly higher plasma amprenavir AUC(0-12) (22 %), similar plasma total amprenavir C12 values and approximately 117 % higher plasma unbound amprenavir C12 values compared to subjects with normal hepatic function receiving the standard fosamprenavir / ritonavir 700 mg /100 mg twice daily regimen.

In subjects with moderate hepatic impairment (Child-Pugh score of 7-9), a reduced dose of fosamprenavir 450 mg twice daily with a reduced dosing frequency of ritonavir 100 mg once daily is predicted to deliver similar plasma amprenavir C_{max} and AUC(0-12), but approximately 35 % lower plasma total amprenavir C12 values and approximately 88 % higher plasma unbound amprenavir C12 values than achieved in subjects with normal hepatic function receiving the standard fosamprenavir with ritonavir 700 mg / 100 mg twice daily regimen. Predicted exposures are based on extrapolation from data observed following administration of fosamprenavir 300 mg twice daily with ritonavir 100 mg once daily in subjects with moderate hepatic impairment.

In subjects with severe hepatic impairment (Child-Pugh score of 10-13), a reduced dose of fosamprenavir 300 mg twice daily with a reduced dosing frequency of ritonavir 100 mg once daily delivered 19% lower plasma amprenavir C_{max}, 23% lower AUC(0-12), and 38% lower C12 values, but similar unbound plasma amprenavir C12 values than achieved in subjects with normal hepatic function receiving the standard fosamprenavir with ritonavir 700 mg / 100 mg twice daily regimen. Despite reducing the dosing frequency of ritonavir, subjects with severe hepatic impairment had 64% higher ritonavir C_{max}, 40% higher ritonavir AUC(0-24), and 38% higher ritonavir C12 than achieved in subjects with normal hepatic function receiving the standard fosamprenavir with ritonavir 700 mg / 100 mg twice daily regimen.

Fosamprenavir with ritonavir was generally well-tolerated in subjects with mild, moderate, or severe hepatic impairment, and these regimens had similar adverse event and clinical laboratory profiles as previous studies of HIV-1 infected subjects with normal hepatic function.

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). Toxicity was not aggravated when juvenile animals were treated as compared with adult animals, but the data did indicate a steeper dose response.

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. In long-term carcinogenicity studies with fosamprenavir in mice and rats, there were increases in hepatocellular adenomas and hepatocellular carcinomas in mice at exposure levels equivalent to 0.1 to 0.3-fold those in humans given 700 mg of fosamprenavir plus 100 mg ritonavir twice daily, and increases in hepatocellular adenomas and thyroid follicular cell adenomas in rats at exposure levels equivalent to 0.3 to 0.6-fold those in humans given 700 mg of fosamprenavir plus 100 mg ritonavir twice daily. The relevance of the hepatocellular findings in the rodents for humans is uncertain; however, there is no evidence from clinical trials or marketed use to suggest that these findings are of clinical significance. Repeat dose studies with fosamprenavir in rats produced effects consistent with hepatic enzyme induction, which predisposes rats to thyroid neoplasms. The thyroid tumorigenic potential is regarded to be species-specific. The clinical relevance of these findings is unknown. In rats only there was an increase in interstitial cell hyperplasia in males at exposure levels equivalent to 0.5-fold those in humans, and an increase in uterine endometrial adenocarcinoma in females at an exposure level equivalent to 1.1-fold those in humans. The incidence of endometrial findings was slightly increased over concurrent controls, but within background range for female rats. The relevance of the uterine endometrial adenocarcinomas for humans is uncertain; however there is no evidence from clinical trials or marketed use to suggest that these findings are of clinical significance.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

<u>Tablet core:</u>
Microcrystalline cellulose
Croscarmellose sodium
Povidone K30
Magnesium stearate
Colloidal anhydrous silica

Tablet film-coat:
Hypromellose
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 Special precautions for disposal

Any unused medicinal product should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

ViiV Healthcare UK Limited
980 Great West Road
Brentford
Middlesex
TW8 9GS
United Kingdom

8. MARKETING AUTHORISATION NUMBER

EU/1/04/282/001

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 12 July 2004
Date of renewal of authorisation: 15 May 2009.

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency (EMA) http://www.ema.europa.eu

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).

Excipients:
Methyl parahydroxybenzoate (E218) 1.5 mg/ml
Propyl parahydroxybenzoate (E216) 0.2 mg/ml

For the full list of 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, adolescents and children of 6 years and above in combination with other antiretroviral medicinal products.

In moderately antiretroviral experienced adults, Telzir in combination with low dose ritonavir has not been shown to be as effective as lopinavir / ritonavir. No comparative studies have been undertaken in children or adolescents.

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.

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.

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

Telzir suspension is administered orally.

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

Telzir is also available as 700 mg film-coated tablets.

Adults

In adults, the oral suspension **should** be taken **without** food and on an empty stomach.

Please refer to the table below for the dosing recommendations in adults.

Paediatric patients (from 6 years of age)

In paediatric patients, the oral suspension **should** be taken **with** food in order to aid palatability and assist compliance (see section 5.2).

Telzir oral suspension is the recommended option for the most accurate dosing in children based on body weight.

Please refer to the table below for the dosing recommendations in paediatric patients.

No dosing recommendations can be made for children weighing less than 25 kg.

Children less than 6 years of age

Telzir with ritonavir is not recommended in children below 6 years due to insufficient data on pharmacokinetics, safety and antiviral response (see section 5.2).

Dosing recommendations for Telzir with ritonavir

Age	Body weight	Telzir dose (TWICE DAILY)	Ritonavir dose (TWICE DAILY)
Adult (≥18 years)		Tablet or Oral suspension 700 mg (1 tablet or 14 ml suspension) Oral suspension should be taken **without** food	Capsule or Solution 100 mg
6-17 years	≥39 kg	Tablet or Oral suspension 700 mg (1 tablet or 14 ml suspension) Oral suspension should be taken **with** food	Capsule or Solution 100 mg

	33-38 kg	Oral suspension 18 mg/kg (0.36 ml/kg); maximum 700 mg or 14 ml Oral suspension should be taken **with** food	Capsule or Solution 100 mg
	25-32 kg	Oral suspension 18 mg/kg (0.36 ml/kg) Oral suspension should be taken **with** food	Solution 3 mg/kg
	<25 kg	No dosing recommendations	
<6 years		Not recommended	

Elderly (over 65 years of age)

The pharmacokinetics of fosamprenavir have not been studied in this patient population (see section 5.2). Therefore, no recommendations can be made in this patient population.

Renal impairment

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

Hepatic impairment

For adults with mild hepatic impairment (Child-Pugh score: 5-6) the recommended dose is 700 mg fosamprenavir twice daily with 100 mg ritonavir **once** daily.

For adults with moderate hepatic impairment (Child-Pugh score: 7-9) the recommended dose is 450 mg fosamprenavir (i.e. 9 ml Telzir oral suspension) twice daily with 100 mg ritonavir **once** daily. This adjusted dose has not been evaluated in a clinical study and has been derived from extrapolation (see section 5.2).

For adults with severe hepatic impairment (Child-Pugh score: 10-15): fosamprenavir should be used with caution and at a reduced dose of 300 mg fosamprenavir twice daily with 100 mg ritonavir **once** daily.

Overall, even with these dose adjustments for adults with hepatic impairment, some patients may have higher or lower than anticipated amprenavir and/or ritonavir plasma concentrations as compared to patients with normal hepatic function, due to increased inter-patient variability (see section 5.2), therefore close monitoring of safety and virologic response is warranted.

In this patient population, the oral suspension **should** be taken **without** food and on an empty stomach.

No dose recommendation can be made for children and adolescents with hepatic impairment as no studies have been conducted in these age groups.

4.3 Contraindications

Hypersensitivity to fosamprenavir, amprenavir, or ritonavir, or to any of the excipients listed in section 6.1.

Telzir must not be administered concurrently with medicinal products with narrow therapeutic windows that are substrates of cytochrome P450 3A4 (CYP3A4), e.g. alfuzosin, amiodarone, astemizole, bepridil, cisapride, dihydroergotamine, ergotamine, pimozide, quetiapine, quinidine, terfenadine, oral midazolam (for caution on parenterally administered midazolam, see section 4.5), oral triazolam, sildenafil used for the treatment of pulmonary arterial hypertension (for use of sildenafil in patients with erectile dysfunction, see sections 4.4 and 4.5).

Co-administration of paritaprevir and fosamprenavir/ritonavir is contraindicated due to the expected increase of paritaprevir exposure and the lack of clinical data assessing the magnitude of this increase (see section 4.5).

Concomitant use of Telzir with simvastatin or lovastatin is contraindicated because of increased plasma concentrations of lovastatin and simvastatin which can increase the risk of myopathy, including rhabdomyolysis (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).

Combination of rifampicin with Telzir with concomitant low-dose ritonavir is contraindicated (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 precautions for use

While effective viral suppression with antiretroviral therapy has been proven to substantially reduce the risk of sexual transmission, a residual risk cannot be excluded. Precautions to prevent transmission should be taken in accordance with national guidelines.

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.

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.

<u>Liver disease</u>

Telzir with ritonavir should be used with caution and at reduced doses in adults with mild, moderate or severe hepatic impairment (see section 4.2).

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 reactions. In case of concomitant antiviral therapy for hepatitis B or C, please refer also to the relevant Summary of Product Characteristics for these medicinal products.

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 halofantrine or lidocaine (systemic) is not recommended.

PDE5 inhibitors used for the treatment of erectile dysfunction: The use of Telzir concomitantly with PDE5 inhibitors (e.g. sildenafil, tadalafil, vardenafil) is not recommended (see section 4.5). Co-administration of Telzir with low dose ritonavir and these medicinal products is expected to substantially increase their concentrations and may result in PDE5 inhibitor-associated adverse events such as hypotension, visual changes and priapism (see section 4.5). Note that co-administration of Telzir with low dose ritonavir with sildenafil used for the treatment of pulmonary arterial hypertension is contraindicated (see section 4.3).

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 there may be an increased risk of hepatic transaminase elevations and hormonal levels may be altered with co-administration of fosamprenavir, ritonavir and oral contraceptives, alternative non-hormonal methods of contraception are recommended for women of childbearing potential (see section 4.5).
No data are available on the co-administration of fosamprenavir and ritonavir with oestrogens and/or progestogens when used as hormonal replacement therapies. The efficacy and safety of these therapies with fosamprenavir and ritonavir has not been established.

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

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

Hepatitis C virus (HCV) Direct-Acting Antivirals: When hepatitis C virus direct-acting antiviral (DAA) drugs, which are metabolised by CYP3A4 or are inducers/inhibitors of CYP3A4, are co-administered with fosamprenavir/ritonavir, altered plasma concentrations of medications are expected due to inhibition or induction of CYP3A4 enzyme activity (see section 4.3 and 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.

Weight and metabolic parameters

An increase in weight and in levels of blood lipids and glucose may occur during antiretroviral therapy. Such changes may in part be linked to disease control and life style. For lipids, there is in some cases evidence for a treatment effect, while for weight gain there is no strong evidence relating this to any particular treatment. For monitoring of blood lipids and glucose reference is made to established HIV treatment guidelines. Lipid disorders should be managed as clinically appropriate.

Immune Reactivation Syndrome

In HIV-infected patients with severe immune deficiency at the time of institution of combination antiretroviral therapy (CART), an inflammatory reaction to asymptomatic or residual opportunistic pathogens may arise and cause serious clinical conditions, or aggravation of symptoms. Typically, such reactions have been observed within the first few weeks or months of initiation of CART. Relevant examples are cytomegalovirus retinitis, generalised and/or focal mycobacterium infections, and *Pneumocystis carinii* pneumonia. Any inflammatory symptoms should be evaluated and treatment instituted when necessary. Autoimmune disorders (such as Graves' disease) have also been reported to occur in the setting of immune reactivation; however, the reported time to onset is more variable and can occur many months after initiation of treatment.

Osteonecrosis

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

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. Similarily, administration of fosamprenavir with ritonavir may modify the pharmacokinetics of other active substances that share this metabolic pathway.

Interaction studies have only been performed in adults.

Unless otherwise stated, studies detailed below have been performed with the recommended dosage of fosamprenavir/ritonavir (i.e. 700/100 mg twice daily), and the interaction was assessed under steady-state conditions where drugs were administered for 10 to 21 days,

Drugs by Therapeutic Area	**Interaction** **Geometric mean change (%)** **(Possible mechanism)**	**Recommendation concerning co-administration**
ANTIRETROVIRAL MEDICINAL PRODUCTS *Non-nucleoside reverse transcriptase inhibitors:*		
Efavirenz 600 mg once daily	No clinically significant interaction is observed.	No dosage adjustment necessary.
Nevirapine 200 mg twice daily	No clinically significant interaction is observed.	No dosage adjustment necessary.
Etravirine (Study conducted in 8 patients)	Amprenavir AUC ↑↑ 69% Amprenavir C_{min} ↑ 77% Amprenavir C_{max} ↑ 62% Etravirine AUC ↔[a] Etravirine C_{min}↔[a] Etravirine C_{max}↔[a] [a] Comparison based on historic control.	Telzir may require dose reduction (using oral suspension).
Nucleoside / Nucleotide reverse transcriptase inhibitors:		
Abacavir **Lamivudine** **Zidovudine** Study performed with amprenavir. No FPV/RTV drug interaction studies.	No clinically significant interaction is expected.	No dosage adjustment necessary.

Didanosine chewable tablet No drug interaction studies.	No clinically significant interaction is expected.	No dose separation or dosage adjustment necessary (see Antacids).
Didanosine gastro-resistant capsule No drug interaction studies.	No clinically significant interaction is expected.	No dosage adjustment necessary.
Tenofovir 300 mg once daily	No clinically significant interaction observed.	No dosage adjustment necessary.

Protease Inhibitors: According to current treatment guidelines, dual therapy with protease inhibitors is generally not recommended.		
Lopinavir / ritonavir 400 mg/100 mg twice daily **Lopinavir / ritonavir** 533 mg/133 mg twice daily (Telzir 1400 mg twice daily)	Lopinavir: C_{max} ↑ 30% Lopinavir: AUC ↑ 37% Lopinavir: C_{min} ↑ 52% Amprenavir: C_{max} ↓ 58% Amprenavir: AUC ↓ 63% Amprenavir: C_{min} ↓ 65% Lopinavir: C_{max} ↔* Lopinavir: AUC ↔* Lopinavir: C_{min} ↔* * compared to lopinavir / ritonavir 400 mg/100 mg twice daily Amprenavir: C_{max} ↓ 13%* Amprenavir: AUC ↓ 26%* Amprenavir: C_{min} ↓ 42 %* * compared to fosamprenavir / ritonavir 700 mg/100 mg twice daily (Mixed CYP3A4 induction/inhibition, Pgp induction)	Concomitant use is not recommended.
Indinavir **Saquinavir** **Nelfinavir** No drug interaction studies.		No dose recommendations can be given.

Atazanavir 300 mg once daily	Atazanavir: C_{max} ↓ 24%* Atazanavir: AUC ↓ 22%* Atazanavir: C_{min}↔* *compared to atazanavir/ ritonavir 300 mg/ 100 mg once daily Amprenavir: C_{max} ↔ Amprenavir: AUC ↔ Amprenavir: C_{min} ↔	No dosage adjustment necessary.
Integrase inhibitors		
Raltegravir 400 mg twice daily	<u>Fasting state</u> Amprenavir : C_{max} ↓ 14% (-36%; +15%) AUC ↓ 16% (-36%; +8%) C_{min} ↓ 19% (-42%; +13%) Raltegravir: C_{max} ↓ 51% (-75%; -3%) AUC ↓ 55% (-76%; -16%) C_{min} ↓ 36 % (-57%; -3%) <u>Fed state</u> Amprenavir: C_{max} ↓ 25% (-41%; -4%) AUC ↓ 25% (-42%; -3%) C_{min} ↓ 33% (-50%; -10%) Raltegravir: C_{max} ↓ 56% (-70%; -34%) AUC ↓ 54% (-66%; -37%) C_{min} ↓ 54 % (-74%; -18%)	Concomitant use is not recommended. Significant reductions in exposure and Cmin observed for both amprenavir and raltegravir (especially in fed conditions) may result in virological failure in patients.
Dolutegravir 50 mg once daily	<u>Dolutegravir</u> C_{max} ↓ 24% AUC ↓ 35% Cτ ↓ 49% Amprenavir: C_{max} ↔ Amprenavir: AUC ↔ Amprenavir: C_{min} ↔	No dosage adjustment of fosamprenavir or dolutegravir is recommended based on observed exposure-response relationships of clinical data. Caution is warranted and close monitoring is recommended when this combination is given in integrase inhibitor-resistant patients.
CCR5-receptor antagonists		

Maraviroc 300 mg twice daily	Maraviroc: AUC_{12} ↑ 2.49 Maraviroc: C_{max} ↑ 1.52 Maraviroc: C_{12} ↑ 4.74 Amprenavir: AUC_{12} ↓ 0.65 Amprenavir: C_{max} ↓ 0.66 Amprenavir: C_{12} ↓ 0.64 Ritonavir AUC_{12} ↓ 0.66 Ritonavir C_{max} ↓ 0.61 Ritonavir C_{12} ↔ 0.86	Concomitant use is not recommended. Significant reductions in amprenavir C_{min} observed may result in virological failure in patients.

Anti-hepatitis C virus medicinal products		
Telaprevir *(PK data from telaprevir prescribing information)*	Amprenavir ↓ AUC 0.53 (0.49-0.58) C_{max} 0.65 (0.59-0.70) C_{min} 0.44 (0.40-0.50) Telaprevir ↓ AUC 0.68 (0.63-0.72) C_{max} 0.67 (0.63-0.71) C_{min} 0.70 (0.64-0.77) Mechanism unknown.	Not recommended.
Boceprevir	Not studied. Results from studies with other HIV protease inhibitors and boceprevir suggest that co-administration of fosamprenavir/ritonavir with boceprevir is likely to lead to subtherapeutic levels of fosamprenavir and boceprevir.	Not recommended.
Simeprevir **Daclatasvir**	Not studied. Results from studies with other HIV protease inhibitors and simeprevir or daclatasvir, suggest that co-administration with fosamprenavir/ritonavir is likely to lead to increased plasma exposures of simeprevir or daclatasvir due to CYP3A4 enzyme inhibition.	Not recommended.
Paritaprevir (co-formulated with ritonavir and ombitasvir and co-administered with dasabuvir)	Not studied. Results from studies with other HIV protease inhibitors and paritaprevir/ritonavir/ ombitasvir +/- dasabuvir suggest that co-	Contraindicated (see section 4.3).

	administration of fosamprenavir/ritonavir with paritaprevir/ritonavir/ ombitasvir +/- dasabuvir is likely to lead to increased plasma exposures of paritaprevir due to CYP3A4 enzyme inhibition and higher ritonavir dose.	
ANTIARRHYTHMICS		
Amiodarone **Bepridil** **Quinidine** **Flecainide** **Propafenone**	Amiodarone: ↑ expected Bepridil: ↑ expected Quinidine: ↑ expected (CYP3A4 inhibition by FPV/RTV) Flecainide: ↑ expected Propafenone: ↑ expected (CYP2D6 inhibition by RTV)	Contraindicated (see section 4.3). Potential for serious and/or life-threatening reactions such as cardiac arrhythmias.
ERGOT DERIVATIVES		
Dihydroergotamine **Ergotamine** **Ergonovine** **Methylergonovine**	Dihydroergotamine: ↑ expected Ergonovine: ↑ expected Ergotamine: ↑ expected Methylergonovine: ↑ expected (CYP3A4 inhibition by FPV/RTV)	Contraindicated (see section 4.3). Potential for serious and/or life-threatening reactions such as acute ergot toxicity characterized by peripheral vasospasm and ischemia of the extremities and other tissues.
GASTROINTESTINAL MOTILITY AGENTS		
Cisapride	Cisapride: ↑ expected (CYP3A4 inhibition by FPV/RTV)	Contraindicated (see section 4.3). Potential for serious and/or life-threatening reactions such as cardiac arrhythmias.
ANTIHISTAMINES (HISTAMINE H1 RECEPTOR ANTAGONISTS)		
Astemizole **Terfenadine**	Astemizole: ↑ expected Terfenadine: ↑ expected (CYP3A4 inhibition by FPV/RTV)	Contraindicated (see section 4.3). Potential for serious and/or life-threatening reactions such as cardiac arrhythmias.
NEUROLEPTIC		
Pimozide	Pimozide: ↑ expected	Contraindicated (see section 4.3). Potential for serious

	(CYP3A4 inhibition by FPV/RTV)	and/or life-threatening reactions such as cardiac arrhythmias.
ANTIPSYCHOTICS		
Quetiapine	Due to CYP3A inhibition by Telzir, concentrations of quetiapine are expected to increase.	Concomitant administration of Telzir and quetiapine is contra-indicated as it may increase quetiapine-related toxicity. Increased plasma concentrations of quetiapine may lead to coma.

INFECTION *Antibacterials:*		
Clarithromycin Study performed with amprenavir. No FPV/RTV drug interaction studies.	Clarithromycin: moderate ↑ expected (CYP3A4 inhibition)	Use with caution.
Erythromycin No drug interaction studies.	Erythromycin: ↑ expected (CYP3A4 inhibition by FPV/RTV	Use with caution.
Anti-mycobacterial:		
Rifabutin 150 mg every other day	Rifabutin: C_{max} ↓ 14%* Rifabutin: AUC(0-48) ↔* 25-O-desacetylrifabutin: C_{max} ↑ 6-fold* 25-O-desacetylrifabutin: AUC(0-48) ↑ 11-fold* *compared to rifabutin 300 mg once daily Amprenavir exposure unchanged when compared to historical data. (Mixed CYP3A4 induction/inhibition)	The increase of 25-O-desacetylrifabutin (active metabolite) could potentially lead to an increase of rifabutin related adverse events, notably uveitis. A 75 % reduction of the standard rifabutin dose (i.e. to 150 mg every other day) is recommended. Further dose reduction may be necessary (see section 4.4).
Rifampicin 600 mg once daily (Amprenavir without ritonavir) No FPV/RTV drug interaction studies	Amprenavir: AUC ↓ 82% Significant ↓ APV expected (CYP3A4 induction by rifampicin)	Contraindicated (see section 4.3.) The decrease in amprenavir AUC can result in virological failure and resistance development. During attempts to overcome the decreased exposure by increasing the dose of other

		protease inhibitors with ritonavir, a high frequency of liver reactions was seen.

Anti-fungals:		
Ketoconazole 200 mg once daily for four days **Itraconazole** No drug interaction studies.	Ketoconazole: C_{max} ↑ 25% Ketoconazole: AUC ↑ 2.69-fold. Amprenavir: C_{max} ↔ Amprenavir: AUC ↔ Amprenavir: C_{min} ↔ Itraconazole: ↑ expected (CYP3A4 inhibition by FPV/RTV)	High doses (> 200 mg/day) of ketoconazole or itraconazole are not recommended.
ANTACIDS, HISTAMINE H_2 RECEPTOR ANTAGONIST AND PROTON-PUMP INHIBITORS		
Single 30 ml dose of antacid suspension (equivalent to 3.6 grams aluminium hydroxide and 1.8 grams magnesium hydroxide (Telzir 1400 mg single dose) **Ranitidine** 300 mg single dose (Telzir 1400 mg single dose) **Esomeprazole** 20 mg once daily	Amprenavir: C_{max} ↓ 35% Amprenavir: AUC ↓ 18% Amprenavir: C_{min} (C_{12h}) ↔ Amprenavir: C_{max} ↓ 51% Amprenavir: AUC ↓ 30% Amprenavir: C_{min} (C_{12h}) ↔ Amprenavir C_{max} ↔ Amprenavir AUC ↔ Amprenavir C_{min} (C_{12h}) ↔ (Increase in gastric pH)	No dosage adjustment necessary with antacids, proton-pump inhibitors or histamine H_2 receptor antagonists.
ANTICONVULSANTS		
Phenytoin 300 mg once daily	Phenytoin: C_{max} ↓ 20% Phenytoin: AUC ↓ 22% Phenytoin: C_{min} ↓ 29% (Modest induction of CYP3A4 by FPV/RTV) Amprenavir: C_{max} ↔	It is recommended that phenytoin plasma concentrations be monitored and phenytoin dose increased as appropriate.

	Amprenavir: AUC ↑ 20% Amprenavir: C_{min} ↑ 19%	

Phenobarbital **Carbamazepine** No drug interaction studies.	Amprenavir: ↓ expected (Modest CYP3A4 induction)	Use with caution (see section 4.4).
Lidocaine (by systemic route) No drug interaction studies.	Lidocaine: ↑ expected (CYP3A4 inhibition by FPV/RTV)	Concomitant use is not recommended. It may cause serious adverse reactions (see section 4.4).
Halofantrine No drug interaction studies.	Halofantrine: ↑ expected (CYP3A4 inhibition by FPV/RTV)	Concomitant use is not recommended. It may cause serious adverse reactions (see section 4.4).
PDE5 INHIBITORS		
Sildenafil **Vardenafil** **Tadalafil** No drug interaction studies.	PDE5 inhibitors: ↑ expected (CYP3A4 inhibition by FPV/RTV)	Concomitant use is not recommended. It may result in an increase in PDE5 inhibitor associated adverse reactions, including hypotension, visual changes and priapism (refer to PDE5 inhibitor prescribing information). Patients should be warned about these possible side effects when using PDE5 inhibitors with Telzir/ritonavir (see section 4.4). Note that co-administration of Telzir with low dose ritonavir with sildenafil used for the treatment of pulmonary arterial hypertension is contraindicated (see section 4.3).
INHALED/NASAL STEROIDS		
Fluticasone propionate 50 µg intranasal 4 times daily) for 7 days (Ritonavir 100 mg capsules twice daily for 7 days)	Fluticasone propionate: ↑ Intrinsic cortisol levels: ↓ 86 %. The effects of high fluticasone systemic exposure on ritonavir plasma levels are unknown.	Concomitant use is not recommended unless the potential benefit of treatment outweighs the risk of systemic corticosteroid effects (see section 4.4). A dose reduction of the glucocorticoid with close monitoring of local and systemic effects or a switch to a glucocorticoid, which is

	Greater effects may be expected when fluticasone propionate is inhaled. (CYP3A4 inhibition by FPV/RTV)	not a substrate for CYP3A4 (e.g. beclomethasone) should be considered. In case of withdrawal of glucocorticoids, progressive dose reduction may have to be performed over a longer period (see section 4.4).
ALPHA 1-ADRENORECEPTOR ANTAGONIST		
Alfuzosin,	Potential for increased alfuzosin concentrations which can result in hypotension. The mechanism of interaction is CYP3A4 inhibition by fosamprenavir/ritonavir.	Co-administration of TELZIR/ritonavir with alfuzosin is contraindicated (see section 4.3).

HERBAL PRODUCTS		
St. John's wort *(Hypericum perforatum)*	Amprenavir ↓ expected (CYP3A4 induction by St. John's wort)	Herbal preparations containing St John's wort must not be combined with Telzir (see section 4.3). If a patient is already taking St John's wort, check amprenavir, ritonavir and HIV RNA 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.
HMG-COA REDUCTASE INHIBITORS		
Lovastatin **Simvastatin** No drug interaction studies.	Lovastatin: ↑ expected Simvastatin: ↑ expected (CYP3A4 inhibition by FPV/RTV)	Contraindicated (see section 4.3). Increased concentrations of HMG-CoA reductase inhibitors may cause myopathy, including rhabdomyolysis. Pravastatin or fluvastatin are recommended because their metabolism is not dependent on CYP 3A4 and interactions are not expected with protease inhibitors.
Atorvastatin 10 mg once daily for 4 days	Atorvastatin: C_{max} ↑ 184% Atorvastatin: AUC ↑ 153%	Doses of atorvastatin no greater than 20 mg/day

	Atorvastatin: C_{min} ↑ 73% Amprenavir: C_{max} ↔ Amprenavir: AUC ↔ Amprenavir: C_{min} ↔ (CYP3A4 inhibition by FPV/RTV)	should be administered, with careful monitoring for atorvastatin toxicity.
IMMUNOSUPPRESSANTS		
Cyclosporin **Rapamycin** **Tacrolimus** No drug interaction studies.	Cyclosporin: ↑ expected Rapamycin: ↑ expected Tacrolimus: ↑ expected (CYP3A4 inhibition by FPV/RTV)	Frequent therapeutic concentration monitoring of immunosuppressant levels is recommended until levels have stabilised (see section 4.4).

BENZODIAZEPINES		
Midazolam No drug interaction studies.	Midazolam: ↑ expected (3-4 fold for parenteral midazolam) Based on data with other protease inhibitors plasma concentrations of midazolam are expected to be significantly higher when midazolam is given orally. (CYP3A4 inhibition by FPV/RTV)	Telzir/ritonavir should not be co-administered with orally administered midazolam (see section 4.3), whereas caution should be used with co-administration of Telzir/ritonavir and parenteral midazolam. If Telzir/ritonavir is co-administered with parenteral midazolam, it should be done in an intensive care unit (ICU) or similar setting which ensures close clinical monitoring and appropriate medical management in case of respiratory depression and/or prolonged sedation. Dosage adjustment for midazolam should be considered, especially if more than a single dose of midazolam is administered.
TRICYCLIC ANTIDEPRESSANTS		
Desipramine **Nortriptyline** No drug interaction studies.	Tricyclic antidepressant: ↑ expected (Mild CYP2D6 inhibition by RTV)	Careful monitoring of the therapeutic and adverse reactions of tricyclic antidepressants is recommended (see section 4.4).
OPIOIDS		

Methadone ≤ 200 mg once daily	(R-) methadone: C_{max} ↓ 21% (R-) methadone: AUC ↓ 18% (CYP induction by FPV/RTV)	The decrease of (R-) methadone (active enantiomer) is not expected to be clinically significant. As a precaution, patients should be monitored for withdrawal syndrome.
ORAL ANTICOAGULANTS		
Warfarin **Other oral anticoagulants** No drug interaction studies.	Possible ↓ or ↑ of antithrombotic effect. (Induction and/or inhibition of CYP2C9 by RTV)	Reinforced monitoring of the International Normalised Ratio is recommended (see section 4.4).

ORAL CONTRACEPTIVES		
Ethinyl estradiol 0.035 mg/norethisterone 0.5 mg once daily	Ethinyl estradiol: C_{max} ↓28% Ethinyl estradiol: AUC ↓37% Norethisterone: C_{max} ↓ 38% Norethisterone: AUC ↓ 34% Norethisterone: C_{min} ↓ 26 (CYP3A4 induction by FPV/RTV) Amprenavir: C_{max} ↔* Amprenavir: AUC ↔* Amprenavir: C_{min} ↔* * compared to historical data Ritonavir: C_{max} ↑ 63%* Ritonavir: AUC ↑ 45%* * compared to historical data Clinically significant hepatic transaminase elevations occurred in some subjects.	Alternative non-hormonal methods of contraception are recommended for women of childbearing potential (see section 4.4).
SELECTIVE SEROTONIN REUPTAKE INHIBITORS (SSRIS)		
Paroxetine 20 mg once daily	Paroxetine: C_{max} ↓ 51% Paroxetine: AUC ↓ 55% Amprenavir: C_{max} ↔* Amprenavir: AUC ↔* Amprenavir: C_{min} ↔*	Dose titration of paroxetine based on a clinical assessment of antidepressant response is recommended. Patients on stable dose of paroxetine who start

	* compared to historical data Mechanism unknown.	treatment with Telzir and ritonavir should be monitored for antidepressant response.

4.6 Fertility, 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.

Breast-feeding

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 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 in adults and that the adverse reaction profile detailed in this section is based on the experience in adults with the Telzir film coated tablets.

Summary of safety profile

The adverse reaction profile was similar across all the respective adult studies: antiretroviral naïve patients (APV30002, ESS100732), protease inhibitor experienced (twice daily dosing, APV30003) patients. This is based on safety data from a total of 864 patients exposed to fosamprenavir/ritonavir in these three studies.

The most frequently (> 5% of adult subjects treated) reported adverse reactions with fosamprenavir/ritonavir combination were gastrointestinal reactions (nausea, diarrhoea, abdominal pain and vomiting) and headache. Most adverse reactions associated with fosamprenavir/ritonavir combination therapies were mild to moderate in severity, early in onset and rarely treatment limiting. More serious adverse reactions such as serious skin rashes and hepatic transaminase elevations have also been reported (cf paragraph Description of selected adverse reactions).

Tabulated summary of adverse reactions

Adverse reactions are listed by MedDRA system organ class and absolute frequency. Frequencies are defined as: Very common (≥ 1/10), Common (≥ 1/100 to < 1/10), Uncommon (≥ 1/1,000 to < 1/100), Rare (≥ 1/10,000 to < 1/1,000) or Very rare (< 1/10,000), or Not known.

Frequency categories for the reactions below have been based on clinical trials and postmarketing data.

Most of the adverse reactions below were reported from three large clinical studies in adults, where the adverse events were of at least moderate intensity (Grade 2 or more) occurring in at least 1% of patients and reported by investigators as being attributable to the medicinal products used in the studies.

Body System	Adverse reaction	Frequency
Nervous system disorders	Headache, dizziness, oral paraesthesia	Common
Gastrointestinal disorders	Diarrhoea Loose stools, nausea, vomiting, abdominal pain	Very common Common
Skin and subcutaneous tissue disorders	Stevens Johnson syndrome Angioedema Rash (see text below "rash/cutaneous reactions")	Rare Uncommon Common
General disorders and administration site conditions	Fatigue	Common
Investigations	Blood cholesterol increased Blood triglycerides increased Alanine aminotransferase increased Aspartate aminotransferase increased Lipase increased	Very common Common Common Common Common

<u>Description of selected adverse reactions</u>

<u>Rash / cutaneous reactions:</u> 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 cases of rash, including Stevens-Johnson syndrome are rare. 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 adult patients, included:
increased ALT (*common*), AST (*common*), serum lipase (*common*) and triglycerides (*common*).

Metabolic parameters: weight and levels of blood lipids and glucose may increase during antiretroviral therapy (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.

Immune Reactivation Syndrome: in HIV-infected patients with severe immune deficiency at the time of initiation of combination antiretroviral therapy (CART), an inflammatory reaction to asymptomatic or residual opportunistic infections may arise. Autoimmune disorders (such as Graves' disease) have also been reported to occur in the setting of immune reactivation; however, the reported time to onset is more variable and these events can occur many months after initiation of treatment (see section 4.4).

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

Paediatric / other populations

Children and adolescents: the adverse reaction profile in children and adolescents is based on integrated safety data from two studies (APV29005 Week 24 data and APV20003 Week 168 data [final data]) in which 158 HIV-1 infected subjects 2 to 18 years of age received fosamprenavir with ritonavir with background nucleoside reverse transcriptase inhibitor therapy (see section 5.1 for information on dosing regimens applied for each age group). 79 % of subjects received greater than 48 weeks of exposure.
Overall the safety profile in these 158 children and adolescents was similar to that observed in the adult population. Vomiting occurred more frequently amongst paediatric patients. Drug-related adverse reactions were more common in APV20003 (57%) where subjects received once daily fosamprenavir / ritonavir when compared to APV29005 (33%) where subjects received twice daily fosamprenavir / ritonavir.
No new safety concerns were identified from analyses of 48 week data from studies APV29005 or APV20002, in which 54 subjects 4 weeks to <2 years of age received twice daily fosamprenavir / ritonavir with background nucleoside reverse transcriptase inhibitor therapy and 5 subjects received only single doses of fosamprenavir with or without ritonavir.

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

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

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 overdose 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: J05AE07

Mechanism of action

The *in vitro* antiviral activity observed with fosamprenavir is due to the presence of trace amounts of amprenavir. Amprenavir is a competitive inhibitor of the 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.

Administration of fosamprenavir 700 mg twice daily with ritonavir 100 mg twice daily results in plasma amprenavir concentrations (data from study APV30003 in antiretroviral experienced patients) which results in protein adjusted median ratios of C_{min}/IC_{50} and C_{min}/IC_{95} of 21.7 (range 1.19-240) and 3.21 (range 0.26-30.0), respectively.

Antiviral activity *in vitro*

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 (IC_{50}) 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). The relationship between *in vitro* anti-HIV-1 activity of amprenavir and the inhibition of HIV-1 replication in humans has not been defined.

Resistance

In vivo

a)ART-naïve or PI-naïve patients

Various regimens have been assessed in the amprenavir/fosamprenavir development programs with and without co-administration of ritonavir. Analysis of the virological failure samples across these regimens defined four main resistance pathways: V32I+I47V, I50V, I54L/M and I84V. Additional mutations observed which may contribute to resistance were: L10V/F/R, I13V, K20R/T, L33F/V, M36I, M46I/L, I47V/L Q58E, I62V, L63P, V77I, I85V, and I93L.

When ART naïve adult patients were treated with the currently approved doses of fosamprenavir/ritonavir, as for other ritonavir boosted PI regimens, the mutations described were infrequently observed. Sixteen of 434 ART-naïve patients who received fosamprenavir 700 mg/ritonavir 100 mg twice daily in ESS100732 experienced virological failure by Week 48 with 14 isolates genotyped. Three of 14 isolates had protease resistance mutations. One resistance mutation was observed in each of 3 isolates: K20K/R, I54I/L and I93I/L respectively

Among the 81 PI-naïve paediatric patients treated with fosamprenavir / ritonavir, 15 patients met protocol-defined virological failure through 48 weeks in APV29005 and up to 108 weeks in APV20003. Treatment-emergent major or APV-associated protease mutations were observed in virus isolated from 2 patients. Resistance patterns were similar to those observed in adults.

b) PI-experienced patients

Amprenavir

In the studies of PI-experienced adult patients, PRO30017 (amprenavir 600 mg / ritonavir 100 mg twice daily in sub-study A and B with 80 and 37 patients respectively), the following mutations emerged in patients with virological failure: L10F/I/V, V11I, I13V, K20R, V32I, L33F, E34Q, M36I, M46I/L, I47V, G48V, I50V, I54L/M/T/V, Q58E, D60E, I62V, A71V, V77I, V82A/I, I84V, I85V, L90M and I93L/M.

Fosamprenavir

In the studies of PI-experienced adult patients, APV30003 and its extension, APV30005 (fosamprenavir 700 mg / ritonavir 100 mg twice daily: n=107), the following mutations emerged in patients experiencing virological failure through 96 weeks: L10F/I, L24I, V32I, L33F, M36I, M46I/L, I47V, I50V, I54L/M/S, A71I/T/V, G73S, V82A, I84V, and L90M.

In the paediatric studies APV20003 and APV29005, 77 PI-experienced patients were treated with fosamprenavir / ritonavir-based regimens and 43 patients met study-defined virologic failure criteria through 48 weeks in APV29005 and up to 108 weeks in APV20003. Treatment-emergent major protease or APV-associated mutations were observed in virus isolated from 1 patient in APV29005 and 6 patients from APV20003. The mutational profiles were similar to those described for PI-experienced adults treated with fosamprenavir / ritonavir.

Antiviral activity according to genotypic/phenotypic resistance

Genotypic resistance testing

Genotypic interpretation systems may be used to estimate the activity of amprenavir / ritonavir or fosamprenavir / ritonavir in subjects with PI-resistant isolates. The current (July 2006) ANRS AC-11 algorithm for fosamprenavir / ritonavir defines resistance as the presence of the mutations V32I+I47A/V, or I50V, or at least four mutations among: L10F/I/V, L33F, M36I, I54A/L/M/S/T/V, I62V, V82A/C/F/G, I84V and L90M and is associated with increased phenotypic resistance to fosamprenavir with ritonavir as well as reduced likelihood of virological response (resistance). Conclusions regarding the relevance of particular mutations or mutational patterns are subject to change with additional data, and it is recommended to always consult current interpretation systems for analysing resistance test results.

Phenotypic resistance testing

Clinically validated phenotypic interpretation systems may be used in association with the genotypic data to estimate the activity of amprenavir / ritonavir or fosamprenavir / ritonavir in patients with PI-resistant isolates. Resistance testing diagnostic companies have developed clinical phenotypic cut-offs for FPV/RTV that can be used to interpret resistance test results.

Clinical experience

Clinical experience with fosamprenavir boosted with ritonavir is mainly based on two open label studies, one in antiretroviral naïve patients (study ESS100732), and one study in antiretroviral experienced patients (study APV30003). Both of these studies compared fosamprenavir/ritonavir with lopinavir / ritonavir.

Antiretroviral Naïve Adult Patients

In a randomised open-label study (ESS100732 - KLEAN) in antiretroviral naïve patients, fosamprenavir (700 mg) co-administered with low dose ritonavir (100 mg) in a twice daily regimen

including abacavir / lamivudine (600 mg / 300 mg) fixed dose combination tablet once daily showed comparable efficacy over 48 weeks to lopinavir / ritonavir (400 mg / 100 mg) given twice daily in combination with abacavir / lamivudine (600 mg / 300 mg once daily).

Non-inferiority was demonstrated between fosamprenavir co-administered with ritonavir and lopinavir / ritonavir based on the proportions of patients achieving plasma HIV-1 RNA levels < 400 copies/ml at 48 weeks (primary endpoint). In the Time to loss of virological response (TLOVR) analysis for the ITT(E) population, the proportion of patients achieving <400 copies/ml was 73 % (315 / 434) in the fosamprenavir with ritonavir group compared to 71 % (317 / 444) of patients receiving lopinavir / ritonavir, with a 95 % confidence interval of the difference of [-4,84%; 7;05%].

Efficacy outcomes by subgroups are described in the table below.

Table 1 Efficacy Outcome at Week 48 in ESS100732 (ART-Naïve Patients)

	FPV/RTV 700 mg/100 mg BID (n= 434)	**LPV/RTV 400 mg/100 mg BID (n=444)**
ITT-E Population TLOVR analysis	Proportion with HIV-1 RNA < 400 copies/ml	
All Subjects	72.5 %	71.4%
Baseline HIV-1 RNA < 100,000 copies/ml	69.5 % (n=197)	69.4% (n=209)
Baseline HIV-1 RNA ≥ 100,000 copies/ml	75.1% (n=237)	73.2% (n=235)
	Proportion with HIV-1 RNA < 50 copies/ml	
All Subjects	66%	65%
Baseline HIV-1 RNA < 100,000 copies/ml	67% (n=197)	64% (n=209)
Baseline HIV-1 RNA ≥ 100,000 copies/ml	65% (n=237)	66% (n=235)
	Median Change from baseline in CD4 cells (cells/µl)	
ITT-E observed analysis	176 (n=323)	191 (n=336)

Following completion of the 48 week treatment period, subjects at European and Canadian sites were eligible to participate in a study extension to Week 144 maintaining their treatment regimen as per the original randomisation. Only 22% of the original population of the KLEAN study was enrolled in the study extension

Efficacy outcomes are described in the table below.

Table 2 Efficacy Outcome at Weeks 96 and 144 in ESS100732 Extension (ART-Naïve Patients)

	FPV/RTV 700 mg/100 mg	**LPV/RTV 400 mg/100 mg BID**

	BID (n= 105)	(n=91)
ITT (Ext) Population TLOVR analysis	Proportion with HIV-1 RNA < 400 copies/ml	
Week 96	93%	87%
Week 144	83%	70%
	Proportion with HIV-1 RNA < 50 copies/ml	
Week 96	85%	75%
Week 144	73%	60%
ITT (Ext) Observed analysis	Median Change from baseline in CD4 cells (cells/µl)	
Week 96	292 (n=100)	286 (n=84)
Week 144	300 (n=87)	335 (n=66)

Antiretroviral Experienced Adult 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 (primary end-point) and other efficacy outcomes by subgroup are described in the tables below:

Table 3 Efficacy at Week 48 Outcomes in APV30003 ITT(E) Population (ART-experienced Patients)

	FPV/RTV BID (N=107)	**LPV/RTV BID (N=103)**
AAUCMB Observed Analysis	Mean (n)	Mean (n)
All Patients	-1.53 (105)	-1.76 (103)
1000 – 10,000 copies/ml	-1.53 (41)	-1.43 (43)
>10,000 – 100,000 copies/ml	-1.59 (45)	-1.81 (46)
>100,000 copies/ml	-1.38 (19)	-2.61 (14)
FPV/RTV BID vs LPV/RTV BID	AAUCMB Mean Diff (97.5% CI)	
All Patients	0.244 (-0.047, 0.536)	
1000 – 10,000 copies/ml	-0.104 (-0.550, 0.342)	
>10,000 – 100,000 copies/ml	0.216 (-0.213, 0.664)	
>100,000 copies/ml	1.232 (0.512, 1.952)	
AAUCMB Observed Analysis	Mean (n)	Mean (n)
All Patients	-1.53 (105)	-1.76 (103)
CD4-count <50	-1.28 (7)	-2.45 (8)
≥50	-1.55 (98)	-1.70 (95)
<200	-1.68 (32)	-2.07 (38)
≥ 200	-1.46 (73)	-1.58 (65)
GSS to OBT[1] 0	-1.42 (8)	-1.91 (4)
1	-1.30 (35)	-1.59 (23)
≥ 2	-1.68 (62)	-1.80 (76)
All Patients, RD=F Analysis[2]	n (%)	n(%)
Subjects (%) with plasma HIV-1 RNA <50 copies/ml	49 (46%)	52 (50%)
Subjects (%) with plasma HIV-1 RNA <400 copies/ml	62 (58%)	63 (61%)
Subjects with >1 $\log_{10}$ change from baseline in plasma HIV-1 RNA	62 (58%)	71 (69%)

Change from baseline in CD4 cells (cells/µl)	Median (n)	Median (n)
All Patients	81 (79)	91 (85)

Key: [1]GSS to OBT: Genotypic Sensitivity Score to Optimised Background. GSS was derived using ANRS 2007 guidelines. [2]RD=F: Rebound or discontinuation equal failure analysis which is equivalent to TLOVR. FPV/RTV BID – Fosamprenavir with ritonavir twice daily, LPV/RTV BID – Lopinavir / ritonavir twice daily

Table 4 AAUCMB at Week 48 by genotypic sensitivity score in OBT and baseline resistance to FPV/RTV

	Week 48 AAUCMB (n)		
Genotypic Sensitivity Score in OBT	**All Subjects**	**Susceptiple to FPV/RTV < 4 mutations from score**	**Resistant to FPV/RTV ≥ 4 mutations from score**
0	-1.42 (8)	-1.83 (4)	-1.01 (4)
1	-1.30 (35)	-1.42 (29)	-0.69 (6)
≥ 2	-1.68 (62)	-1.76 (56)	-0.89 (6)
All patients	-1.53 (105)	-1.65 (89)	-0.85 (16)

As shown in the above table, there were only 16 patients harbouring baseline virus with resistance to FPV/RTV according to the ANRS score. Data from this small number further analysed by GSS subgroups need to be interpreted with caution.

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

Children and adolescent patients above the age of six

Fosamprenavir tablets and oral suspension with ritonavir in combination with NRTIs have been evaluated in protease inhibitor naïve and experienced children and adolescent patients. The benefit in this age group has mainly been derived from study APV29005, an open label 48 week study evaluating the pharmacokinetic profiles, safety, and antiviral activity of fosamprenavir with ritonavir administered twice daily to HIV 1 protease inhibitor experienced and naive patients 2 to 18 years of age. Results through 48 weeks of treatment are provided below.

APV29005 enrolled 30 patients aged 6 to 11 (the majority of whom were treated with fosamprenavir / ritonavir 18/3 mg/kg twice daily or the adult tablet regimen) and 40 patients aged 12 to 18 (the majority of whom were treated with the adult tablet regimen).

Table 5. Baseline Characteristics and Efficacy Outcomes at Week 48 in APV29005 ITT(E) Population

	Patients aged 6 to 11 N=30	Patients aged 12 to 18 N=40
Baseline Characteristics		

ART/PI status, n (%)		
ART-naïve	2 (7)	14 (35)
ART-experienced, PI-naïve	8 (27)	12 (30)
PI-experienced	20 (67)	14 (35)
Median duration of prior ART exposure, weeks		
NRTI	386	409
PI	253	209
Median plasma HIV-1 RNA log10 copies/mL	4.6 (n=29)	4.7
>100,000 copies/ml, n (%)	9 (31)	13 (33)
Median CD4 cells/µl	470	250
CD4 count < 350 cells/µl, n (%)	10 (33)	27 (68)
Efficacy Outcomes		
Patients with plasma HIV-1 RNA <400 copies/ml, Snapshot analysis	16 (53%)	25 (63%)
Median change from baseline in CD4 cells (cells/µl), observed analysis	210 (n=21)	140 (n=35)

These data were further substantiated by the supportive study APV20003; however, a different dosage regimen than that of study APV29005 was used.

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 C_{max} as compared to the oral tablet formulation. However, the bioequivalence could not be demonstrated when the oral suspension was given with food. Therefore for adult patients 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_{max} values were approximately 30 % lower and C_{min} values were approximately 28 % higher with fosamprenavir.

Co-administration of ritonavir with fosamprenavir increase plasma amprenavir AUC by approximately 2-fold and plasma $C_{\tau,ss}$ by 4- to 6-fold, compared to values obtained when fosamprenavir is administered alone.

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 $AUC_{0\text{-}tau}$ was 39.6 (34.5–45.3) h*μg/ml.

Administration of the fosamprenavir oral suspension formulation with a high fat meal (967 kcal, 67 grams fat, 33 grams protein, 58 grams carbohydrate) reduced plasma amprenavir AUC(0-∞) by 28% and C_{max} by 46% and delayed T_{max} by 0.72 hours. For adult patients the fosamprenavir oral suspension should be taken **without** food and on an empty stomach. In children and adolescents the fosamprenavir oral suspension should be taken **with food**. The dose recommendations for this population therefore take into account the observed food effect (see section 4.2).

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.

Biotransformation

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

In a clinical study on pharmacokinetics of fosamprenavir in paediatric patients, eight subjects 12 to 18 years of age received the standard fosamprenavir adult tablet dose of 700 mg twice daily (with ritonavir 100 mg twice daily). Compared to the historical adult population receiving fosamprenavir /

ritonavir 700 / 100 mg twice daily, 12 to 18 year old subjects had 20 % lower plasma APV AUC(0-24), 23 % lower C_{max}, and 20 % lower C_{min} values. Children 6 to 11 years of age (n=9) receiving fosamprenavir / ritonavir 18 / 3 mg/kg twice daily had 26 % higher AUC(0-24) and similar C_{max} and C_{min} values when compared to the historical adult population receiving fosamprenavir / ritonavir 700 / 100 mg twice daily.

APV20002 is a 48 week, Phase II, open label study designed to evaluate the pharmacokinetics, safety, tolerability and antiviral activity of fosamprenavir with and without ritonavir in paediatric subjects 4 weeks to < 2 years of age. Compared to the historical adult population receiving fosamprenavir with ritonavir 700 mg / 100 mg twice daily, a subset of five pediatric subjects ages 6 to < 24-months receiving fosamprenavir / ritonavir 45/7 mg/kg twice daily demonstrated that despite an approximate 5-fold increase in fosamprenavir and ritonavir doses on a mg/kg basis, plasma amprenavir AUC(0-τ) was approximately 48 % lower, C_{max} 26 % lower, and Cτ 29 % lower in the paediatric subjects. No dosing recommendations can be made for the very young (children < 2 years of age) and Telzir with ritonavir is not recommended for this patient population (see section 4.2).

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.

The plasma amprenavir pharmacokinetics were evaluated in a 14 day repeat-dose study in HIV-1 infected adult subjects with mild, moderate, or severe hepatic impairment receiving fosamprenavir with ritonavir compared to matched control subjects with normal hepatic function.

In subjects with mild hepatic impairment (Child-Pugh score of 5-6), the dosage regimen of fosamprenavir 700 mg twice daily with a reduced dosing frequency of ritonavir 100 mg once daily provided slightly higher plasma amprenavir C_{max} (17 %), slightly higher plasma amprenavir AUC(0-12) (22 %), similar plasma total amprenavir C12 values and approximately 117 % higher plasma unbound amprenavir C12 values compared to subjects with normal hepatic function receiving the standard fosamprenavir / ritonavir 700 mg /100 mg twice daily regimen.

In subjects with moderate hepatic impairment (Child-Pugh score of 7-9), a reduced dose of fosamprenavir 450 mg twice daily with a reduced dosing frequency of ritonavir 100 mg once daily is predicted to deliver similar plasma amprenavir C_{max} and AUC(0-12), but approximately 35 % lower plasma total amprenavir C12 values and approximately 88 % higher plasma unbound amprenavir C12 values than achieved in subjects with normal hepatic function receiving the standard fosamprenavir with ritonavir 700 mg / 100 mg twice daily regimen. Predicted exposures are based on extrapolation from data observed following administration of fosamprenavir 300 mg twice daily with ritonavir 100 mg once daily in subjects with moderate hepatic impairment.

In subjects with severe hepatic impairment (Child-Pugh score of 10-13), a reduced dose of fosamprenavir 300 mg twice daily with a reduced dosing frequency of ritonavir 100 mg once daily delivered 19% lower plasma amprenavir C_{max}, 23% lower AUC(0-12), and 38% lower C12 values, but similar unbound plasma amprenavir C12 values than achieved in subjects with normal hepatic

function receiving the standard fosamprenavir with ritonavir 700 mg / 100 mg twice daily regimen. Despite reducing the dosing frequency of ritonavir, subjects with severe hepatic impairment had 64% higher ritonavir C_{max}, 40% higher ritonavir AUC(0-24), and 38% higher ritonavir C12 than achieved in subjects with normal hepatic function receiving the standard fosamprenavir with ritonavir 700 mg / 100 mg twice daily regimen.

Fosamprenavir with ritonavir was generally well-tolerated in subjects with mild, moderate, or severe hepatic impairment, and these regimens had similar adverse event and clinical laboratory profiles as previous studies of HIV-1 infected subjects with normal hepatic function.

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). Toxicity was not aggravated when juvenile animals were treated as compared with adult animals, but the data did indicate a steeper dose response.

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 development 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. In long-term carcinogenicity studies with fosamprenavir in mice and rats, there were increases in hepatocellular adenomas and hepatocellular carcinomas in mice at exposure levels equivalent to 0.1 to 0.3-fold those in humans given 700 mg of fosamprenavir plus 100 mg ritonavir twice daily, and increases in hepatocellular adenomas and thyroid follicular cell adenomas in rats at exposure levels equivalent to 0.3 to 0.6-fold those in humans given 700 mg of fosamprenavir plus 100 mg ritonavir twice daily. The relevance of the hepatocellular findings in the rodents for humans is uncertain; however, there is no evidence from clinical trials or marketed use to suggest that these findings are of clinical significance. Repeat dose studies with fosamprenavir in rats produced effects consistent with hepatic enzyme induction, which predisposes rats to thyroid neoplasms. The thyroid tumorigenic potential is regarded to be species-specific. The clinical relevance of these findings is unknown. In rats only there was an increase in interstitial cell hyperplasia in males at exposure levels equivalent to 0.5-fold those in humans, and an increase in uterine endometrial adenocarcinoma in females at an exposure level equivalent to 1.1-fold those in humans. The incidence of endometrial findings was slightly increased over concurrent controls, but within background range for female rats. The relevance of the uterine endometrial adenocarcinomas for humans is uncertain; however there is no evidence from clinical trials or 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. The pack also includes a polyethylene syringe-adapter and a 10 ml oral dosing syringe comprised of a polypropylene barrel (with ml graduations) and a polyethylene plunger.

6.6 Special precautions for disposal

Any unused medicinal product should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

ViiV Healthcare UK Limited
980 Great West Road
Brentford
Middlesex
TW8 9GS
United Kingdom

8. MARKETING AUTHORISATION NUMBER

EU/1/04/282/002

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 12 July 2004
Date of renewal of authorisation: 15 May 2009.

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency (EMA) http://www.ema.europa.eu

ANNEX II

A. MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

A MANUFACTURER(S) 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

Glaxo Wellcome S.A., Avenida de Extremadura 3, 09400 Aranda de Duero Burgos, Spain

Oral suspension
Aspen Bad Oldesloe GmbH, Industriestrasse 32-36, D-23843, Bad Oldesloe, Germany

or

Glaxo Operations UK Ltd (trading as GlaxoWellcome Operations), Harmire Road, Barnard Castle, Co. Durham DL12 8DT, United Kingdom

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 OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to restricted medical prescription (See Annex I: Summary of Product Characteristics, section 4.2).

C OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic Safety Update Reports**

The marketing authorisation holder shall submit periodic safety update reports for this product in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk Management Plan (RMP)**

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.
An updated RMP should be submitted

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

If the submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER 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 SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach 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

ViiV Healthcare UK Limited
980 Great West Road
Brentford
Middlesex
TW8 9GS
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/04/282/001

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

telzir 700 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC:
SN:
NN:

PARTICULARS TO APPEAR 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 SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach 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

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12. MARKETING AUTHORISATION NUMBER(S)

EU/1/04/282/001

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Only applicable to outer carton

PARTICULARS TO APPEAR ON THE OUTER 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 SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach 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

ViiV Healthcare UK Limited
980 Great West Road
Brentford
Middlesex
TW8 9GS
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/04/282/002

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

telzir 50 mg/ml

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC:
SN:
NN:

PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING

BOTTLE LABEL 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)

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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 SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach 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

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12. MARKETING AUTHORISATION NUMBER(S)

EU/1/04/282/002

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Only applicable to outer carton

B. PACKAGE LEAFLET

Package leaflet: Information for the user

Telzir 700 mg film-coated tablets
Fosamprenavir

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- **If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.**

What is in this leaflet

1. What Telzir is and what it is used for
2. What you need to know before you take Telzir
3. How to take Telzir
4. Possible side effects
5. How to store Telzir
6. Contents of the pack and other information

1. What Telzir is and what it is used for

Telzir is used to treat HIV (human immunodeficiency virus) infection.

Telzir is a type of medicine known as an anti-retroviral. It is taken with low doses of another medicine, ritonavir, which boosts the level of Telzir in the blood. Telzir belongs to a group of anti-retroviral medicines called *protease inhibitors*. Protease is an enzyme produced by HIV which enables the virus to multiply in white blood cells *(CD4 cells)* in your blood. By stopping protease from working, Telzir stops HIV multiplying and infecting more CD4 cells.

Telzir with low doses of ritonavir is used in combination with other anti-retroviral medicines (‘combination therapy’) to treat adults, adolescents and children aged over 6 years infected with HIV.

HIV can become resistant to anti-HIV medicines. To avoid this happening, and to stop your illness getting worse, it is very important that you keep taking all your medicines exactly as prescribed.

Telzir will not stop you passing on HIV. HIV infection is spread by sexual contact with someone who’s got the infection, or by transfer of infected blood (for example by sharing needles).

2. What you need to know before you take Telzir

Telzir is to be taken in combination with low doses of ritonavir and other antiretroviral medicines. It is therefore important that you carefully read the package leaflet 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 allergic** to fosamprenavir, amprenavir or any of the other ingredients of this medicine (listed in section 6), or to ritonavir.
- **if you are taking any of these medicines:**

- alfuzosin (used to treat **a prostate problem**)
- astemizole or terfenadine (commonly used to treat **allergy** symptoms – these medicines may be available without prescription)
- pimozide (used to treat **schizophrenia**)
- quetiapine (used to treat **schizophrenia**, **bipolar disorder** and **major depressive disorder**)
- cisapride (used to relieve **indigestion**)
- ergot derivatives (used to treat **headaches**)
- rifampicin (used to treat **tuberculosis**)
- amiodarone, quinidine, flecainide and propafenone (**heart medicines**)
- bepridil (used to treat **high blood pressure**)
- oral midazolam or oral triazolam **(**used to treat **anxiety)**
- products containing St John's wort (*Hypericum perforatum*)
- lovastatin, simvastatin (used to lower **cholesterol**)
- sildenafil if used to treat **pulmonary arterial hypertension**, (a condition affecting the blood vessels to your lungs)
- paritaprevir (used to treat hepatitis C virus infection)

→Tell your doctor if any of these applies to you.

Take special care with Telzir
Talk to your doctor or pharmacist before taking Telzir:

- **If you have a known allergy to medicines containing sulphonamide**. You may also be allergic to Telzir.
- **If you have liver disease**. Your doctor may lower your dose of Telzir and ritonavir depending on the amount of liver damage. You will be monitored while you are taking Telzir. If your liver disease gets worse, you may need to stop taking Telzir for a while, or permanently. People with hepatitis B or C taking combination therapy are at increased risk of getting severe liver problems.
- **If you have haemophilia**. Increased bleeding may occur while taking protease inhibitors (such as Telzir). 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 antiretroviral medicines including protease inhibitors, there have been reports of increased sugar in the blood and diabetes getting worse. Also, some people have become diabetic while taking these medicines.
- If you are taking any other medicines. See section 'Other medicines and Telzir'.

→Tell your doctor if any of these apply to you. You will need extra check-ups, including blood tests, while you're taking your medication.

Your doctor will monitor your blood glucose levels before and during treatment with Telzir.

Look out for important symptoms
Some people taking medicines for HIV infection develop other conditions, which can be serious. These include:

- Flare up of old infections
- Change in your body shape
- Problems with your bones.

You need to know about important signs and symptoms to look out for while you're taking Telzir. **Please read the information on 'Other side effects of combination therapy for HIV' in section 4 of this leaflet.** If you have any questions about this information or the advice given:
→Talk to your doctor.

You may get a skin rash. However you can still continue to take Telzir. It can be treated with antihistamines. Rarely, the skin rash can be severe and serious (*Stevens Johnson syndrome*). If this happens, Telzir must be stopped immediately and you must never take it again.

Protect other people. HIV infection is spread by sexual contact with someone who has the infection, or by transfer of infected blood (for example, by sharing injection needles). You can still pass on HIV when taking this medicine, although the risk is lowered by effective antiretroviral therapy. Discuss with your doctor the precautions needed to avoid infecting other people.

Other medicines and Telzir
Tell your doctor or pharmacist if you're taking or have recently taken any other medicines – these include herbal medicines or other medicines you bought without a prescription. Your doctor will decide if these medicines are suitable for you to take with Telzir and ritonavir. This is **very important**, as Telzir or ritonavir can strengthen or weaken the effects of other medicines. This can sometimes lead to serious medical conditions.

There are some medicines that must not be taken with Telzir. You must check the list of medicines under 'Don't take Telzir' at the beginning of section 2 of this leaflet.

These medicines are not recommended with Telzir/ritonavir:
- doses of ketoconazole and itraconazole greater than 200 mg per day (used to treat **fungal infections**)
- doses of rifabutin greater than 150 mg every other day (an **antibiotic**)
- lidocaine given by injection
- halofantrine (used to treat **malaria**)
- sildenafil, vardenafil or tadalafil (used to treat **erectile dysfunction**)
- doses of atorvastatin greater than 20 mg per day (used to lower **cholesterol**)
- fluticasone propionate and similar medicines used to treat **asthma**, unless considered essential. In this case close monitoring is required.
- lopinavir/ritonavir combination (used to treat **HIV infection**)
- raltegravir (used to treat **HIV infection**)
- telaprevir, boceprevir, simeprevir, daclatasvir (used to treat **hepatitis C virus infection**)
- maraviroc (used to treat **HIV infection**)

You will be closely monitored if you are taking these medicines with Telzir/ritonavir:
- atorvastatin up to 20 mg per day (used to lower **cholesterol**)
- carbamazepine, phenobarbital, phenytoin (used to treat **epilepsy**)
- cyclosporin, rapamycin, tacrolimus (used to suppress the **immune system**)
- dolutegravir (used to treat **HIV infection**)
- desipramine, nortriptyline, paroxetine and similar medicines (used to treat **depression**)
- warfarin and other medicines that **stop blood clotting**
- injectable midazolam (used to treat **anxiety**)
- clarithromycin, erythromycin (an **antibiotic**)
- methadone (a **heroin substitute**)

Your dose of Telzir may need to be changed if you are taking
- etravirine (used to treat **HIV infection**)

Hormonal contraception
Taking Telzir and ritonavir while taking the contraceptive pill may harm your liver and may stop the contraceptive from working properly.
→ **Use an alternative non-hormonal type of contraception such as a condom.**
No studies have been done on the use of Telzir/ritonavir with other hormonal therapies, such as hormone replacement therapy (HRT).

Pregnancy
If you are pregnant, think you may be pregnant, or are planning to have a baby:
→**Ask your doctor or pharmacist for advice before** taking this medicine.

Breast-feeding
Women who are HIV-positive must not breast-feed because HIV infection can be passed on to the baby in breast milk. It is not known whether the ingredients in Telzir can also pass into your breast milk. If you are breast-feeding, or thinking about breast-feeding:
→Talk to your doctor immediately.

Driving and using machines
Telzir can make you feel dizzy and have other side effects that make you less alert.
→ **Don't drive or operate machinery** unless you're feeling well.

Stay in regular contact with your doctor
Telzir helps to control your condition, but it is not a cure for HIV infection. You need to keep taking it every day to stop your illness getting worse. You may still develop other infections and illnesses linked to HIV infection.
→ **Keep in touch with your doctor**, and **don't stop taking Telzir** without your doctor's advice.

3. How to take Telzir

Always take this medicine exactly as your doctor or pharmacist has told you. It is very important that you take the **full** daily dose of Telzir and ritonavir as prescribed by your doctor. **Do not take more** than the recommended dose. Check with your doctor or pharmacist if you are not sure.

Swallow the tablets whole, with some water or another drink. Telzir tablets can be taken with or without food. Telzir is also available as a liquid (oral suspension) for people who are unable to swallow tablets. (Read the package leaflet of Telzir oral suspension for guidance on whether to take it with or without food.)

Adults
The recommended dose is **one 700 mg Telzir tablet twice daily** with 100 mg ritonavir twice daily.

Children from 6 years of age and weighing at least 39 kg
Children can take the adult tablet dose of **one 700 mg Telzir tablet twice daily** with ritonavir 100 mg twice daily if they can swallow the tablets whole.

Children from 6 years of age and weighing less than 39 kg
Use Telzir oral suspension.

Adults with liver disease
If you have mild liver disease, the dose is **one Telzir tablet (700 mg) twice daily** with 100 mg ritonavir **only once daily.** If you have moderate or severe liver disease the dose of Telzir has to be lowered. This dose adjustment cannot be made with Telzir tablets. You must take Telzir oral suspension.

If you take too much Telzir
If you have taken more than the prescribed dose of Telzir:
→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 your treatment as before. **Don't take a double dose to make up for a missed dose.**

Don't stop Telzir without advice
Take Telzir for as long as your doctor recommends. Don't stop unless your doctor advises you to.

4. Possible side effects

During HIV therapy there may be an increase in weight and in levels of blood lipids and glucose. This is partly linked to restored health and life style, and in the case of blood lipids sometimes to the HIV medicines themselves. Your doctor will test for these changes.

Like all medicines, this medicine can cause side effects, but not everyone gets them. When treating HIV, it can be hard to tell whether side effects are caused by Telzir, by other medicines taken at the same time or by the HIV disease itself. For this reason, it is very important to **talk to your doctor about any changes in your health.**

Very common side effects

These may affect **more than 1 in 10 people**:

- Diarrhoea
- Increase in *cholesterol* (a type of blood fat).

Common side effects

These may affect **up to 1 in 10 people**:

- Increases in *triglycerides* (a type of blood fat).
- Feeling sick or being sick (*nausea or vomiting*), pain in the stomach, loose stools
- Skin rashes *(*red, raised or itchy) – if the skin rash is severe, you may have to stop taking this medicine
- Headache, feeling dizzy
- Feeling tired
- Increases in enzymes produced by the liver called *transaminases*, increases of an enzyme produced by the pancreas called *lipase.*
- Tingling or numbness around the lips and mouth.

Uncommon side effects

These may affect **up to 1 in 100 people**:

- Swelling of the face, lips and tongue (*angioedema*).

Rare side effects

These may affect **up to 1 in 1000 people**:

- A severe or life-threatening skin reaction (*Stevens Johnson syndrome*).

You may experience muscle problems

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*). If you notice any muscle problems:
→Tell your doctor.

Haemophiliacs may bleed more

In patients with **haemophilia type A and B**, there have been reports of increased bleeding while taking protease inhibitors.
If this happens to you:
→Talk to your doctor immediately.

If you get any side effects

→Talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet.

Other side effects of combination therapy for HIV

Old infections may flare up

People with advanced HIV infection (AIDS) have weak immune systems and are more likely to develop serious infections (opportunistic infections). When these people start treatment, they may find that old, hidden infections flare up, causing signs and symptoms of inflammation. These symptoms are probably caused by the body's immune system becoming stronger, so that the body starts to fight these infections.

In addition to the opportunistic infections, autoimmune disorders (a condition that occurs when the immune system attacks healthy body tissue) may also occur after you start taking medicines for the treatment of your HIV infection. Autoimmune disorders may occur many months after the start of treatment. If you notice any symptoms of infection or other symptoms such as muscle weakness, weakness beginning in the hands and feet and moving up towards the trunk of the body, palpitations, tremor or hyperactivity, please inform your doctor immediately to seek necessary treatment.

If you get any symptoms of infection or signs of inflammation while you're taking Telzir:
→**Tell your doctor immediately. Don't take other medicines for the infection** without your doctor's advice.

You may have problems with your bones
Some people taking combination therapy for HIV develop a condition called *osteonecrosis*. With this condition, parts of the bone tissue die because of reduced blood supply to the bone.

People may be more likely to get this condition:

- if they have been taking combination therapy for a long time
- if they are also taking anti-inflammatory medicines called corticosteroids
- if they drink alcohol
- if their immune systems are very weak
- if they are overweight.

Signs to look out for include:

- **stiffness in the joints**
- **aches and pains** (especially in the hip, knee or shoulder)
- **difficulty moving**.

If you notice any of these symptoms:
→**Tell your doctor**.

Reporting of side effects
If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Telzir

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the carton and the bottle.

Telzir does not require any special storage conditions.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help to protect the environment.

6. Contents of the pack and other information

What Telzir contains

- **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).

What Telzir looks like and contents of the pack

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 also available as an oral suspension for those patients unable to swallow the tablets.

Marketing Authorisation Holder and Manufacturer

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Glaxo Wellcome S.A.
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Spain

Marketing Authorisation Holder

ViiV Healthcare UK Limited
980 Great West Road
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This leaflet was last revised in

Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu.

Package leaflet: Information for the user

Telzir 50 mg/ml oral suspension
Fosamprenavir

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- **If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.**

What is in this leaflet:

1. **What Telzir is and what it is used for**
2. **What you need to know before you take Telzir**
3. **How to take Telzir**
4. **Possible side effects**
5. **How to store Telzir**
6. **Contents of the pack and other information**

1. What Telzir is and what it is used for

Telzir is used to treat HIV (human immunodeficiency virus) infection.

Telzir is a type of medicine known as an anti-retroviral. It is taken with low doses of another medicine, ritonavir, which boosts the level of Telzir in the blood. Telzir belongs to a group of anti-retroviral medicines called *protease inhibitors*. Protease is an enzyme produced by HIV which enables the virus to multiply in white blood cells *(CD4 cells)* in your blood. By stopping protease from working, Telzir stops HIV multiplying and infecting more CD4 cells

Telzir with low doses of ritonavir is used in combination with other anti-retroviral medicines (‘combination therapy’) to treat adults, adolescents and children aged over 6 years infected with HIV.

HIV can become resistant to anti-HIV medicines. To avoid this happening, and to stop your illness getting worse, it is very important that you keep taking all your medicines exactly as prescribed.

Telzir will not stop you passing on HIV. HIV infection is spread by sexual contact with someone who’s got the infection, or by transfer of infected blood (for example by sharing needles).

2. What you need to know before you take Telzir

Telzir is to be taken in combination with low doses of ritonavir and other antiretroviral medicines. It is therefore important that you carefully read the package leaflet 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 allergic** to fosamprenavir, amprenavir or any of the other ingredients of this medicine (listed in section 6), or to ritonavir.

- **if you are taking any of these medicines:**

- alfuzosin (used to treat **a prostate problem**)
- astemizole or terfenadine (commonly used to treat **allergy** symptoms – these medicines may be available without prescription)
- pimozide (used to treat **schizophrenia**)
- quetiapine (used to treat **schizophrenia**, **bipolar disorder** and **major depressive disorder**)
- cisapride (used to relieve **indigestion**)
- ergot derivatives (used to treat **headaches**)
- rifampicin (used to treat **tuberculosis**)
- amiodarone, quinidine, flecainide and propafenone (**heart medicines**)
- bepridil (used to treat **high blood pressure**)
- oral midazolam or oral triazolam **(**used to treat **anxiety)**
- products containing St John's wort (*Hypericum perforatum*)
- lovastatin, simvastatin (used to lower **cholesterol**)
- sildenafil if used to treat **pulmonary arterial hypertension**, (a condition affecting the blood vessels to your lungs)
- paritaprevir (used to treat hepatitis C virus infection)

→Tell your doctor if any of these applies to you.

Take special care with Telzir
Talk to your doctor or pharmacist before taking Telzir:

- **If you have a known allergy to medicines containing sulphonamide**. You may also be allergic to Telzir.
- **If you have liver disease**. Your doctor may lower your dose of Telzir and ritonavir depending on the amount of liver damage. You will be monitored while you are taking Telzir. If your liver disease gets worse, you may need to stop taking Telzir for a while, or permanently. People with hepatitis B or C taking combination therapy are at increased risk of getting severe liver problems.
- **If you have haemophilia**. Increased bleeding may occur while taking protease inhibitors (such as Telzir). 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 antiretroviral medicines including protease inhibitors, there have been reports of increased sugar in the blood and diabetes getting worse. Also, some people have become diabetic while taking these medicines.
- If you are taking any other medicines. See section 'Other medicines and Telzir'.

→Tell your doctor if any of these apply to you. You will need extra check-ups, including blood tests, while you're taking your medication.

Your doctor will monitor your blood glucose levels before and during treatment with Telzir.

Look out for important symptoms
Some people taking medicines for HIV infection develop other conditions, which can be serious. These include:

- Flare up of old infections
- Change in your body shape
- Problems with your bones.

You need to know about important signs and symptoms to look out for while you're taking Telzir. **Please read the information on 'Other side effects of combination therapy for HIV' in section 4 of this leaflet.** If you have any questions about this information or the advice given:
→Talk to your doctor.

You may get a skin rash.
However you can still continue to take Telzir. It can be treated with antihistamines. Rarely, the skin rash can be severe and serious (*Stevens Johnson syndrome*). If this happens, Telzir must be stopped immediately and you must never take it again.

Protect other people
HIV infection is spread by sexual contact with someone who has the infection, or by transfer of infected blood (for example, by sharing injection needles). You can still pass on HIV when taking this medicine, although the risk is lowered by effective antiretroviral therapy. Discuss with your doctor the precautions needed to avoid infecting other people.

Other medicines and Telzir
Tell your doctor or pharmacist if you're taking or have recently taken any other medicines – these include herbal medicines or other medicines you bought without a prescription.
Your doctor will decide if these medicines are suitable for you to take with Telzir and ritonavir. This is **very important**, as Telzir or ritonavir can strengthen or weaken the effects of other medicines. This can sometimes lead to serious medical conditions.

There are some medicines that must not be taken with Telzir. You must check the list of medicines under 'Don't take Telzir' at the beginning of section 2 of this leaflet.

These medicines are not recommended with Telzir/ritonavir:
- doses of ketoconazole and itraconazole greater than 200 mg per day (used to treat **fungal infections**)
- doses of rifabutin greater than 150 mg every other day (an **antibiotic**)
- lidocaine given by injection
- halofantrine (used to treat **malaria**)
- sildenafil, vardenafil or tadalafil (used to treat **erectile dysfunction**)
- doses of atorvastatin greater than 20 mg per day (used to lower **cholesterol**)
- fluticasone propionate and similar medicines used to treat **asthma**, unless considered essential. In this case close monitoring is required.
- lopinavir/ritonavir combination (used to treat **HIV infection**)
- raltegravir (used to treat **HIV infection**)
- telaprevir,boceprevir, simeprevir, daclatasvir (used to treat **hepatitis C virus infection**)
- maraviroc (used to treat **HIV infection**)

You will be closely monitored if you are taking these medicines with Telzir/ritonavir:
- atorvastatin up to 20 mg per day (used to lower **cholesterol)**
- carbamazepine, phenobarbital, phenytoin (used to treat **epilepsy**)
- cyclosporin, rapamycin, tacrolimus (used to suppress the **immune system**)
- dolutegravir (used to treat **HIV infection**)
- desipramine, nortriptyline, paroxetine and similar medicines (used to treat **depression**)
- warfarin and other medicines that **stop blood clotting**
- injectable midazolam (used to treat **anxiety**)
- clarithromycin, erythromycin (an **antibiotic**)
- methadone (a **heroin substitute**)

Your dose of Telzir may need to be changed if you are taking
- etravirine (used to treat **HIV infection**)

Hormonal contraception
Taking Telzir and ritonavir while taking the contraceptive pill may harm your liver and may stop the contraceptive from working properly.
→ **Use an alternative non-hormonal type of contraception such as a condom.**
No studies have been done on the use of Telzir/ritonavir with other hormonal therapies, such as hormone replacement therapy (HRT).

Taking Telzir and food
Adults should take the Telzir oral suspension **without food** and on an empty stomach.
Children and adolescents should take the Telzir oral suspension **with food.**

Pregnancy
If you are pregnant, think you may be pregnant, or are planning to have a baby:
→**Ask your doctor or pharmacist for advice before** taking this medicine.

Breast-feeding
Women who are HIV-positive must not breast-feed because HIV infection can be passed on to the baby in breast milk. It is not known whether the ingredients in Telzir can also pass into your breast milk. If you are breast-feeding, or thinking about breast-feeding:
→**Talk to your doctor immediately.**

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

Driving and using machines
Telzir can make you feel dizzy and have other side effects that make you less alert.
→ **Don't drive or operate machinery** unless you're feeling well.

Stay in regular contact with your doctor
Telzir helps to control your condition, but it is not a cure for HIV infection. You need to keep taking it every day to stop your illness getting worse. You may still develop other infections and illnesses linked to HIV infection.
→ **Keep in touch with your doctor**, and **don't stop taking Telzir** without your doctor's advice.

3. How to take Telzir

Always take this medicine exactly as your doctor or pharmacist has told you. It is very important that you take the **full** daily dose of Telzir and ritonavir as prescribed by your doctor. **Do not take more** than the recommended dose. Check with your doctor or pharmacist if you are not sure.

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

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

Adults
Adults should take Telzir oral suspension **without** food and on an empty stomach.
The recommended dose is **14 ml Telzir oral suspension** (700 mg fosamprenavir) **twice daily** with 100 mg ritonavir (as capsule or oral solution) twice daily.

Children from 6 years of age and weighing at least 25 kg
Children should take the Telzir oral suspension **with food.**

Your doctor will work out the right dose based on your **weight.**

The recommended dose is **0.36 ml/kg** of Telzir oral suspension (18 mg per kg fosamprenavir) **twice daily** with 3 mg/kg ritonavir oral solution twice daily.

No dosing recommendations can be made for children weighing less than 25 kg.

Children can take the adult dose of ritonavir capsules (100 mg twice daily) if they weigh at least 33 kg and can swallow the capsules whole.

As an alternative to taking Telzir oral suspension:
Children can take the adult dose of **one 700 mg Telzir tablet twice daily (**with ritonavir 100 mg twice daily) if they weigh at least 39 kg and can swallow the tablets whole.

Children less than 6 years of age
Telzir is not recommended for children less than 6 years old.

Adults with liver disease
If you have mild liver disease, the dose is **14 ml Telzir oral suspension** (700 mg fosamprenavir) **twice daily** with 100 mg ritonavir only once daily**.** If you have moderate liver disease the dose is **9 ml Telzir oral suspension** (450 mg fosamprenavir) twice daily with 100 mg ritonavir **only once daily**. If you have severe liver disease the dose is 6 ml Telzir oral suspension (300 mg fosamprenavir) twice daily with 100 mg ritonavir **only once daily.**

Step by step instructions
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** and keep it safely.
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. **Turn the bottle** upside down.
6. **Pull out the syringe plunger** until the first portion of your full dose is withdrawn.
7. **Turn the bottle the right way up** and remove the syringe from the adapter.
8. **Put the syringe into your mouth,** placing the tip of the syringe against the inside of your cheek. **Slowly push the plunger in**, allowing time to swallow. **Don't** push too hard and squirt the liquid into the back of the throat or you may choke.
9. **Repeat** steps **4** to **8** in the same way **until you have taken the whole dose**.
10. **Do not leave the syringe in the bottle**. Take the syringe and the adapter off and wash them thoroughly in clean water. Let them dry completely before you use them again.
11. **Close the bottle** tightly with the cap.

If you take too much Telzir
If you have taken more than the prescribed dose of Telzir:
→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 your treatment as before. **Don't take a double dose to make up for a missed dose.**

Don't stop Telzir without advice
Take Telzir for as long as your doctor recommends. Don't stop unless your doctor advises you to.

4. Possible side effects

During HIV therapy there may be an increase in weight and in levels of blood lipids and glucose. This is partly linked to restored health and life style, and in the case of blood lipids sometimes to the HIV medicines themselves. Your doctor will test for these changes.

Like all medicines, this medicine can cause side effects, but not everyone gets them. When treating HIV, it can be hard to tell whether side effects are caused by Telzir, by other medicines taken at the

same time or by the HIV disease itself. For this reason, it is very important to **talk to your doctor about any changes in your health.**

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These may affect **more than 1 in 10 people**:
- Diarrhoea
- Increase in *cholesterol* (a type of blood fat).

Common side effects
These may affect **up to 1 in 10 people**:
- Increases in *triglycerides* (a type of blood fat).
- Feeling sick or being sick (*nausea or vomiting*), pain in the stomach, loose stools
- Skin rashes *(*red, raised or itchy) – if the skin rash is severe, you may have to stop taking this medicine
- Headache, feeling dizzy
- Feeling tired
- Increases in enzymes produced by the liver called *transaminases*, increases of an enzyme produced by the pancreas called *lipase.*
- Tingling or numbness around the lips and mouth.

Uncommon side effects
These may affect **up to 1 in 100 people**:
- Swelling of the face, lips and tongue (*angioedema*).

Rare side effects
These may affect **up to 1 in 1000 people**:
- A severe or life-threatening skin reaction (*Stevens Johnson syndrome*).

You may experience muscle problems
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*). If you notice any muscle problems:
→Tell your doctor.

Haemophiliacs may bleed more
In patients with haemophilia type A and B, there have been reports of increased bleeding while taking protease inhibitors. If this happens to you:
→Talk to your doctor immediately.

If you get any side effects
→Talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet.

Other side effects of combination therapy for HIV

Old infections may flare up
People with advanced HIV infection (AIDS) have weak immune systems and are more likely to develop serious infections (opportunistic infections). When these people start treatment, they may find that old, hidden infections flare up, causing signs and symptoms of inflammation. These symptoms are probably caused by the body's immune system becoming stronger, so that the body starts to fight these infections.

In addition to the opportunistic infections, autoimmune disorders (a condition that occurs when the immune system attacks healthy body tissue) may also occur after you start taking medicines for the treatment of your HIV infection. Autoimmune disorders may occur many months after the start of

treatment. If you notice any symptoms of infection or other symptoms such as muscle weakness, weakness beginning in the hands and feet and moving up towards the trunk of the body, palpitations, tremor or hyperactivity, please inform your doctor immediately to seek necessary treatment.

If you get any symptoms of infection or signs of inflammation while you're taking Telzir:
→Tell your doctor immediately. Don't take other medicines for the infection without your doctor's advice.

You may have problems with your bones
Some people taking combination therapy for HIV develop a condition called *osteonecrosis*. With this condition, parts of the bone tissue die because of reduced blood supply to the bone.

People may be more likely to get this condition:

- if they have been taking combination therapy for a long time
- if they are also taking anti-inflammatory medicines called corticosteroids
- if they drink alcohol
- if their immune systems are very weak
- if they are overweight.

Signs to look out for include:

- stiffness in the joints
- **aches and pains** (especially in the hip, knee or shoulder)
- difficulty moving.

If you notice any of these symptoms:
→Tell your doctor.

Reporting of side effects
If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Telzir

Keep this medicine out of the sight and reach of children.

Do not freeze. Telzir does not require any other special storage conditions.

Do not use this medicine after the expiry date which is stated on the carton and the bottle.

Throw away the bottle 28 days after first opening it, but do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help to protect the environment.

6. Contents of the pack and other information

What Telzir contains

- **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).

What Telzir looks like and contents of the pack

Telzir is supplied in plastic bottles containing 225 ml 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 also available as 700 mg film-coated tablets.

Marketing Authorisation Holder and Manufacturer

Manufacturer	**Marketing Authorisation Holder**
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Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu.