AUSTRALIAN PRODUCT INFORMATION

TELZIR (FOSAMPRENAVIR CALCIUM) TABLETS

1 NAME OF THE MEDICINE

Fosamprenavir calcium

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each TELZIR tablet contains 700 mg of fosamprenavir, as fosamprenavir calcium.

Fosamprenavir is converted in humans to amprenavir. Each TELZIR 700 mg tablet is equivalent to approximately 600 mg of amprenavir.

Fosamprenavir calcium is a white to cream coloured solid.
For the full list of excipients, see Section 6.1 LIST OF EXCIPIENTS.

3 PHARMACEUTICAL FORM

TELZIR are biconvex, capsules-shaped, pinked coloured tablets marked with GXLL7 on one face.

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 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.

4.2 DOSE AND METHOD OF ADMINISTRATION

A physician experienced in the management of HIV infection should initiate therapy.

Fosamprenavir is administered orally.

The tablet can be taken with or without food.

Higher than approved dose combinations of fosamprenavir with ritonavir are not recommended for use (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

Adults (greater than or equal to 18 years of age)
Antiretroviral naïve patients. The recommended dose is 1400 mg fosamprenavir once daily with 200 mg ritonavir once daily or 700 mg (one tablet) fosamprenavir twice daily with 100 mg ritonavir twice daily. Both regimens must be administered in combination with other antiretroviral agents.

Protease inhibitor experienced patients. The recommended dose 700 mg (one tablet) fosamprenavir twice daily with 100 mg ritonavir twice daily. This regimen must be administered in combination with other antiretroviral agents.

The once daily administration of fosamprenavir plus ritonavir is not recommended in protease inhibitor experienced patients.

Each TELZIR 700 mg tablet is equivalent to approximately 600 mg of amprenavir.

Children and adolescent patients (6-18 years of age)
The tablet regimens of fosamprenavir 700 mg twice daily plus 100 mg ritonavir twice daily (for protease inhibitor naïve or experienced patients) may be used in children and adolescents if they weigh at least 39 kg and can swallow the tablets whole.

The tablet can be taken with or without food.

Children (less than 6 years of age)
The safety and efficacy of fosamprenavir in combination with ritonavir has not yet been established in this patient population (see Section 5.1 PHARMACODYNAMIC PROPERTIES, Clinical trials).

Elderly
The pharmacokinetics of fosamprenavir in combination with ritonavir has not been studied in patients over 65 years of age (see Section 5.2 PHARMACOKINETIC PROPERTIES).

Renal impairment
No initial dose adjustment is considered necessary in patients with renal impairment (see Section 5 PHARMACOLOGICAL PROPERTIES).

Hepatic impairment
Fosamprenavir is converted in man to amprenavir. The principal route of amprenavir and ritonavir elimination is hepatic metabolism.

For adults with mild hepatic impairment (C-P score: 5-6). Fosamprenavir should be used with caution and at a reduced dose of 700 mg fosamprenavir twice daily with 100 mg ritonavir once daily.

For adults with moderate (C-P score 7-9) or severe (C-P score 10-15) hepatic impairment. Use of fosamprenavir is not recommended as the reduced dose required in hepatic impairment cannot be achieved using the 700 mg tablet. Alternative options should be considered.

Even with these dose adjustments for adults with hepatic impairment, some subjects may have higher than anticipated amprenavir and ritonavir plasma concentrations due to inter-patient variability, therefore appropriate laboratory tests for liver function should be conducted prior to initiating therapy and at periodic intervals during treatment (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

No dose recommendation can be made for children (2 years to less than 12 years of age) and adolescents (12 to 17 years of age) with hepatic impairment.

4.3 CONTRAINDICATIONS

Known hypersensitivity to fosamprenavir, amprenavir, and ritonavir or to any of the excipients of these medicinal products.

Fosamprenavir in combination with ritonavir must not be administered concurrently with medicinal products with narrow therapeutic windows that are substrates of cytochrome P450 3A4 (CYP3A4). Co-administration may result in competitive inhibition of the metabolism of these medicinal products and create the potential for serious and/or life-threatening adverse events such as cardiac arrhythmia (for example, astemizole, terfenadine, cisapride, pimozide), hypotension (for example, the alpha blocker alfuzosin), prolonged sedation or respiratory depression (for example, triazolam, midazolam, quetiapine) or peripheral vasospasm or ischaemia (for example, ergotamine, dihydroergotamine and ergometrine) (see Section 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS).

Fosamprenavir/ritonavir must not be administered concomitantly with the antipsychotic medicinal product lurasidone. Please refer to the full prescribing information for ritonavir for other potential drug interactions (see Section 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS).

Fosamprenavir/ritonavir must not be administered concomitantly with sildenafil when used for the treatment of pulmonary arterial hypertension (for use of sildenafil in patients with erectile dysfunction see Section 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS). There is increased potential for sildenafil-associated serious adverse events.

Ritonavir also inhibits CYP2D6 *in vitro* and *in vivo* but to a lesser extent than CYP3A4. Fosamprenavir in combination with ritonavir should not be co-administered with medicinal products that are highly dependent on CYP2D6 metabolism and for which elevated plasma concentrations are associated with serious and/or life-threatening results. These medicinal products include flecainide and propafenone (please refer to the full prescribing information of ritonavir for further details) (see Section 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS).

Fosamprenavir in combination with ritonavir must not be administered concurrently with rifampicin due to expected large decreases in plasma concentrations of amprenavir (see

Section 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS).

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

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

Fosamprenavir contains a sulphonamide moiety. The potential for cross-sensitivity between drugs in the sulphonamide class and fosamprenavir is unknown. In the pivotal studies of fosamprenavir, there was no evidence of an increased risk of rashes in patients with a history of sulphonamide allergy that received fosamprenavir versus those who received fosamprenavir and did not have a sulphonamide allergy. Yet, the fosamprenavir/ritonavir combination 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.

Use of fosamprenavir with ritonavir at higher than approved dosages has resulted in elevated transaminase levels in some subjects and are not recommended for use.

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. These interactions may lead to:

- Clinically significant adverse reactions from greater exposures of fosamprenavir/ritonavir or concomitant medications.
- Loss of therapeutic effect of fosamprenavir/ritonavir or concomitant medications and possible development of resistance.

Therefore, co-administration of fosamprenavir/ritonavir is not recommended with HCV DAA drugs, which are metabolised by CYP3A4 or are inducers/inhibitors of CYP3A4, because of the potential for an interaction (for example telaprevir, boceprevir, simeprevir, paritaprevir). In case of concomitant HCV DAA therapy for hepatitis C, please refer to the relevant product information for these medications.

Rash/cutaneous reactions
Most patients with mild or moderate rash can continue the fosamprenavir. 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 subjects included in the clinical development programme.

Fosamprenavir 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 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)).

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

Hyperglycaemia
New onset of diabetes mellitus, hyperglycaemia or exacerbation of existing diabetes mellitus have been reported in patients receiving antiretroviral therapy, including protease inhibitors. Some patients required either initiation or dose adjustments of insulin or oral hypoglycaemic agents for treatment of these events. In some cases, diabetic ketoacidosis has occurred. A causal relationship between protease inhibitor therapy and these events has not been established.

Body fat changes
Combination antiretroviral therapy, including regimens containing a protease inhibitor, may be associated with increased body fat in some patients. A causal relationship has not been established.

Lipid elevations
Treatment with fosamprenavir has resulted in increases in the concentration of triglycerides and cholesterol. Triglyceride and cholesterol testing should be performed prior to initiating therapy with fosamprenavir and at periodic intervals during therapy. Lipid disorders should be managed as clinically appropriate.

Immune reconstitution syndrome
In HIV-infected patients with severe immune deficiency at the time of initiation of antiretroviral therapy (ART), an inflammatory reaction to asymptomatic or residual opportunistic infections 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 ART. Relevant examples are cytomegalovirus retinitis, generalised and/or focal mycobacterial infections and *Pneumocystis jiroveci (P. carinii)* pneumonia. Any inflammatory symptoms must be evaluated without delay and treatment initiated when necessary. Autoimmune disorders (such as Graves' disease, polymyositis and Guillain-Barre syndrome) have also been reported to occur in the setting of immune reconstitution, however, the time to onset is more variable, and can occur many months after initiation of treatment and sometimes can be an atypical presentation.

Information for patients
Patients should be advised that TELZIR, or any other current antiretroviral therapy, does not cure HIV. Patients may still develop opportunistic infections and other complications of HIV infection. Current antiretroviral therapies, including TELZIR, have not been proven to prevent

the risk of transmission of HIV to others through sexual contact or blood contamination. Appropriate precautions should continue to be taken.

Use in hepatic impairment
Amprenavir and ritonavir are both principally metabolised by the liver. Fosamprenavir with ritonavir should be used with caution and at reduced doses in adults with mild, moderate or severe hepatic impairment (see Section 4.2 DOSE AND METHOD OF ADMINISTRATION). Patients with underlying hepatitis B or C or marked elevations in transaminases prior to treatment may be at increased risk of developing transaminase elevations. Appropriate laboratory testing should be conducted prior to initiating therapy and at periodic intervals during treatment.

Use in renal impairment
Since the renal clearance of amprenavir and ritonavir is negligible, increased plasma concentrations are not expected in patients with renal impairment. Because amprenavir and ritonavir are highly protein bound, it is unlikely that haemodialysis or peritoneal dialysis will significantly remove them.

Use in the elderly
See Section 4.2 DOSE AND METHOD OF ADMINISTRATION and Section 5.2 PHARMACOKINETIC PROPERTIES.

Paediatric use
Children (0-6 years of age)
The pharmacokinetics safety and efficacy of fosamprenavir in children below 6 years of age has not yet been fully established (see Section 5.1 PHARMACODYNAMIC PROPERTIES, Clinical trials).

Children and adolescent patients (6-18 years of age)
Fosamprenavir tablets may be used in children and adolescents if they weigh at least 39 kgs and can swallow the tablets whole (see Section 4.2 DOSE AND METHOD OF ADMINISTRATION).

If vomiting occurs within 30 minutes after dosing, the dose should be repeated.

Effects on laboratory tests
See Section 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS), Table 8.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

(See Section 4.3 CONTRAINDICATIONS and Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

Both amprenavir the active metabolite of fosamprenavir and ritonavir are inhibitors of the cytochrome P450 3A4 enzyme (CYP3A4). Consequently, fosamprenavir in combination with ritonavir may increase plasma levels of medicines that have a narrow therapeutic window and are substrates of CYP3A4 and should not be administered concurrently. Other medicinal products that are inducers, inhibitors or substrates of CYP3A4 may also result in serious and/or life-threatening drug interactions. Caution is, therefore, advised whenever

fosamprenavir in combination with ritonavir is co-administered with such products (see Section 4.3 CONTRAINDICATIONS).

Co-administration of fosamprenavir/ritonavir with other antineoplastics metabolised by CYP3A (for example dasatinib, nilotinib, ibrutinib, vinblastine and everolimus) may increase concentrations of these medicinal products, potentially increasing the risk of adverse events usually associated with these agents. Please refer to the relevant product information for these medications.

Co-administration of fosamprenavir and ritonavir with halofantrine is not recommended as halofantrine concentrations may be increased, potentially increasing the risk of serious adverse effects such as cardiac arrhythmia.

The HMG-CoA reductase inhibitors lovastatin and simvastatin are highly dependent on CYP3A4 for metabolism, thus concomitant use of fosamprenavir and ritonavir with simvastatin or lovastatin is not recommended due to an increased risk of myopathy, including rhabdomyolysis. Caution must also be exercised if fosamprenavir and ritonavir are used concurrently with atorvastatin, which is metabolised to a lesser extent by CYP3A4. In this situation, a reduced dose of atorvastatin should be considered. If treatment with an HMG-CoA reductase inhibitor is indicated, pravastatin or fluvastatin are recommended.

Concomitant use of fosamprenavir with ritonavir and fluticasone propionate 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.

Although the isozyme(s) responsible for bepridil metabolism has (have) not been elucidated, the metabolic pathways primarily responsible for bepridil metabolism are mediated by the CYP450 enzyme system. Because amprenavir and ritonavir are inhibitors of the CYP3A4 isozyme, the CYP450 isozyme most commonly responsible for drug metabolism, and because increased plasma bepridil exposure may increase the risk of life-threatening arrhythmia, caution is warranted when amprenavir and bepridil are co-administered.

Serious and/or life-threatening drug interactions could occur between amprenavir and amiodarone, lidocaine (systemic), tricyclic antidepressants, quinidine and warfarin. Concentration monitoring (warfarin - monitor International Normalised Ratio) of these agents is recommended as this should minimise the risk of potential safety problems with concomitant use.

Concomitant use of PDE5 inhibitors (e.g. sildenafil) for the treatment of erectile dysfunction in patients receiving the fosamprenavir/ritonavir combination is not recommended. Concomitant use of fosamprenavir and ritonavir with PDE5 inhibitors is expected to substantially increase PDE5 inhibitor concentrations and may result in PDE5 inhibitor associated adverse events, including hypotension, syncope, visual changes and priapism.

Co-administration of amprenavir with rifabutin results in a 200% increase in rifabutin plasma concentrations (AUC). When ritonavir is co-administered a larger increase in rifabutin concentrations is expected. A reduction of rifabutin dosage of at least 75% the recommended dose is recommended when administered with fosamprenavir and ritonavir and patients clinically monitored.

Concomitant use of the fosamprenavir/ritonavir combination and products containing *Hypericum perforatum* (also known as St. John's wort) is not recommended. A

pharmacokinetic study with indinavir indicates that *Hypericum perforatum* may reduce amprenavir and/or ritonavir serum concentrations when administered concomitantly.

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.

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.

Fosamprenavir/ritonavir must not be administered concomitantly with sildenafil when used for the treatment of pulmonary arterial hypertension. There is increased potential for sildenafil-associated serious adverse events (see Section 4.3 CONTRAINDICATIONS).

Ritonavir, as well as being a potent inhibitor of CYP3A4, is also an inhibitor of CYP2D6 and an inducer of CYP1A2, CYP2C9 and glucuronosyl transferase. Fosamprenavir in combination with ritonavir should not be co-administered with medicinal products that are highly dependent on CYP2D6 metabolism and for which elevated plasma concentrations are associated with serious and/or life-threatening results. These medicinal products include flecainide and propafenone (see Section 4.3 CONTRAINDICATIONS). The full prescribing information of Norvir (ritonavir) should be referred to prior to undertaking the dosing regimen of fosamprenavir and ritonavir.

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 fosamprenavir and ritonavir.

Interaction studies have only been performed in adults.

Interactions involving CYP3A4
The medications listed below include examples of substrates, inhibitors, or inducers of CYP3A4 that could interact with fosamprenavir in combination with ritonavir when used concomitantly. This list is not exhaustive. In some cases the clinical significance of these potential interactions is unknown and has not been studied. Patients should therefore be monitored for toxicities associated with such medicines when they are used in combination with fosamprenavir and ritonavir.

Interactions involving CYP2D6
Ritonavir is an inhibitor of CYP2D6. Therefore, fosamprenavir in combination with ritonavir may result in increased plasma concentrations of medicinal products that are primarily metabolised by CYP2D6 (see Section 4.3 CONTRAINDICATIONS and Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

Additional associations, precautions for use
Drug interaction studies were performed with TELZIR and other drugs likely to be co-administered or drugs commonly used as probes for pharmacokinetic interactions. The effects of co-administration on AUC, C_{max} and C_{min} values are summarised in Table 1 (effect of other drugs on amprenavir) and Table 3 (effect of TELZIR on other drugs). In addition, since TELZIR delivers comparable amprenavir plasma concentrations as Agenerase, drug interaction data derived from studies with Agenerase are provided in Tables 2 and 4. For information regarding clinical recommendations, see Tables 5 and 6.

Table 1: Drug Interactions: Pharmacokinetic Parameters for Amprenavir in the Presence of the Co-administered Drug After Administration of TELZIR

Co-administered Drug(s) and Dose(s)	Dose of fosamprenavir [a]	n	% Change in amprenavir Pharmacokinetic Parameters (90% CI)		
			C_{max}	AUC	C_{min}
Antacid (MAALOX TC) 30 mL single dose	1,400 mg single dose	30	↓35 (↓24 to ↓42)	↓18 (↓9 to ↓26)	↑14 (↓7 to ↑39)
Atorvastatin 10 mg Once daily for 4 days	1,400 mg twice daily for 2 weeks	16	↓18 (↓34 to ↑1)	↓27 (↓41 to ↓12)	↓12 (↓27 to ↑6)
Atorvastatin 10 mg Once daily for 4 days	700 mg twice daily plus RTV100 mg twice daily for 2 weeks	16	⇔	⇔	⇔
Efavirenz 600 mg Once daily for 2 weeks	1,400 mg Once daily plus RTV 200 mg Once daily for 2 weeks	16	⇔	↓13 (↓30 to ↑7)	↓36 (↓8 to ↓56)
Efavirenz 600 mg Once daily plus RTV 100 mg Once daily for 2 weeks	1,400 mg Once daily plus RTV 200 mg Once daily for 2 weeks	16	↑18 (↑1 to ↑38)	↑11 (0 to ↑24)	⇔
Efavirenz 600 mg Once daily for 2 weeks	700 mg twice daily plus RTV 100 mg twice daily for 2 weeks	16	⇔	⇔	↓17 (↓4 to ↓29)
Esomeprazole 20 mg once daily for 2 weeks	1,400 mg twice daily for 2 weeks	25	⇔	⇔	⇔
Esomeprazole 20 mg once daily for 2 weeks	700 mg twice daily plus ritonavir 100 mg twice daily for 2 weeks	23	⇔	⇔	⇔
Ethinyl estradiol/ norethisterone 0.035 mg/0.5 mg once daily. for 21 days	700 mg twice daily plus ritonavir 100 mg-twice daily for 21 days	25	⇔	⇔	⇔
Nevirapine 200 mg twice daily for 2 weeks	1,400 mg twice daily for 2 weeks	17	↓25 (↓37 to ↓10)	↓33 (↓45 to ↓20)	↓35 (↓50 to ↓15)
Nevirapine 200 mg twice daily. for 2 weeks	700 mg twice daily plus ritonavir 100 mg twice daily for 2 weeks	17	⇔	↓11 (↓23 to ↑3)	↓19 (↓32 to ↓4)

Co-administered Drug(s) and Dose(s)	**Dose of fosamprenavir [a]**	**n**	**% Change in amprenavir Pharmacokinetic Parameters (90% CI)**		
			C_{max}	**AUC**	**C_{min}**
Lopinavir/Ritonavir 533 mg/133 mg twice daily for 2 weeks	1,400 mg twice daily for 2 weeks	18	↓13[b] (↓26 to ↑2)	↓26[b] (↓15 to ↓35)	↓42[b] (↓30 to ↓52)
Lopinavir/Ritonavir 400 mg/100 mg twice daily for 2 weeks	700 mg twice daily plus RTV 100 mg twice daily for 2 weeks	18	↓58 (↓42 to ↓70)	↓63 (↓51 to ↓72)	↓65 (↓54 to ↓73)
Ranitidine 300 mg single dose	1,400 mg single dose	30	↓51 (↓43 to ↓58)	↓30 (↓22 to ↓37)	⇔ (↓19 to ↑21)
Maraviroc 300 mg twice daily	700 mg twice daily plus RTV 100 mg twice daily (12 h)	14	↓34 (↓25 to ↓41)	↓35 (↓29 to ↓41)	↓36 (↓27 to ↓43)
Maraviroc 300 mg once daily	1400 mg once plus RTV 100 mg once daily (24h)	14	↓29 (↓20 to ↓38)	↓30 (↓23 to ↓36)	↓15 (↓3 to ↓25)

a. Concomitant baseline medication is also shown in this column where appropriate.
b. Compared with fosamprenavir 700 mg twice daily plus RTV 100 mg twice daily.
↑ = Increase; ↓ = Decrease; ⇔ = No change (↑ or ↓<10%); NA = C_{min} not calculated for single-dose study.

Table 2: Drug Interactions: Pharmacokinetic Parameters for Amprenavir After Administration of Agenerase in the Presence of the Co-administered Drug

Co-administered Drug(s) and Dose(s)	Dose of Agenerase [a]	n	% Change in amprenavir Pharmacokinetic Parameters (90% CI)		
			C_{max}	AUC	C_{min}
Clarithromycin 500mg twice daily for 4 days	1200mg twice daily for 4 days	12	↓35 (↑1 to ↑31)	↑18 (↑8 to ↑29)	↑39 (↑31 to ↑47)
Delavirdine 600mg twice daily for 10 days	600mg twice daily for 10 days	9	↑40*	↑130*	↑125*
Ethinyl estradiol/ norethisterone 0.035mg/1mg for 1 cycle	1200mg twice daily for 28 days	10	⇔	↓22 (↓35 to ↓8)	↓20 (↓41 to ↑8)
Indinavir 800mg three times daily for 2 weeks (fasted)	750 or 800mg three times daily for 2 weeks (fasted)	9	↑18 (↓13 to ↑58)	↑33 (↓2 to ↑73)	↑25 (↓27 to ↑116)
Ketoconazole 400mg single dose	1200mg single dose	12	↓16 (↓25 to ↓6)	↑31 (↑20 to ↑42)	NA
Lamivudine 150mg single dose	600mg single dose	11	⇔	⇔	NA
Nelfinavir 750mg three times daily for 2 weeks (fed)	750 or 800mg three times daily for 2 weeks (fed)	6	↓14 (↓38 to ↑20)	⇔	↑189 (↑52 to ↑448)
Rifabutin 300mg once daily for 10 days	1200mg-twice daily for 10 days	5	⇔	↓15 (↓28 to 0)	↓15 (↓38 to ↑17)
Rifabutin 300mg once daily for 4 days	1200mg twice daily for 4 days	11	↓70 (↓76 to ↓62)	↓82 (↓84 to ↓78)	↓92 (↓95 to ↓89)
Saquinavir 800mg three times daily for 2 weeks (fed)	750 or 800mg three times daily for 2 weeks (fed)	7	↓37 (↓54 to ↓14)	↓32 (↓49 to ↓9)	↓14 (↓52 to ↑54)
Zidovudine 300mg single dose	600mg single dose	12	⇔	↓13 (↓2 to ↑31)	NA

* Median percent change, confidence interval not reported.

a. Concomitant baseline medication is also shown in this column where appropriate.

↑ = Increase; ↓ = Decrease; ⇔ = No change (↑ or ↓<10%); NA = C_{min} not calculated for single-dose study.

Table 3: Drug Interactions: Pharmacokinetic Parameters for Co-administered Drug in the Presence of Amprenavir After Administration of TELZIR

Co-administered Drugs and Dose(s)	Dose of fosamprenavir [a]	n	% Change in Pharmacokinetic Parameters of Co-administered Drug (90% CI)		
			C_{max}	AUC	C_{min}
Atorvastatin 10 mg once daily for 4 days	1,400 mg twice daily for 2 weeks	16	↑304 (↑205 to ↑437)	↑130 (↑100 to ↑164)	↓10 (↓27 to ↑12)
Atorvastatin 10 mg Once daily for 4 days	700 mg twice daily plus RTV 100 mg twice daily for 2 weeks	16	↑184 (↑126 to ↑257)	↑153 (↑115 to ↑199)	↑73 (↑45 to ↑108)
Esomeprazole 20 mg once daily for 2 weeks	1,400 mg twice daily for 2 weeks	25	⇔	↑55 (↑39 to ↑73)	ND
Esomeprazole 20 mg once daily for 2 weeks	700 mg twice daily plus ritonavir 100 mg twice daily for 2 weeks	23	⇔	⇔	ND
Ethinyl oestradiol 0.035 mg once daily for 21 days	700 mg twice daily plus ritonavir 100 mg twice daily for 21 days	25	↓28 (↓21 to ↓35)	↓37 (↓30 to ↓42)	ND
Nevirapine 200 mg twice daily. for 2 weeks	1,400 mg twice daily for 2 weeks	17	↑25 (↑14 to ↑37)	↑29 (↑19 to ↑40)	↑34 (↑20 to ↑49)
Nevirapine 200 mg twice daily. for 2 weeks	700 mg twice daily plus ritonavir 100 mg twice daily for 2 weeks	17	↑13 (↑3 to ↑24)	↑14 (↑5 to ↑24)	↑22 (↑9 to ↑35)
Lopinavir/Ritonavir[b] 533 mg/133 mg twice daily for 2 weeks	1,400 mg twice daily for 2 weeks	18	⇔[c]	⇔[c]	⇔[c]
Lopinavir/Ritonavir[b] 400 mg/100 mg twice daily for 2 weeks	700 mg twice daily plus RTV 100 mg twice daily for 2 weeks	18	↑30 (↓15 to ↑47)	↑37 (↓20 to ↑55)	↑52 (↓28 to ↑82)
Maraviroc 300 mg twice daily	700 mg twice daily plus RTV 100 mg twice daily (12 h)	14	↑52 (↑27 to ↑82)	↑149 (↑119 to ↑182)	↑374 (↑303 to ↑457)
Maraviroc 300 mg once daily	1400 mg once plus RTV 100 mg once daily (24h)	14	↑45 (↑20 to ↑74)	↑126 (↑99 to ↑158)	↑80 (↑53 to ↑113)

c. Concomitant baseline medication is also shown in this column where appropriate.
d. Data represent LPV concentrations.
e. Compared with LPV/RTV 400 mg/100 mg.

↑ = Increase; ↓ = Decrease; ⇔ = No change (↑ or ↓<10%); NA = C_{min} not calculated for single-dose study. ND = interaction cannot be determined as **C_{min}** was below the lower limit of quantification

Table 4: Drug Interactions: Pharmacokinetic Parameters for Co-administered Drug in the Presence of Amprenavir After Administration of Agenerase

Co-administered Drug(s) and Dose(s)	Dose of Agenerase [a]	n	% Change in Pharmacokinetic Parameters of Co-administered Drug (90% CI)		
			C_{max}	AUC	C_{min}
Clarithromycin 500mg twice daily for 4 days	1200mg twice daily for 4 days	12	↓10 (↓24 to ↑7)	⇔	⇔
Delavirdine 600mg twice daily for 10 days	600mg twice daily for 10 days	9	↓47*	↓61*	↓88*
Ethinyl estradiol/ norethisterone 0.035mg/1mg for 1 cycle	1200mg twice daily for 28 days	10	⇔	⇔	↑32 (↓3 to ↑79)
Ketoconazole 400mg single dose	1200mg single dose	12	↑19 (↑8 to ↑33)	↑44 (↑31 to ↑59)	NA
Lamivudine 150mg single dose	600mg single dose	11	⇔	⇔	NA
Methadone 44 to 100mg once daily for >30 days	1200mg twice daily for 10 days	16	R-Methadone (active)		
			↓25 (↓32 to ↓18)	↓13 (↓21 to ↓5)	↓21 (↓32 to ↓9)
			S-Methadone (inactive)		
			↓48 (↓55 to ↓40)	↓40 (↓46 to ↓32)	↓53 (↓60 to ↓43)
Norethisterone 1mg for 1 cycle	1200mg twice daily for 28 days	10	⇔	↑18 (↑1 to ↑38)	↑45 (↑13 to ↑88)
Rifabutin 300mg once daily for 10 days	1200mg twice daily for 10 days	5	↑119 (↑82 to ↑164)	↑193 (↑156 to ↑235)	↑271 (↑171 to ↑409)
Rifabutin 300mg once daily for 4 days	1200mg twice daily for 4 days	11	⇔	⇔	ND
Zidovudine 300mg single dose	600mg single dose	12	⇔	↑31 (↑19 to ↑45)	NA

* Median percent change, confidence interval not reported.

a. Concomitant baseline medication is also shown in this column where appropriate.

↑ = Increase; ↓ = Decrease; ⇔ = No change (↑ or ↓<10%); NA = C_{min} not calculated for single-dose study; ND = interaction cannot be determined as **C_{min}** was below the lower limit of quantification.

Table 5: Drugs That Should Not Be Co-administered With TELZIR

Drug Class/Drug Name	Clinical Comment
Antiarrhythmics: Flecainide	**CONTRAINDICATED** if TELZIR is co-prescribed with **ritonavir** due to potential for serious and/or life-threatening reactions such as cardiac arrhythmias secondary to increases in plasma concentrations of antiarrhythmics.
Antihistamines: Astemizole, terfenadine	**CONTRAINDICATED** due to potential for serious and/or life-threatening reactions such as cardiac arrhythmias.
Antimycobacterials: Rifampicin	May lead to loss of virologic response and possible resistance to TELZIR or to the class of protease inhibitors.
Ergot derivatives: Dihydroergotamine, ergotamine	**CONTRAINDICATED** due to potential for serious and/or life-threatening reactions such as acute ergot toxicity characterized by peripheral vasospasm and ischaemia of the extremities and other tissues.
GI motility agents: Cisapride	**CONTRAINDICATED** due to potential for serious and/or life-threatening reactions such as cardiac arrhythmias.
Herbal products: St. John's wort (hypericum perforatum)	May lead to loss of virologic response and possible resistance to TELZIR or to the class of protease inhibitors.
HMG co-reductase inhibitors: Lovastatin, simvastatin	Potential for serious reactions such as risk of myopathy including rhabdomyolysis.
Neuroleptic: Pimozide	**CONTRAINDICATED** due to potential for serious and/or life-threatening reactions such as cardiac arrhythmias.
Non-nucleoside reverse transcriptase inhibitor: Delavirdine	May lead to loss of virologic response and possible resistance to delavirdine.
Sedative/hypnotics: Midazolam, triazolam, quetiapine	**CONTRAINDICATED** due to potential for serious and/or life-threatening reactions such as prolonged or increased sedation or respiratory depression.
Oral contraceptives: Ethinyl oestradiol/norethisterone	Alternative methods of non-hormonal contraception are recommended. **TELZIR/ritonavir:** Increased risk of transaminase elevations. No data are available on the use of TELZIR/ritonavir with other hormonal therapies, such as HRT for postmenopausal women (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE). **TELZIR without ritonavir:** May lead to loss of virologic response (see Section 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS, Table 2).

Antipsychotics: lurasidone.	**CONTRAINDICATED** due to potential for serious and/or life-threatening reactions
PDE5 inhibitors: Sildenafil	**CONTRAINDICATED** when used for the treatment of pulmonary arterial hypertension. There is increased potential for sildenafil-associated serious adverse events.
Alpha blockers: Alfuzosin	**CONTRAINDICATED** due to potential for serious and/or life-threatening reactions such as hypotension

Table 6: Established and other Potentially Significant Drug Interactions: Alteration in dose or regimen may be recommended based on drug interaction studies or predicted Interaction (Information in the table applies to TELZIR with or without ritonavir, unless otherwise indicated.)

Concomitant Drug Class: Drug Name	Effect on Concentration of Amprenavir or Concomitant Drug	Clinical Comment
HIV-Antiviral Agents		
Non-nucleoside reverse transcriptase inhibitor: Efavirenz	**TELZIR:** ↓Amprenavir **TELZIR/ritonavir:** ↓Amprenavir	Appropriate doses of the combinations with respect to safety and efficacy have not been established. An additional 100 mg/day (300 mg total) of ritonavir is recommended when efavirenz is administered with TELZIR/ritonavir once daily. No change in the ritonavir dose is required when efavirenz is administered with TELZIR plus ritonavir twice daily.
Non-nucleoside reverse transcriptase inhibitor: Nevirapine	**TELZIR:** ↓Amprenavir ↑Nevirapine **TELZIR/ritonavir:** ↓Amprenavir ↑Nevirapine	Co-administration of nevirapine and TELZIR without ritonavir is not recommended. No dosage adjustment required when nevirapine is administered with TELZIR/ritonavir twice daily. The combination of nevirapine administered with TELZIR/ritonavir once-daily regimen has not been studied.
HIV protease inhibitor: Atazanavir	**TELZIR:** Interaction has not been evaluated. **TELZIR/ritonavir:**	Appropriate doses of the combinations with respect to safety and efficacy have not been established.

Concomitant Drug Class: Drug Name	Effect on Concentration of Amprenavir or Concomitant Drug	Clinical Comment
	↓Atazanavir ↔Amprenavir	
HIV protease inhibitors: Indinavir, nelfinavir	**TELZIR:** ↑Amprenavir Effect on indinavir and nelfinavir is not well established. **TELZIR/ritonavir:** Interaction has not been evaluated.	Appropriate doses of the combinations with respect to safety and efficacy have not been established.
HIV protease inhibitors: Lopinavir/ritonavir	↓Amprenavir ↓Lopinavir	An increased rate of adverse events has been observed with co-administration of these medications. Appropriate doses of the combinations with respect to safety and efficacy have not been established.
HIV protease inhibitor: Saquinavir	**TELZIR:** ↓Amprenavir Effect on saquinavir is not well established. **TELZIR/ritonavir:** Interaction has not been evaluated.	Appropriate doses of the combination with respect to safety and efficacy have not been established.
Other Agents		
Antiarrhythmics: Amiodarone, lidocaine (systemic), and quinidine	↑Antiarrhythmics	Caution is warranted and therapeutic concentration monitoring, if available, is recommended for antiarrhythmics when co-administered with TELZIR.
Antiarrhythmic: Bepridil	↑Bepridil	Use with caution. Increased bepridil exposure may be associated with life-threatening reactions such as cardiac arrhythmias.
Anticoagulant: Warfarin		Concentrations of warfarin may be affected. It is recommended that

Concomitant Drug Class: Drug Name	Effect on Concentration of Amprenavir or Concomitant Drug	Clinical Comment
		INR (international normalized ratio) be monitored.
Anticonvulsants: Carbamazepine, phenytoin	↓Amprenavir	Use with caution. TELZIR may be less effective due to decreased amprenavir plasma concentrations in patients taking these agents concomitantly.
Antifungals: Ketoconazole, itraconazole	↑Ketoconazole ↑Itraconazole	Increase monitoring for adverse events due to ketoconazole or itraconazole. **TELZIR:** Dose reduction of ketoconazole or itraconazole may be needed for patients receiving more than 400 mg ketoconazole or itraconazole per day. **TELZIR/ritonavir:** High doses of ketoconazole or itraconazole (>200 mg/day) are not recommended.
Antimycobacterial: Rifabutin	↑Rifabutin and rifabutin metabolite	A complete blood count should be performed weekly and as clinically indicated in order to monitor for neutropenia in patients receiving TELZIR and rifabutin. **TELZIR:** A dosage reduction of rifabutin by at least half the recommended dose is required. **TELZIR/ritonavir:** Dosage reduction of rifabutin by at least 75% of the usual dose of 300 mg/day is recommended (a maximum dose of 150 mg every other day or 3 times per week).
Benzodiazepines: Alprazolam, clorazepate, diazepam	↑Benzodiazepines	Clinical significance is unknown; however, a decrease in benzodiazepine dose may be needed.
Calcium channel blockers: Diltiazem, felodipine, nifedipine, nicardipine,	↑Calcium channel blockers	Caution is warranted and clinical monitoring of patients is recommended.

Concomitant Drug Class: Drug Name	Effect on Concentration of Amprenavir or Concomitant Drug	Clinical Comment
nimodipine, verapamil, amlodipine, isradipine		
Corticosteroid: Dexamethasone	↓Amprenavir	Use with caution. TELZIR may be less effective due to decreased amprenavir plasma concentrations in patients taking these agents concomitantly.
Oral Contraceptives: Ethinyl oestradiol/ norethisterone	Ethinyl oestradiol/ norethisterone	Because hormonal levels may be altered, alternative methods of non-hormonal contraception are recommended.
Histamine H_2-receptor antagonists: Cimetidine, famotidine, nizatidine, ranitidine	**TELZIR:** ↓Amprenavir **TELZIR/ritonavir:** Interaction not evaluated	Use with caution. TELZIR may be less effective due to decreased amprenavir plasma concentrations in patients taking these agents concomitantly.
HMG-CoA reductase inhibitor: Atorvastatin	↑Atorvastatin	Use ≤20 mg/day of atorvastatin with careful monitoring, or consider other HMG-CoA reductase inhibitors such as fluvastatin, pravastatin, or rosuvastatin in combination with TELZIR.
Immunosuppressants: Cyclosporin, tacrolimus, rapamycin	↑Immunosuppressant	Therapeutic concentration monitoring is recommended for immunosuppressant agents when co-administered with TELZIR.
Inhaled/nasal steroid: Fluticasone	**TELZIR:** ↑Fluticasone **TELZIR/ritonavir:** ↑Fluticasone	Concomitant use of fluticasone propionate and TELZIR (without ritonavir) may increase plasma concentrations of fluticasone propionate. Use with caution. Consider alternatives to fluticasone propionate, particularly for long-term use. Concomitant use of fluticasone propionate and TELZIR/ritonavir may increase plasma concentrations of fluticasone propionate, resulting in significantly reduced serum cortisol concentrations. Co-administration

Concomitant Drug Class: Drug Name	Effect on Concentration of Amprenavir or Concomitant Drug	Clinical Comment
		of fluticasone propionate and TELZIR/ritonavir is not recommended unless the potential benefit to the patient outweighs the risk of systemic corticosteroid side effects (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).
Narcotic analgesic: Methadone	↓Methadone	No dose adjustment is necessary when TELZIR/ritonavir is co-administered with methadone.
PDE5 inhibitors: Sildenafil,tadalafil, vardenafil	↑Sildenafil ↑Tadalafil ↑Vardenafil	Use with caution at reduced doses with increased monitoring for adverse events. TELZIR/ritonavir must not be administered concomitantly with sildenafil when used for the treatment of pulmonary arterial hypertension.
Proton pump inhibitors: Esomeprazole, lansoprazole, omeprazole, pantoprazole, rabeprazole	**TELZIR:** ↔Amprenavir ↑Esomeprazole **TELZIR/ritonavir:** ↔Amprenavir ↔Esomeprazole	Proton pump inhibitors can be administered at the same time as a dose of TELZIR with no change in plasma amprenavir concentrations.
Tricyclic antidepressants: Amitriptyline, imipramine	↑Tricyclics	Therapeutic concentration monitoring is recommended for tricyclic antidepressants when co-administered with TELZIR.

Antiretroviral agents

Non-nucleoside reverse transcriptase inhibitors

Nevirapine: The AUC and C_{min} of amprenavir were decreased by 11% and 19%, respectively, with C_{max} unchanged when fosamprenavir (700 mg twice daily) plus ritonavir (100 mg twice daily) was given concomitantly with nevirapine (200 mg twice daily). The AUC, C_{max} and C_{min} of nevirapine were increased by 14%, 13% and 22%, respectively. Therefore, if nevirapine is given in combination with fosamprenavir (700 mg twice daily) plus ritonavir (100 mg twice daily), no dose adjustment is necessary. The fosamprenavir with ritonavir once daily regimen has not been studied.

Delavirdine: No dose recommendations can be given for the co-administration of the fosamprenavir/ritonavir combination and delavirdine.

Nucleoside/nucleotide reverse transcriptase inhibitors
No dose adjustment is considered necessary when the following antiretroviral agents are co-administered with fosamprenavir: zidovudine, didanosine, stavudine, lamivudine, abacavir and tenofovir.

Protease inhibitors
No dose recommendation can be given for the use of fosamprenavir and ritonavir in combination with other protease inhibitors. Available interaction data are presented in Tables 1-4.

Atazanavir: Co-administration of fosamprenavir (700 mg twice daily) plus ritonavir (100 mg twice daily) with atazanavir (300 mg once daily) for 10 days had no effect on steady-state plasma amprenavir pharmacokinetics. Atazanavir plasma $AUC_{(0-\tau)}$ decreased by 22%, C_{max} by 24% and $C\tau$ remained unchanged relative to values obtained from atazanavir (300 mg once daily) plus ritonavir (100 mg once daily).

Integrase inhibitors
Raltegravir: There is potential for a pharmacokinetic interaction with co-administration of fosamprenavir/ritonavir 700/100 mg twice daily and raltegravir 400 mg twice daily. This may lead to reductions in the C_{min} of both medicinal products. The clinical significance of these reductions is unknown.

Dolutegravir: Amprenavir pharmacokinetics were unchanged following co-administration of fosamprenavir/ritonavir 700/100 mg twice daily with dolutegravir 50 mg once daily. Dolutegravir $AUC_{(0-\tau)}$, C_{max}, and $C\tau$ were reduced by 35%, 24%, and 49%, respectively, when combined fosamprenavir/ritonavir. No dosage adjustment of fosamprenavir or dolutegravir is recommended based on observed exposure-response relationships of clinical data. Caution is warranted and clinical monitoring is recommended when these combinations are given in integrase inhibitor-resistant patients.

CCR5-receptor antagonists
Maraviroc: A decrease in amprenavir C_{12h} of 36% was observed when fosamprenavir 700 mg and ritonavir 100 mg twice daily were co-administered with maraviroc 300 mg twice daily and a decrease in amprenavir C_{24h} of 15% when fosamprenavir 1400 mg and ritonavir 100 mg once daily were co-administered with maraviroc 300 mg once daily (see Table 1). Clinical studies showed comparable efficacy between fosamprenavir/ritonavir with maraviroc 150 mg twice daily and other boosted PIs with maraviroc 150 mg twice daily. Maraviroc exposures are increased by approximately 2-fold when administered with fosamprenavir/ritonavir (see Table 3). If fosamprenavir/ritonavir is co-administered with maraviroc, the recommended dose of maraviroc is 150 mg twice daily. No dosage adjustment is required for fosamprenavir with ritonavir.

Anti-hepatitis C medicinal products
Telaprevir: Concomitant administration of fosamprenavir with ritonavir and telaprevir results

in reduced steady-state exposure to both amprenavir and telaprevir. The mechanism of interaction is unknown. Concomitant administration of fosamprenavir with ritonavir and telaprevir is not recommended.

Antibiotics / antifungals
Clarithromycin: Ritonavir increases plasma concentrations of clarithromycin. A reduction in the clarithromycin dose should be considered when co-administered with fosamprenavir and ritonavir in patients with renal impairment.

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

Ketoconazole/itraconazole: Amprenavir and ritonavir both increase plasma concentrations of ketoconazole and are expected to increase itraconazole concentrations. High doses of ketoconazole and itraconazole (> 200 mg/day) should not be used concomitantly with fosamprenavir and ritonavir without assessing the risk/benefit ratio and increased monitoring for adverse events due to ketoconazole and itraconazole.

Rifabutin: Co-administration of amprenavir with rifabutin results in a 200% increase in rifabutin plasma concentrations (AUC) and an increase of rifabutin related adverse events. When ritonavir is co-administered a larger increase in rifabutin concentrations may occur. A reduction of rifabutin dosage of at least 75% the recommended dose is recommended when administered with fosamprenavir and ritonavir. Further dose reduction may be necessary (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

Rifampicin: Co-administration with TELZIR may lead to loss of virologic response and possible resistance to TELZIR or to the class of protease inhibitors.

Other medicinal products
Antacids: No dose adjustment for any of the respective medicinal products is considered necessary when administered concomitantly.

Histamine H_2-receptor antagonist: No dose adjustment for any of the respective medicinal products is considered necessary when administered concomitantly.

Proton pump inhibitors: Co-administration of esomeprazole (20 mg once daily) with fosamprenavir (700 mg twice daily) in combination with ritonavir (100 mg twice daily) for 14 days did not alter plasma amprenavir AUC, C_{max} or C_{min} and did not alter plasma esomeprazole AUC or C_{max}; esomeprazole T_{max} was delayed 1 hour. No dose adjustment for any of the respective medicinal products is considered necessary when administered concomitantly.

For some substances that can cause serious or life-threatening adverse experiences, such as amiodarone, quinidine, lidocaine (by systemic route), tricyclic antidepressants and warfarin (monitor INR), plasma concentration monitoring is available. For these medicinal products, concentration monitoring should reduce the potential for safety problems with concomitant use with fosamprenavir and ritonavir.

Anticonvulsant drugs
Phenytoin: The AUC and C_{min} of amprenavir were increased by 20% and 19%, respectively, with C_{max} unchanged when fosamprenavir (700 mg twice daily) plus ritonavir (100 mg twice daily) was given concomitantly with phenytoin (300 mg once daily). The AUC, C_{max} and C_{min} of phenytoin were decreased by 22%, 20% and 29% respectively. Therefore, if fosamprenavir plus ritonavir is given in combination with phenytoin, no change to the fosamprenavir plus ritonavir dosage regimen is required. However, it is recommended that phenytoin plasma concentrations be monitored and phenytoin dose increased as appropriate. The fosamprenavir with ritonavir once daily regimen has not been studied.

Other anticonvulsants: Concomitant administration of other anticonvulsant agents known as enzymatic inducers (e.g. phenobarbitone and carbamazepine) has not been studied but may lead to a decrease in the plasma concentrations of amprenavir.

Benzodiazepines: Alprazolam, clorazepate, diazepam and flurazepam: serum concentrations may be increased, which could increase their activity (see Section 4.3 CONTRAINDICATIONS).

Calcium channel blockers: Amlodipine, diltiazem, felodipine, isradipine, nicardipine, nifedipine, nimodipine, nisoldipine and verapamil: serum concentrations of these medicines may be increased, which could increase their activity and toxicity.

Dexamethasone: May induce CYP3A4 and decrease plasma concentrations of amprenavir.

PDE5 inhibitors: Based on data for ritonavir and other protease inhibitors, plasma concentrations of PDE5 inhibitors (e.g. sildenafil) are expected to substantially increase when co-administered with fosamprenavir and ritonavir and may result in an increase in PDE5 inhibitor associated adverse events. Concomitant use of PDE5 inhibitors for the treatment of erectile dysfunction or pulmonary arterial hypertension is not recommended. Concomitant use of fosamprenavir/ritonavir is contraindicated in patients being treated with sildenafil for pulmonary arterial hypertension (see Section 4.3 CONTRAINDICATIONS).

Fosamprenavir/ritonavir must not be administered concomitantly with sildenafil when used for the treatment of pulmonary arterial hypertension. There is increased potential for sildenafil associated serious adverse events (see Section 4.3 CONTRAINDICATIONS).

Fluticasone propionate (interaction with ritonavir): Systemic corticosteroid effects including Cushing's syndrome and adrenal suppression have been reported in patients receiving ritonavir and inhaled or intranasally administered fluticasone propionate; this interaction is also expected with other corticosteroids metabolised via the P450 3A pathway (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

Therefore, concomitant use of fluticasone propionate and ritonavir should be avoided, unless the potential benefit to the patient outweighs the risk of systemic corticosteroid side effects.

Halofantrine: Plasma concentrations of halofantrine may increase when co-administered with fosamprenavir and ritonavir and may result in an increase in halofantrine associated adverse

events, such as cardiac arrhythmia. Concomitant use is not recommended (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

HMG-CoA reductase inhibitors: HMG-CoA reductase inhibitors which are highly dependent on CYP3A4 for metabolism, such as atorvastatin, lovastatin and simvastatin, are expected to have markedly increased plasma concentrations when co-administered with fosamprenavir and ritonavir. Since increased concentrations of HMG-CoA reductase inhibitors may cause myopathy, including rhabdomyolysis, the combination of these medicinal products with fosamprenavir and ritonavir is not recommended.

When used with fosamprenavir and ritonavir, doses of atorvastatin no greater than 20 mg/day should be administered, with careful monitoring for atorvastatin toxicity. The metabolism of pravastatin and fluvastatin is not dependent on CYP3A4, and interactions are not expected with protease inhibitors. If treatment with an HMG-CoA reductase inhibitor is indicated, pravastatin or fluvastatin is recommended (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

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

Methadone: Co-administration of fosamprenavir 700 mg and ritonavir 100 mg twice daily with methadone once daily (≤ 200 mg) for 14 days decreased the active (R-) methadone enantiomer $AUC_{(0-\tau)}$ and C_{max} by 18% and 21%. Unbound fraction of R-methadone was increased at 2 hours (12.4% vs. 8.5%) and 6 hours (11.5% vs. 9.3%), but plasma unbound R-methadone (active) concentrations at 2 hours and 6 hours were not significantly altered. Based on historical comparison, methadone did not appear to alter plasma amprenavir pharmacokinetic parameters. Similar effects on methadone concentrations were observed when amprenavir (without ritonavir) and methadone were co-administered. On the basis of these data no dose adjustment is necessary when fosamprenavir/ritonavir is co-administered with methadone.

Paroxetine: Plasma concentrations of paroxetine may be significantly decreased when co-administered with fosamprenavir and ritonavir. Any paroxetine dose adjustment should be guided by clinical effect (tolerability and efficacy).

Steroids: Co-administration of fosamprenavir 700 mg twice daily + ritonavir 100 mg twice daily with Brevinor (ethinly estradiol (EE) 0.035 mg/norethisterone (NE) 0.5 mg) once daily decreased plasma EE $AUC_{(0-\tau)}$ and C_{max} by 37% and 28%, respectively, and decreased plasma NE $AUC_{(0-\tau)}$, C_{max}, and $C\tau$ by 34%, 38% and 26%, respectively. Steady-state plasma amprenavir pharmacokinetic (PK) parameters were not significantly affected by co-administration with Brevinor; however, ritonavir $AUC_{(0-\tau)}$ and C_{max} were 45% and 63% higher, respectively, compared to historical data in female subjects dosed with fosamprenavir/ritonavir alone. In addition to the decreased hormonal contraceptive exposures, co-administration of fosamprenavir with ritonavir and Brevinor resulted in clinically significant hepatic transaminase elevations in some healthy subjects. Therefore, alternative non-hormonal methods of contraception are recommended for women of

childbearing potential (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

St. John's wort: Serum levels of amprenavir can be reduced by concomitant use of the herbal preparation St. John's wort *(Hypericum perforatum)* (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

Antineoplastic agents: When antineoplastic agents (for example dasatinib, nilotinib, ibrutinib, vinblastine and everolimus) that are metabolised by CYP3A are co-administered with Fosamprenavir with/without ritonavir, plasma concentrations of these antineoplastic medications may be increased and could increase the risk of adverse events usually associated with these antineoplastic agents. In case of concomitant administration with antineoplastic agents metabolized by CYP3A, please refer to the relevant product information for these medications.

Antipsychotics:
Quetiapine: Due to CYP3A inhibition by fosamprenavir, concentrations of quetiapine are expected to increase. Concomitant administration of fosamprenavir and quetiapine is contraindicated as it may increase quetiapine-related toxicity. Increased plasma concentrations of quetiapine may lead to coma.

Lurasidone: Concomitant administration of fosamprenavir /ritonavir with lurasidone

4.6 IS CONTRAINDICATED DUE TO THE POTENTIAL FOR SERIOUS AND/OR LIFE-THREATENING REACTIONS **(SEE SECTION 4.3 CONTRAINDICATIONS).FERTILITY, PREGNANCY AND LACTATION**

Effects on fertility
Fertility in male and female rats was unaffected by oral fosamprenavir dose resulting in systemic exposures (plasma AUC) to amprenavir that were similar to that seen in humans treated with the maximum recommended dose of fosamprenavir in combination with ritonavir.

Use in pregnancy
(Pregnancy Category B3)

Embryo-foetal development was unaffected by oral treatment of pregnant rats and rabbits with fosamprenavir during the period of organogenesis. Systemic plasma exposure (AUC) to amprenavir in these studies was similar (rats) or lower (rabbits) than exposure in patients in clinical studies with fosamprenavir. In view of the low exposure in rabbits, the potential developmental toxicity of fosamprenavir has not been fully determined.

Placental transfer of amprenavir has been observed following administration of fosamprenavir/ritonavir 700/100 mg twice daily to pregnant women (see Section 5.2 PHARMACOKINETIC PROPERTIES*,* Special Populations, Pregnancy). As of 31st July 2017, fosamprenavir has been evaluated in the Antiretroviral Pregnancy Registry (APR) in 157 women and included 120 exposures during the first trimester and 36 exposures during the second/third trimester; with 4 birth defects reported in live born infants. However, there are no adequate and well controlled trials in pregnant women and the safe use of fosamprenavir

in human pregnancy has not been established. Limited data on the use of fosamprenavir during pregnancy from the APR and case reports are not sufficient to inform a drug-associated risk of birth defects and miscarriage.

Fosamprenavir should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Use in lactation
Health experts recommend that where possible HIV infected women do not breast feed their infants in order to avoid transmission of HIV. In settings where formula feeding is not feasible, local official lactation and treatment guidelines should be followed when considering breast feeding during antiretroviral therapy. It is expected that amprenavir may be secreted into human milk based on animal data. There is no information on the transfer or effects of amprenavir on the breastfed infant or the effects of the drug on milk production.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

No studies on the effects of fosamprenavir in combination with ritonavir on the ability to drive and use machines have been performed.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

The safety of fosamprenavir in combination with ritonavir has been studied in adults in controlled clinical trials (n = 534), in combination with various other antiretroviral agents. The most frequently (> 5% of adult subjects treated) reported undesirable effects were gastrointestinal events (nausea, diarrhoea, abdominal pain and vomiting) and headache. Most undesirable effects associated with fosamprenavir/ritonavir combination therapies were mild to moderate in severity, early in onset and rarely treatment limiting. For many of these events, it is unclear whether they are related to the fosamprenavir/ritonavir combination, to concomitant treatment used in the management of HIV disease or to the disease process.

Table 7 summarises the most common (≥ 2%) Grade 2-4 drug-related adverse events reported in all subjects enrolled in APV30002 or APV30003 while receiving randomised therapy.

Table 7: The most common (≥2%) Grade 2-4 drug-related adverse events reported in all subjects enrolled in APV30002 or APV30003 while receiving randomised therapy.

	APV30002 (Treatment-naïve patients)		APV30003 (Treatment-experienced patients)	
	fosamprenavir/ ritonavir Once daily N=322 n (%)	nelfinavir twice daily N=327 n (%)	fosamprenavir/ ritonavir twice daily N=106 n (%)	lopinavir/ ritonavir twice daily N=103 n (%)
Diarrhoeaσ	28 (9)	51 (16)	12 (11)	10 (10)
Loose stools	3 (<1)	2 (<1)	2 (2)	1 (<1)
Nausea	21 (7)	16 (5)	3 (3)	9 (9)
Vomitingσ	19 (6)	12 (4)	3 (3)	5 (5)
Drug Hypersensitivity	24 (7)	19 (6)	0	1 (<1)
Rashσ	5 (2)	5 (2)	3(3)	0
Anorexia	3 (<1)	0 (0)	0 (0)	5 (5)
Fatigueσ	11 (3)	6 (2)	1(<1)	1(<1)
Headache	8 (2)	9 (3)	3 (3)	2 (2)
Pyrexia	3 (<1)	5 (2)	0	0
Gastro oesophageal reflux disease	0 (0)	0 (0)	1 (1)	2 (2)
Gastritisσ	1 (<1)	0 (0)	2 (2)	0 (0)
Abdominal painσ	8 (2)	6 (2)	1 (<1)	2 (2)
Abdominal distension	3 (1)	0	3 (3)	1 (<1)
Abdominal pain upper	4 (1)	2 (<1)	(1 (<1)	3 (3)
ALT increased	8 (2)	7 (2)	0	0
AST increased	8 (2)	6 (2)	0	0
Lipase increase	3 (<1)	0 (0)	1 (1)	2 (2)
Hyperlipidaemiaσ	1 (<1)	0	2 (2)	0
Blood triglycerides increased	6 (2)	2 (<1)	0	1 (<1)
Hyper-triglyceridaemia	3 (<1)	5 (2)	4 (4)	2 (2)

σ Not Otherwise Specified (NOS)
Note: A minimum of 48 weeks of data are presented for APV30002; 48-week data are presented for APV30003.

In antiretroviral naïve patients (APV30002) receiving TELZIR / ritonavir in combination with abacavir and lamivudine, drug hypersensitivity was commonly[#] reported. All cases were reported as possibly related to abacavir. In cases of reported drug hypersensitivity, abacavir was discontinued and an alternative antiretroviral drug substituted. Few patients withdrew from the study due to these events. (#: Common defined as ≥ 1%, < 10%.)

Nervous system disorders
Common: dizziness, headache and oral paraesthesia.

Gastrointestinal disorders
Common: diarrhoea, nausea, vomiting, abdominal pain and flatulence.

Metabolism and nutrition disorders
Very common: hypercholesterolaemia.

Common: hypertriglyceridaemia.

New onset of diabetes mellitus, hyperglycaemia or exacerbations of existing diabetes mellitus have been reported in patients receiving antiretroviral protease inhibitors (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

Cardiac disorders
Uncommon: myocardial infarction.

Skin and subcutaneous tissue disorders
Common: 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/ritonavir combination. Fosamprenavir/ritonavir combination therapy should be definitively stopped in case of severe rash or in case of rash of slight or moderate intensity associated with systemic or mucosal signs (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

Uncommon: angioedema.

Rare: Stevens-Johnson syndrome (severe or life-threatening cases of rash).

Renal and urinary disorders
Uncommon: renal stones.

Lipohypertrophy
In some patients, an increase in body fat (lipohypertrophy) has been reported with anti-retroviral regimens containing a protease inhibitor. Metabolic abnormalities including hypertriglyceridaemia, hypercholesterolaemia, resistance to insulin and hyperglycaemia have also been reported with protease inhibitors containing regimen. (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

Musculoskeletal and connective tissue disorders
An increase in CPK, myalgia, myositis, and rarely, rhabdomyolysis, have been reported with protease inhibitors, more specifically in association with nucleoside analogues.

There have been reports of increased spontaneous bleeding in haemophiliac patients receiving antiretroviral protease inhibitors (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

Immune system disorders
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).

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

Children and adolescents
The adverse event profile in children and adolescents is based on integrated safety data from two studies (APV29005 and APV20003) in which 126 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 PHARMACODYNAMIC PROPERTIES, Clinical trials). Overall the safety profile in children and adolescents was comparable to that seen in adults.

Clinical laboratory abnormalities (Grade 3 or 4) potentially related to treatment with TELZIR in combination with ritonavir and reported in greater than or equal to 2% of adult subjects are provided in Table 8.

Table 8: Treatment-Emergent Grade 3/4 Laboratory Abnormalities Reported in the Pivotal Safety Studies (Safety Populations)

	APV30002 (Treatment-naïve patients)		APV30003 (Treatment-experienced patients)	
	fosamprenavir/ RTV once daily N=322 n (%)	NFV twice daily N=327 n (%)	fosamprenavir /RTV twice daily N=106 n (%)	LPV/RTV twice daily N=103 n (%)
ALT (>5 ULN)	25 (8)	26 (8)	4 (4)	4 (4)
AST (>5 ULN)	19 (6)	24 (7)	4 (4)	2 (2)
ALT and/or AST	29 (9)	31 (10)	6 (6)	4 (4)
Serum lipase (>2 ULN)	20 (6)	12 (4)	5(5)	12 (12)
Hyperglycaemia (>251mg/dL)	1(<1)	1 (<1)	2 (2)	2 (2)
Triglycerides (>750mg/dL)	16 (6)	7 (2)	11(11)	6 (6)
Cholesterol	1 (<1)	0	0	0

Note: A minimum of 48-week data are presented for APV30002; 48-week data are presented for APV30003.
ULN – Upper Limit of Normal

Routine pharmacovigilance identified oral paraesthesia with fosamprenavir as a safety signal. A review of the key clinical trials for fosamprenavir revealed a trend towards oral paraesthesia (and related AEs), with a frequency category of common (> 1% - < 10%).

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration 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 at http://www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

There is no known antidote for fosamprenavir. Since amprenavir is highly protein bound, dialysis is unlikely to be helpful in reducing blood levels. If overdose occurs, the patient should be monitored for evidence of toxicity (see Section 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)) and standard supportive treatment applied as necessary.

For information on the management of overdose, contact the Poison Information Centre on 131126 (Australia).

5 PHARMACOLOGICAL PROPERTIES

The non-clinical statements were consistent with those in the amprenavir Product Information, or were supported by limited experiments with fosamprenavir.

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of action
Fosamprenavir calcium is a pro-drug of amprenavir. It is the mono-calcium salt of the phosphate ester of amprenavir and is hydrolysed to inorganic phosphate and the active metabolite amprenavir as it is absorbed through the gut epithelium. Amprenavir is a non-peptide competitive inhibitor of the HIV protease. It blocks the ability of the viral protease to cleave the precursor polyproteins necessary for viral replication. Fosamprenavir has been shown to have little or no antiviral activity or enzyme inhibition properties *in vitro.* Any inhibition observed with fosamprenavir in these studies is considered to be due to trace amounts of amprenavir.

Fosamprenavir requires metabolism *in vivo* to generate the active moiety, amprenavir. In the absence of *in vivo* metabolism, fosamprenavir has negligible activity in *in vitro* enzymatic and antiviral assays, and therefore such assays are performed using amprenavir.

Amprenavir is a potent and selective inhibitor of HIV-1 and HIV-2 replication *in vitro.* In isolated experimental settings, synergy was shown *in vitro* in combination with nucleoside analogues including didanosine, zidovudine, abacavir and the protease inhibitor, saquinavir. It has been shown to have an additive effect in combination with indinavir, ritonavir and nelfinavir.

Co-administration of ritonavir with fosamprenavir (at fosamprenavir/ritonavir doses of 700/100 mg twice daily or 1400/200 mg once daily) increased plasma amprenavir AUC by approximately 2-fold and plasma $C_{\tau,ss}$ by 4- to 6-fold, compared to values obtained when fosamprenavir (at a dose of 1400 mg twice daily) is administered alone. Both fosamprenavir/ritonavir combination regimens (700 / 100 mg twice daily and 1400/200 mg once daily) maintain plasma amprenavir concentrations above the mean IC_{50} values for amprenavir against HIV for patients spanning the range from PI-naïve (mean protein-binding adjusted IC_{50} = 0.146 microgram/mL) to heavily PI-experienced (mean protein-binding adjusted IC_{50} = 0.90 microgram/mL).

Resistance *in vitro*
Serial passage experiments have demonstrated the protease mutation I50V to be key to the development of amprenavir resistance *in vitro,* with the triple variant, I50V+M46I/L+I47V, resulting in a greater than 10-fold increase in IC_{50} to amprenavir. This triple mutation resistance profile has not been observed with other protease inhibitors either from *in vitro* studies or in clinical settings. *In vitro* variants resistant to amprenavir remained sensitive to saquinavir, indinavir and nelfinavir, but showed three to five-fold reduced susceptibility to

ritonavir. The triple mutant, I50V+M46I/L+I47V, was unstable during *in vitro* passage in the presence of saquinavir, with loss of the I47V mutation, and the development of resistance to saquinavir resulted in resensitisation to amprenavir. Passage of the triple mutant in either indinavir, nelfinavir or ritonavir resulted in additional protease mutations being selected, leading to dual resistance. Mutation I84V, observed transiently *in vitro* has rarely been selected during amprenavir therapy. Additional recent data from *in vitro* passage experiments have also identified the selection by amprenavir of protease mutations I54M and V32I+I47V.

Resistance *in vivo:* protease inhibitor naïve subjects
The resistance profile seen with amprenavir in clinical practice is different from that observed with other protease inhibitors. Consistent with the first *in vitro* experiments, the development of amprenavir resistance during therapy is, in many cases, associated with the mutation I50V. However, the three alternative mechanisms observed during *in vitro* passage experiments have also been observed to result in the development of resistance during the use of amprenavir in the clinic. Development of resistance to amprenavir during therapy may involve either mutations I50V or I54L/M or V32I+I47V or, rarely, I84V. Each of the four genetic patterns may be accompanied by additional secondary mutations, in particular M46I/L, and produces viruses with reduced susceptibility to amprenavir, some cross-resistance to ritonavir, but susceptibility to indinavir, nelfinavir and saquinavir is retained.

The following summarises the mutations associated with the development of reduced phenotypic susceptibility to amprenavir in subjects treated with amprenavir.

Protease mutations acquired on amprenavir-containing therapy which have been demonstrated to result in reduced phenotypic susceptibility to amprenavir:
I50V or I54L/M or I84V or V32I with I47V

In treatment naïve subjects, significant differences were observed with respect to the emergence of resistance to both the PI and NRTI components of the study regimens between those subjects who received fosamprenavir/ritonavir in combination and those who received fosamprenavir without ritonavir as well as with those who received nelfinavir.

Treatment emergent NRTI resistance was significantly less frequent with fosamprenavir/ritonavir treated subjects (4/32, 13%) compared to the nelfinavir treated subjects (31/54, 57%) ($p < 0.001$).

The incidence of treatment-emergent protease mutations (PRO mutations) associated with resistance to amprenavir was significantly lower in subjects who received fosamprenavir/ritonavir once daily (0/32, 0%) compared with fosamprenavir twice daily without ritonavir (5/29,17%) and was lower than PRO mutations associated with resistance to nelfinavir treated patients (17/54, 31%).

Treatment emergence of NRTI resistance was also less frequent with fosamprenavir/ritonavir treated subjects compared with fosamprenavir alone (4/32 (13%) vs.16/29 (55%)).

In ART-naïve patients administered fosamprenavir without low-dose ritonavir, the following amprenavir resistance-associated mutations have been found either alone or in combination: I54L/M, V32I+I47V and M46I.

Resistance *in vivo:* protease inhibitor-experienced subjects
Many *in vitro* PI-resistant variants and 322 of 433 (74%) clinical PI-resistant variants with multiple protease inhibitor resistance mutations were susceptible to amprenavir. The principal protease mutation associated with cross-resistance to amprenavir following

treatment failure with other protease inhibitors was I84V, particularly when mutations L10I/V/F were also present. See Table 9.

Table 9. Responders at Study Week 48 by Presence of Baseline PI Resistance-Associated Mutations*

PI-mutations†	Fosamprenavir/Ritonavir-twice daily. (n = 88)		Lopinavir/Ritonavir twice daily. (n = 85)	
D30N	21/22	(95%)	17/19	(89%)
N88D/S	20/22	(91%)	12/12	(100%)
L90M	16/31	(52%)	17/29	(59%)
M46I/L	11/22	(50%)	12/24	(50%)
V82A/F/T/S	2/9	(22%)	6/17	(35%)
I54V	2/11	(18%)	6/11	(55%)
I84V	1/6	(17%)	2/5	(40%)

* Results should be interpreted with caution because the subgroups were small.
† Most patients had >1 PI resistance-associated mutation at baseline.

The virologic response based upon baseline phenotype was assessed. Baseline isolates from PI-experienced patients responding to fosamprenavir/ritonavir twice daily had a median shift in susceptibility to amprenavir relative to a standard wild-type reference strain of 0.7 (range: 0.1 to 5.4, n = 62), and baseline isolates from individuals failing therapy had a median shift in susceptibility of 1.9 (range: 0.2 to 14, n = 29). Because this was a select patient population, these data do not constitute definitive clinical susceptibility breakpoints. Additional data are needed to determine clinically relevant breakpoints for TELZIR.

Isolates from 15 of the 20 patients receiving twice-daily fosamprenavir/ritonavir and experiencing virologic failure/ongoing replication were subjected to genotypic analysis. The following amprenavir resistance-associated mutations were found either alone or in combination: V32I, M46I/L, I47V, I50V, I54L/M and I84V.

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

Clinical trials

Treatment-naïve patients:
Study APV30002 was a randomised, open-label, two arm study to compare a regimen containing fosamprenavir 1400 mg + ritonavir 200 mg (N = 322) once daily to nelfinavir 1250 mg twice daily (N = 327), when administered in combination with abacavir 300 mg twice daily and 3TC 150 mg twice daily in HIV-1 infected treatment naïve subjects over a 48 week period. The primary efficacy parameter for study APV30002 was the proportion of subjects with plasma HIV-1 RNA levels below 400 copies/mL at 48 weeks.

In the ITT population, the treatment groups were well matched with regard to demographic characteristics and baseline characteristics. See Table 10.

Table 10: Summary of Baseline Characteristics for APV30002 - ITT Population

	fosamprenavir/ ritonavir once daily N=322	nelfinavir twice daily N=327
Median CD4+ cells/mm^3 (range)	166 (1-813)	177 (1-1055)
Median plasma HIV-1 RNA log_{10} copies/mL, (range)	4.78 (2.65-7.29)	4.83 (3.11-6.74)
HIV-1 RNA copies/mL, n (%) >100,000	136 (42)	144 (44)
CDC Classification C: AIDS, n (%):	67 (21)	73 (22)
Hepatitis B Test Results Positive, n (%)	26 (8)	23 (7)
Hepatitis C Test Results Reactive, n (%)	57 (18)	60 (18)

The median baseline CD4 count was low in both groups. A total of 55% of subjects had a CD4+ cell count < 200 cells/mm^3 at baseline, and 20% of subjects had CD4+ cell counts <50 cells/mm^3. Overall, the baseline characteristics demonstrate that a more advanced treatment naïve population was enrolled in this study compared to the population of previous studies in treatment naïve subjects.

The proportion of subjects at Week 48 with plasma HIV-1 RNA < 400 copies/mL and HIV-1 RNA < 50 copies/mL using the ITT (RD=F)* analysis are summarised in Table 11.

Table 11: Summary of Proportions of Subjects with Plasma HIV-1 RNA < 400 copies/mL and HIV RNA <50 copies/mL at Week 48

Population	fosamprenavir/ ritonavir once daily % (n/N)	nelfinavir twice daily % (n/N)	Stratified Difference	95% CI
HIV RNA <50 copies/mL	55 (177/322)	53 (173/327)	2%	-6%, 10%
HIV RNA <400 copies/mL	69 (221/322)	68 (221/327)	1%	-6%, 8%

Rebound or Discontinuation = Failure

The results from study APV 30002 indicates that, in antiretroviral naïve patients, fosamprenavir given once daily in combination with low dose ritonavir as part of a regimen including abacavir and lamivudine (given twice daily) showed comparable efficacy over 48 weeks compared to nelfinavir given twice daily in combination with abacavir/lamivudine.

Median HIV-1 RNA decreased from a baseline value of 4.78 log_{10} copies/mL in the fosamprenavir/ritonavir once daily group and 4.83 log_{10} copies/mL in the nelfinavir twice daily group to the lower limit of detection of assay (50 copies/mL or 1.69 log_{10} copies/mL) at Week 20 in both groups and remained at this level through Week 48.

Median changes from baseline in plasma HIV-1 RNA were comparable between treatment groups at each time point. The median change in plasma HIV-1 RNA from baseline to Week 48 was -3.08 log_{10} copies/mL in the fosamprenavir/ritonavir once daily group and -2.96 log_{10} copies/mL in the nelfinavir twice daily group.

CD4+ cell counts increased in both treatment groups with median increases from baseline being similar in magnitude at Week 48 (fosamprenavir/ritonavir: 203 cells mm^3; nelfinavir twice daily: 207 cells mm^3).

Treatment-experienced patients:
Study APV30003 was a randomised, parallel group, three-arm, open-label, multicentre, comparative study of two dosage regimens of fosamprenavir 700 mg with ritonavir 100 mg twice daily (N = 105) and fosamprenavir 1400 mg and ritonavir 200 mg once daily (N = 105) versus lopinavir 400 mg and ritonavir 100 mg twice daily (N = 107), in HIV-1-infected subjects with previous PI experience, documented virological failure on a prior PI regimen, and currently receiving antiretroviral therapy. The primary end-point was average area under the curve minus baseline plasma HIV-1 RNA.

In the ITT population, the treatment groups were largely comparable with regard to demographic and baseline characteristics, as indicated in Table 12.

Table 12: Summary of Baseline Characteristics in APV30003 ITT Population

	fosamprenavir/ ritonavir once daily N=105	fosamprenavir/ ritonavir twice daily N=107	lopinavir/ ritonavir twice daily N=103
Median Plasma HIV-1 RNA log_{10} copies/mL (range)	4.19 (1.79-5.80)	4.13 (2.27-5.95)	4.13 (1.69-6.41)
Plasma HIV-1 RNA copies/mL, n(%) <10,000 >10,000 – 100,000 >100,000	 45 (43) 46 (44) 14 (13)	 44 (41) 50 (47) 13 (12)	 43 (42) 48 (47) 12 (12)
Median CD4+ cells/mm^3 (range)	250 (2-1171)	292 (12-845)	234 (8-765)
CDC Classification, n (%): A: Asymptomatic or Lymphadenopathy B: Symptomatic, not AIDS C: AIDS	 39 (37) 30 (29) 36 (34)	 44 (41) 29 (27) 34 (32)	 37 (36) 31 (30) 35 (34)
Hepatitis B Test Results, n (%) Positive	7 (7)	4 (4)	5 (5)
Hepatitis C Test Results, n (%) Reactive	16 (15)	16 (15)	18 (17)

Mean plasma HIV-1 RNA Average Area Under the Curve Minus Baseline (AAUCMB) values at Week 48 are summarised in Table 13 for the ITT population observed analysis.

Table 13: Mean plasma HIV-1 RNA AAUCMB values at Week 48 for the ITT Population.

	fosamprenavir/ ritonavir once daily N=105 Mean (n)	fosamprenavir/ ritonavir twice daily N=107 Mean (n)	lopinavir/ ritonavir twice daily N=103 Mean (n)	Mean Diff (97.5% CI) fosamprenavir/ ritonavir once daily vs lopinavir/ ritonavir twice daily	Mean Diff (97.5% CI) fosamprenavir/ ritonavir twice daily vs lopinavir/ ritonavir twice daily
Total Population	-1.49 (104)	-1.53 (105)	-1.76 (103)	0.267 (-0.017, 0.551)	0.244 (-0.047, 0.536)

AAUCMB: Average Area Under the Curve Minus Baseline

Table 14 provides plasma HIV-1 RNA at week 48 for < 400 and < 50 copies/mL using the ITT rebound or discontinued = failure (RD = F) analysis.

Table 14: Proportion of Subjects with Plasma HIV-1 RNA <400 and <50 copies/mL at Week 48

Population	fosamprenavir/ ritonavir once daily N=105 %(n/N)	fosamprenavir/ ritonavir twice daily N=107 %(n/N)	LPV/RTV twice daily N=103 %(n/N)	Stratified Difference (95% CI) fosamprenavir/ ritonavir once daily vs lopinavir/ ritonavir twice daily	Stratified Difference (95% CI) fosamprenavir/ ritonavir twice daily vs lopinavir/ ritonavir twice daily
HIV RNA <50 copies/mL	37 (39/105)	46 (49/107)	50 (52/103)	-14% (-27%, 0%)	-4% -17%, 10%)
HIV RNA <400 copies/mL	50 (52/105)	58 (62/107)	61 (63/103)	-12% (-25%, 2%)	-2% -15%, 11%)

The fosamprenavir/ritonavir twice daily regimen and the lopinavir/ritonavir twice daily regimen showed similar immunological improvements through 48 weeks of treatment, as measured by median CD4+ cell count and change from baseline.

In PI-experienced HIV-infected subjects with evidence of virological failure, substantial virologic suppression was observed through 48 weeks of treatment with fosamprenavir 700 mg/ritonavir 100 mg twice daily or lopinavir 400 mg/ritonavir 100 mg twice daily dosing in combination with two RTIs. A lower level of virological suppression was observed through 48 weeks of treatment with fosamprenavir 1400 mg/ritonavir 200 mg once daily dosing in combination with two RTIs. After 48 weeks' treatment, the results of this study did not satisfy the criteria for non-inferiority of either fosamprenavir/ritonavir once daily or

fosamprenavir/ritonavir twice daily versus lopinavir/ritonavir twice daily with respect to the primary endpoint, plasma HIV-1 RNA AAUCMB.

Treatment-naïve patients dosed without ritonavir:
APV30001 was a randomised, open-label study where treatment naïve subjects were randomised to either receive fosamprenavir 1400 mg twice daily (N = 166) or nelfinavir 1250 mg twice daily (N = 83), when administered in combination with abacavir 300 mg twice daily and 3TC 150 mg twice daily. Most subjects were male and American Hispanic or black.

The median plasma HIV-1 RNA levels were 4.83 $\log_{10}$ copies/mL, and the median baseline CD4 cell count was 212 cells/mm^3 at baseline. 20% of subjects had a prior history of a CDC class C event.

A greater proportion of subjects prematurely discontinued their randomised PI from the nelfinavir twice daily group (47%) than from the fosamprenavir twice daily (31%) group. More subjects in the nelfinavir twice daily group prematurely discontinued from randomised PI due to insufficient viral load response than in the fosamprenavir twice daily group.

Greater efficacy was obtained with fosamprenavir (66% of patients achieved HIV-1 RNA levels < 400 copies/mL) compared with nelfinavir (51% of patients) through 48 weeks of therapy. The proportions of patients with plasma HIV-1 RNA < 50 copies/mL at Week 48 were also higher in the group treated with fosamprenavir (55% for TELZIR compared with 41% for nelfinavir).

Children and adolescents:
The safety, pharmacokinetic profile, and virologic response of fosamprenavir have been evaluated in paediatric patients 2 to 18 years of age. Use of fosamprenavir in this patient population is supported by evidence from well controlled studies of fosamprenavir in adults with additional data from two open label studies of fosamprenavir in paediatric patients. Very limited data is available for paediatric patients less than 2 years of age.

In one study (APV29005), twice daily dosing regimen (TELZIR with or without ritonavir) were evaluated in combination with other antiretroviral agents while in the second study (APV20003), once daily dosing regimen of TELZIR with ritonavir were evaluated in combination with other antiretroviral agents. Doses and formulations (fosamprenavir tablets or oral suspension, ritonavir capsules or oral solution) were determined by patient weight and age.

APV29005 enrolled 25 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 29 patients aged 12 to 18 (the majority of whom were treated with the adult tablet regimen). Overall, 27 (50%) were PI-naïve, 9 of whom were ART naïve, and 27 (50%) were PI-experienced. Prior NRTI exposure was extensive, with median durations of 421 and 389 weeks for the PI naïve and experienced patients respectively. The median duration of prior PI exposure was 239 weeks. Overall, patients enrolled with a median 4.6 HIV-1 RNA $\log_{10}$ copies/mL (33% of whom had > 100,000 copies/mL at baseline) and a median % CD4+ cell of 18% (37% of whom had % CD4+ of < 15% at baseline).

Through 24 weeks of therapy, 70% (19/27) of protease inhibitor naïve and 56% (15/27) of protease inhibitor experienced patients achieved and maintained a plasma HIV-1 RNA < 400 copies/mL (ITT(E), TLOVR). In the ITT(E) population (observed analysis) at week 24 the median % CD4+ cell counts increased by 8% in the PI-naïve subjects and 4% in the PI experienced subjects.

The once daily study APV20003 enrolled 52 patients aged 6-18. Of these, 26 (50%) were PI-naïve and 26 (50%) were PI-experienced. At week 24 of therapy, 62% (16/26) of protease inhibitor naïve and 42% (11/26) of protease inhibitor experienced patients achieved a plasma HIV-1 RNA < 400 copies/mL (ITT(E), TLOVR). At Week 48 of therapy, 46% (12/26) of protease inhibitor naïve and 31% (8/26) of protease inhibitor experienced patients achieved HIV-1 RNA < 400 copies/mL.

There are currently insufficient data on pharmacokinetics, safety and antiviral response of fosamprenavir with ritonavir in children below 6 years of age.

No direct comparative studies have been undertaken in children or adolescents.

5.2 PHARMACOKINETIC PROPERTIES

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

Amprenavir metabolism is inhibited by ritonavir, via inhibition of CYP3A4, resulting in increased plasma concentrations of amprenavir.

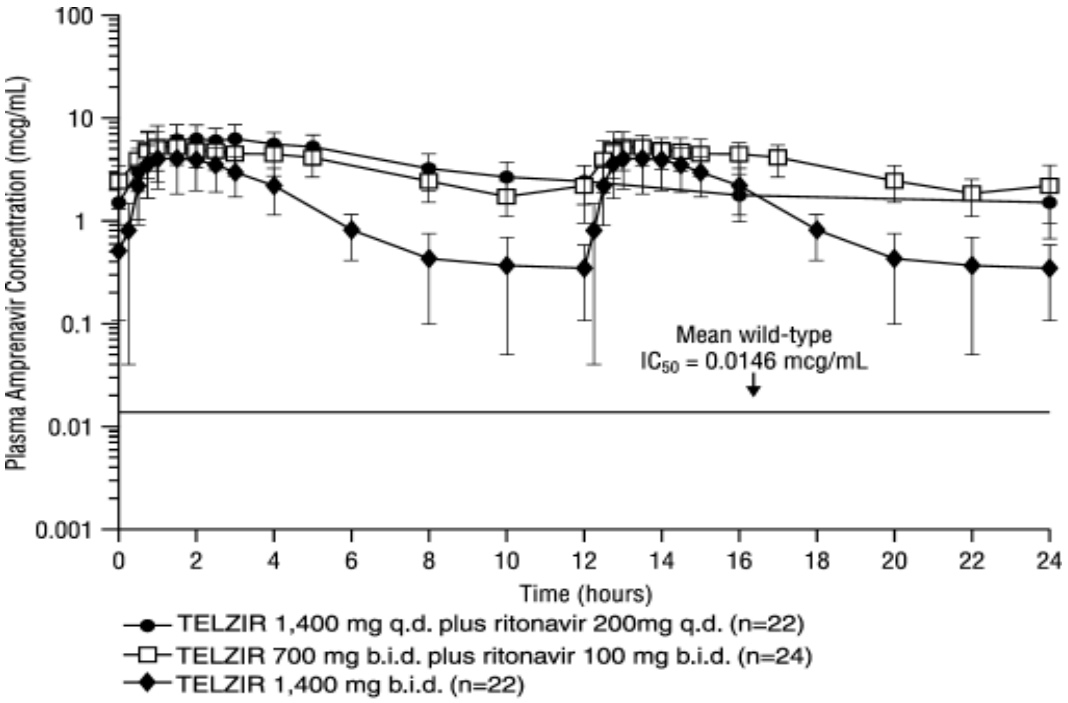
The pharmacokinetic properties of amprenavir following co-administration of fosamprenavir and ritonavir have been evaluated in healthy adult subjects and HIV-infected patients and no substantial differences were observed between these two groups.

Absorption
After multiple dose oral administration of fosamprenavir 1400 mg once daily and ritonavir 200 mg once daily, amprenavir was rapidly absorbed with a geometric mean (95% CI) steady-state peak plasma amprenavir concentration (C_{max}) of 7.24 (6.32-8.28) microgram/mL occurring approximately 2 (0.8-5.0) hours after dosing (T_{max}). The geometric mean steady-state plasma amprenavir trough concentration (C_{min}) was 1.45 (1.16-1.81) microgram/mL and $AUC_{24,ss}$ was 69.4 (59.7-80.8) h.microgram/mL.

After multiple dose oral administration of fosamprenavir 700 mg twice daily and 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) microgram/mL occurring approximately 1.5 (0.75-5.0) hours after dosing (T_{max}). The geometric mean steady-state plasma amprenavir trough concentration (C_{min}) was 2.12 (1.77-2.54) microgram/mL and $AUC_{24,ss}$ was 79.2 (69.0-90.6) h.microgram/mL.

The absolute bioavailability of fosamprenavir in humans has not been established.

Figure 1. Mean (± SD) Steady-State Plasma Amprenavir Concentrations and Mean IC_{50} Values Against HIV from Protease Inhibitor-Naïve Patients (in the Absence of Human Serum)



Administration of the fosamprenavir oral tablet formulation (1400 mg) with a high fat meal did not alter plasma amprenavir pharmacokinetics as compared to the administration of this formulation in the fasted state. Fosamprenavir tablets may be taken without regard to food intake.

Distribution

The apparent volume of distribution is decreased by approximately 40% when fosamprenavir is co-administered with ritonavir, most likely due to an increase in amprenavir bioavailability.

The apparent volume of distribution of amprenavir following administration of fosamprenavir is approximately 430 litres (6 L/kg assuming a 70 kg bodyweight), suggesting a large volume of distribution, with penetration of amprenavir freely into tissues beyond the systemic circulation. The concentration of amprenavir in cerebrospinal fluid is less than 1% of the plasma concentration.

Amprenavir is approximately 90% protein bound. It is bound to the $alpha_1$-acid glycoprotein (AAG) and albumin, but has a higher affinity for AAG.

Metabolism

Following oral administration, fosamprenavir is rapidly and almost completely hydrolysed to amprenavir and inorganic phosphate as it is absorbed through the gut epithelium. 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 is a less potent inhibitor of CYP3A4. Therefore, drugs that are inducers, inhibitors or substrates of CYP3A4 must be used with caution when administered concurrently with fosamprenavir and ritonavir (see Section 4.3 CONTRAINDICATIONS and Section 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS).

Excretion
Following administration of fosamprenavir, the half-life of amprenavir is 7.7 hours. The plasma amprenavir half-life is increased when fosamprenavir is co-administered with ritonavir. The primary route of elimination of amprenavir is via hepatic metabolism with less than 1% excreted unchanged in the urine. The metabolites account for approximately 14% of the administered amprenavir dose in the urine, and approximately 75% in the faeces.

Special populations

Paediatrics
The pharmacokinetics of amprenavir in children (2 years of age and above) and adolescents are similar to those in adults. Dosages of fosamprenavir (oral suspension or tablets) plus ritonavir (oral solution or capsules) were administered to subjects. The dosage regimen studies were on an age/weight basis. Mean steady-state amprenavir pharmacokinetic parameters in this population are presented by dosing regimen and age group in Table 15.

Table 15: Pharmacokinetic parameters in paediatric patients receiving fosamprenavir with ritonavir twice daily

	6 to 11 Years		12 to 18 Years	
Parameter	n	Fosamprenavir 18 mg/kg plus Ritonavir 3 mg/kg Twice daily	N	Fosamprenavir 700 mg plus Ritonavir 100 mg Twice daily
$AUC_{(0-24)}$	9	93.4 (67.8, 129)	8	58.8 (38.8, 89.0)
C_{max} (µg/mL)	9	6.07 (4.40, 8.38)	8	4.33 (2.82, 6.65)
$C\tau$ (µg/mL)	17	2.69 (2.15, 3.36)	24	1.61 (1.21, 2.15)

Currently there are insufficient pharmacokinetic data in children < 2 years of age to support dosing in this age group.

Elderly
The pharmacokinetics of fosamprenavir when given in combination with ritonavir has not been studied in patients over 65 years of age. When treating elderly patients', consideration should be given to potential hepatic, renal or cardiac dysfunction, concomitant disease or other drug therapy.

Impaired renal function
Patients with renal impairment have not been specifically studied. Renal elimination is not a major route of elimination of amprenavir or ritonavir. The impact of renal impairment on amprenavir and ritonavir elimination should be minimal, therefore no dose adjustment of the fosamprenavir/ritonavir combination is considered necessary.

Impaired hepatic function
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 repeat-dose study in HIV-1 infected adult subjects with hepatic impairment receiving fosamprenavir with ritonavir compared to matched control subjects with normal hepatic function.

For subjects with mild hepatic impairment (Child-Pugh (C-P) score of 5-6), a dosage regimen of fosamprenavir 700 mg twice daily with a reduced dosing frequency of ritonavir 100 mg once daily is recommended (see Section 4.2 DOSE AND METHOD OF ADMINISTRATION) based on slightly higher plasma amprenavir C_{max} (17%), slightly higher plasma amprenavir $AUC_{(0-\tau)}$ (22%), and similar $C\tau$ values compared to subjects with normal hepatic function receiving the standard fosamprenavir/ritonavir 700 mg/100 mg twice daily regimen.

For subjects with moderate hepatic impairment (C-P score of 7-9), a dosage regimen of fosamprenavir 450 mg twice daily with a reduced dosing frequency of ritonavir 100 mg once daily is recommended (see Section 4.2 DOSE AND METHOD OF ADMINISTRATION). Although the fosamprenavir 450 mg twice daily + ritonavir 100 mg once daily dosage regimen is predicted to deliver approximately 35% lower plasma total amprenavir $C\tau$ values, plasma unbound amprenavir $C\tau$ values will be approximately 67% higher than achieved in subjects with normal hepatic function receiving the standard fosamprenavir with ritonavir 700 mg/100 mg twice daily regimen.

For subjects with moderate hepatic impairment, the fosamprenavir 700 mg once daily + ritonavir 100 mg once daily regimen delivered 24% lower plasma amprenavir C_{avg}, 65% lower $C\tau$, and approximately 42% lower unbound $C\tau$ compared to subjects with normal hepatic function receiving the standard fosamprenavir/ritonavir 700 mg/100 mg twice daily regimen. Therefore, a fosamprenavir tablet regimen in subjects with moderate hepatic impairment could not achieve comparable plasma amprenavir pharmacokinetics to the fosamprenavir/ritonavir 700 mg/100 mg twice daily regimen in subjects with normal hepatic function.

In subjects with severe hepatic impairment (C-P 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 $AUC_{(0-\tau)}$, and 38% lower $C\tau$ values, but similar unbound plasma amprenavir $C\tau$ 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 C_{avg}, and 38% higher ritonavir $C\tau$ than achieved in subjects with normal hepatic function receiving the standard fosamprenavir with ritonavir 700 mg/100 mg twice daily regimen.

Pregnancy
Amprenavir pharmacokinetic parameters were assessed in 10 HIV-infected pregnant women receiving fosamprenavir/ritonavir 700/100 mg twice daily. Six participants contributed second trimester data and nine contributed to both the third-trimester and postpartum analysis.

Geometric mean amprenavir exposure was lower in the second and third trimester than postpartum. Second trimester vs. postpartum APV geometric mean ratios (90% CI) were: $AUC_{(0-12)}$: 0.65 (0.47, 0.89), C_{max} 0.63 (0.47, 0.85), C12: 0.64 (0.45, 0.93). Third trimester vs. postpartum geometric mean ratios (90% CI) were $AUC_{(0-12)}$ 0.75 (0.57, 1.00), C_{max} 0.81 (0.62, 1.06) C12 0.62 (0.48, 0.92). Geometric mean (95% CI) C12 values were 1.31 (0.97, 1.77), 1.34 (0.95, 1.89), and 2.03 (1.46, 2.83) micrograms/mL for the second trimester, third trimester, and postpartum, respectively and within the range of values in non-pregnant patients. Geometric mean C12 levels for all pregnancy phases were 9–15-fold above the mean APV protein-adjusted IC_{50} of 0.146 mcg/mL for wild-type HIV strains.

Seven infant cord blood samples were analysed and placental transfer of amprenavir has been observed. The mean (SD) umbilical cord amprenavir blood concentration was 0.11 (0.07) mcg/mL. The maternal plasma concentration at delivery was 0.43 (0.29) mcg/mL. The ratio (95% CI) of cord to maternal peripheral plasma concentration was 0.267 (0.241, 0.297)

5.3 PRECLINICAL SAFETY DATA

Genotoxicity
Fosamprenavir was not mutagenic or genotoxic in a battery of *in vitro* and *in vivo* assays. These assays included bacterial reverse mutation (Ames), mouse lymphoma, rat micronucleus, and chromosome aberrations in human lymphocytes.

Carcinogenicity
In long-term carcinogenicity studies, fosamprenavir was administered orally for up to 104 weeks at doses of 250, 400, or 600 mg/kg/day in mice and at doses of 300, 825, or 2250 mg/kg/day in rats. Exposures to amprenavir at these doses were 0.2 to 0.3-fold (mice) and 0.3 to 0.7-fold (rats) those in humans given 1400 mg once daily of fosamprenavir plus 200 mg ritonavir once daily. Exposures in the carcinogenicity studies were 0.1 to 0.3-fold (mice) and 0.3 to 0.6-fold (rats) those in humans given 700 mg of fosamprenavir plus 100 mg ritonavir twice daily. There was an increase in hepatocellular adenomas and hepatocellular carcinomas at all doses in male mice, and in hepatocellular adenomas and thyroid follicular cell adenomas at all doses in male rats and at 825 and 2250 mg/kg/day in female rats. The relevance of the hepatocellular findings in the rodents for humans is uncertain. Repeat dose studies with fosamprenavir in rats produced effects consistent with enzyme induction, which predisposes rats, but not humans, to thyroid neoplasms. In addition, in rats only there was an increase in interstitial cell hyperplasia at 825 and 2250 mg/kg/day, and an increase in uterine endometrial adenocarcinoma at 2250 mg/kg/day. The incidence of endometrial findings was slightly increased over concurrent controls, but within background range for female rats. The relevance of the uterine endometrial adenocarcinoma findings in rats for humans is uncertain. The carcinogenicity of fosamprenavir in combination with ritonavir has not been tested in animals.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Tablet Core:

Microcrystalline cellulose,
Croscarmellose sodium,
Povidone K30,
Magnesium stearate
Colloidal silicon dioxide.

Tablet Coating:

Hypromellose,
Titanium dioxide (E171),
Glycerol triacetate,
Iron oxide red (E172).

6.2 INCOMPATIBILITIES

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 30°C.

6.5 NATURE AND CONTENTS OF CONTAINER

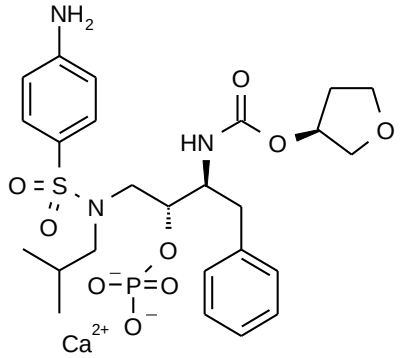
TELZIR film-coated tablets are supplied in High-Density Polyethylene (HDPE) bottles containing 60 tablets.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

6.7 PHYSICOCHEMICAL PROPERTIES

Chemical structure



Fosamprenavir calcium has a solubility approximately 0.31 mg/mL in water at 25°C.

CAS number
226700-81-8

The chemical name of fosamprenavir is (3S)-tetrahydrofuran-3-yl (1S,2R)-3-[[(4-aminophenyl) sulphonyl](isobutyl) amino]-1-benzyl-2-(phosphonooxy) propylcarbamate monocalcium. Fosamprenavir is a single stereoisomer with the (3S)(1S,2R) configuration.

It has a molecular formula of $C_{25}H_{34}CaN_3O_9PS$ and a molecular weight of 623.7.

7 MEDICINE SCHEDULE (POISONS STANDARD)

S4

8 SPONSOR

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9 DATE OF FIRST APPROVAL

26 May 2004

10 DATE OF REVISION

16 November 2018

SUMMARY TABLE OF CHANGES

Section Changed	Summary of new information
4.3	Added new information relating to co-administration of Fosamprenavir/ritonavir and lurasidone.
4.5	Added new information relating to interaction of fosamprenavir/ritonavir with other antineoplastic metabolised by CYP3A and lurasidone.
4.5	Sildenafil, Alfuzosin and lurasidone added to table 5 in alignment with section 4.3 Contraindication
4.5	Added “Antipsychotics” as a new heading

Version 15.0