TELZIR TABLETS and ORAL SUSPENSION
Professional Information

SCHEDULING STATUS:

S4

1. NAME OF THE MEDICINE:

TELZIR TABLETS

(700 mg fosamprenavir)

TELZIR ORAL SUSPENSION

(50 mg/ml fosamprenavir)

2. QUALITATIVE AND QUANTITIVE COMPOSITION:

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

For full list of excipients, see section 6.1.

TELZIR ORAL SUSPENSION: Each ml contains 50 mg fosamprenavir as fosamprenavir calcium (equivalent to approximately 43 mg amprenavir per ml).

Preservatives:

Methyl parahydroxybenzoate	0,15 % *m/v*
Propyl parahydroxybenzoate	0,02 % *m/v*

For full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM:

TELZIR TABLETS:

Pink, film-coated, capsule-shaped, biconvex tablets, debossed ‘GXLL7’ on one face.

TELZIR ORAL SUSPENSION:

White to off-white suspension which has a characteristic bubblegum odour.

4. CLINICAL PARTICULARS:

4.1 Therapeutic indications:

TELZIR in combination with low dose ritonavir is indicated for the treatment of Human Immunodeficiency Virus (HIV) infected patients for use in combination with other antiretroviral medicines.

4.2 Posology and method of administration:

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

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

All regimens must be administered in combination with other antiretroviral medicines.

The importance of complying with the full recommended dosing regimen should be stressed to all patients.

Do not exceed the recommended dose.

Higher than approved dose combinations of TELZIR with ritonavir are not recommended for use (see section 4.4).

Once daily administration of TELZIR with ritonavir is not recommended in protease inhibitor (PI) experienced patients.

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

Tablets:

TELZIR tablets in combination with ritonavir can be taken with or without food.

In addition to tablets, TELZIR is also available as an oral suspension for use in adults unable to swallow tablets.

Therapy naïve patients:

The recommended dose is 1 400 mg TELZIR (2 tablets) once daily with 200 mg ritonavir once daily **or** 700 mg TELZIR (1 tablet) twice daily with 100 mg ritonavir twice daily.

PI-experienced patients:

The recommended dose 700 mg TELZIR (1 tablet) twice daily with 100 mg ritonavir twice daily.

Oral suspension:

TELZIR oral suspension in combination with ritonavir **should** be taken without food and on empty stomach. Shake the bottle vigorously for 20 seconds before first dose is removed. Shake bottle before subsequent doses are removed. Do not mix with other medicines.

Therapy naïve patients:

The recommended dose is 1 400 mg TELZIR (28 ml) once daily with 200 mg ritonavir once daily **or** 700 mg TELZIR (14 ml) twice daily with 100 mg ritonavir twice daily. Both regimens must be administered in combination with other antiretroviral medicines.

PI-experienced patients:

The recommended dose is 700 mg TELZIR (14 ml) twice daily with 100 mg ritonavir twice daily.

Children and Adolescent Patients (2 to 17 years of age):

Tablets:

The TELZIR oral suspension is the recommended formulation for the most accurate dosing in children based on body weight.

The adult tablet regimens of TELZIR 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. Ritonavir 100 mg capsules may be used in children and adolescents taking the TELZIR oral suspension if they weigh at least 33 kg and can swallow the capsules whole.

The tablet can be taken with or without food.

Oral suspension:

The TELZIR oral suspension is the recommended formulation for the most accurate dosing in children based on body weight.

The oral suspension should be taken **with** food by children and adolescents. Shake the bottle before use.

The recommended doses of TELZIR oral suspension with ritonavir are as follows:

Table 2: Dosage Recommendations for paediatric patients

Patient Population	**Age**	**TELZIR/Ritonavir ***
		Dosage regimen - Twice daily
	2-5 years	TELZIR 20 mg/kg
		Ritonavir 3 mg/kg
	≥ 6 years	TELZIR 18 mg/kg
		Ritonavir 3 mg/kg
PI naive	2-5 years	TELZIR 20 mg/kg
		Ritonavir 3 mg/kg
	≥ 6 years	TELZIR 18 mg/kg
		Ritonavir 3 mg/kg
PI experienced	2-5 years	TELZIR 20 mg/kg
		Ritonavir 3 mg/kg
	≥ 6 years	TELZIR 18 mg/kg
		Ritonavir 3 mg/kg
* Maximum dose not to exceed the recommended adult dose. The adult tablet regimen of TELZIR with ritonavir twice daily may be prescribed to children and adolescents weighing at least 39 kg and able to swallow tablets whole. Ritonavir 100 mg capsules may be prescribed to children and adolescents taking the TELZIR oral suspension if they weigh at least 33 kg and can swallow the capsules whole.		

Children less than 2 years of age: The safety and efficacy of TELZIR in combination with ritonavir has not yet been established in this patient population.

Elderly: The pharmacokinetics of fosamprenavir in combination with ritonavir has not been studied in patients over 65 years of age (see section 5.2). When treating elderly patients, consideration should be given to potential hepatic, renal or cardiac dysfunction, concomitant disease or other medicinal therapy.

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

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 (Child-Pugh score: 5-6): TELZIR should be used with caution and at a reduced dose of 700 mg TELZIR twice daily with 100 mg ritonavir once daily.

TELZIR is contra-indicated in patients with severe hepatic impairment.

For adults with moderate hepatic impairment (Child-Pugh score: 7-9): TELZIR should be used with caution and at a reduced dose 450 mg TELZIR twice daily with 100 mg ritonavir once daily.

As it is not possible to achieve this latter TELZIR dose using the tablet formulation, these patients should be treated with TELZIR oral suspension.

Table 3 Dosing Recommendations in Hepatic impairment

Degrees of hepatic Impairment	**TELZIR dose (TWICE DAILY)**	**Ritonavir dose (ONCE DAILY)**
Mild (Child-Pugh score: 5-6)	Tablet or oral suspension 700 mg (1 tablet or 14 ml suspension) Oral suspension should be taken **without** food	Capsule or Solution 100 mg
Moderate (Child-Pugh score: 7-9)	Oral suspension 450 mg (9 ml suspension) Oral suspension should be taken **without** food	Capsule or Solution 100 mg

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, ritonavir or to any of the excipients of these medicines.

Patients with severe hepatic impairment.

Concomitant treatment with ketoconazole.

TELZIR in combination with ritonavir must not be administered concurrently with medicines with narrow therapeutic windows that are substrates of cytochrome P450 3A4 (CYP 3A4).

Co-administration may result in competitive inhibition of the metabolism of these medicines and create the potential for elevated plasma concentrations, leading to serious and life-threatening adverse events such as cardiac dysrrhythmia (e.g. cisapride, pimozide), hypotension (for example, the alpha blocker alfuzosin), prolonged sedation or respiratory depression (e.g. triazolam, midazolam, quetiapine) or peripheral vasospasm or ischaemia (e.g. ergot derivatives) or rhabdomyolysis (e.g. lovastatin and simvastatin) (see section 4.5).

TELZIR/ritonavir must not be administered concomitantly with the antipsychotic medicinal product lurasidone. Please refer to the full prescribing information for ritonavir for other potential interactions (see section 4.5).

TELZIR/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 4.4 and section 4.5). 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. TELZIR in combination with ritonavir should not be co-administered with medicines 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 for ritonavir for further details) (see section 4.5).

TELZIR 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).
Herbal preparations containing St John's Wort (*Hypericum perforatum*) must not be used while taking TELZIR in combination with ritonavir due to the risk of decreased plasma concentrations and reduced clinical effects of amprenavir (see section 4.5).
The pharmacokinetics, safety and efficacy of the TELZIR/ritonavir combination in children below 2 years of age have not yet been established.

4.4 Special warnings and precautions for use:

Opportunistic infections:

Patients should be advised that treatment with the TELZIR/ritonavir combination, or any other current antiretroviral therapy, does not cure HIV and that they may still develop opportunistic infections and other complications of HIV infection, and therefore they should remain under close observation by healthcare professionals experienced in the treatment of patients with associated HIV disease. Regular monitoring of viral load and CD4 counts needs to be done.

The risk of HIV transmission to others:

Patients should be advised that current antiretroviral therapies, including TELZIR/ritonavir combinations, do not prevent the risk of transmission of HIV to others through sexual contact or blood contamination. Appropriate precautions should continue to be taken.

Hypersensitivity:

Fosamprenavir contains a sulphonamide moiety. There is a potential for cross sensitivity between medicines in the sulphonamide class and TELZIR. TELZIR in combination with ritonavir should be used with caution in patients with a known sulphonamide allergy.
The TELZIR oral suspension contains propyl and methyl parahydroxybenzoate. These substances may cause an allergic reaction. This reaction may be delayed.

In antiretroviral naïve patients receiving TELZIR/ritonavir in combination with abacavir and lamivudine, medicine hypersensitivity was commonly reported. All cases were reported as possibly related to abacavir. In cases of reported medicine hypersensitivity, abacavir was discontinued and an alternative antiretroviral medicine substituted. Few patients withdrew from the study due to these events.

Haemophiliac patients:

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

***Hyperglycaemia*:**

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

Hepatic/Renal dysfunction:

Amprenavir and ritonavir are both principally metabolised by the liver. TELZIR with ritonavir should be used with caution and at reduced doses in adults with mild and moderate hepatic impairment (see section 4.2) and should not be used in patients with severe hepatic impairment (see section 4.3).

Patients with underlying hepatitis B or C and 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.
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.

Increase in body fat*:*

Combination anti-retroviral therapy, including regimens containing a protease inhibitor, may be associated with increased body fat in some patients.
Clinical examination should include evaluation for physical signs of increase in body fat.
Patients with evidence of increase in body fat should have a throrough cardiovascular risk assessment.

Lipid elevations:

Treatment with TELZIR plus ritonavir 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 tuberculosis, 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. Auto-immune 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.

Osteonecrosis:

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

Interactions:

Interactions with other medicines have been identified (see section 4.5 and section 4.3).
Caution is advised with the concomitant use of TELZIR and rifabutin, anti-dysrhythmics, anticonvulsants, immunosuppressants, tricyclic antidepressants, oral anticoagulants, and herbal medicines (see section 4.5).
Concomitant use of TELZIR 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 (see section 4.5).
Because there may be an increased risk with co-administration of TELZIR, ritonavir and oral contraceptives, alternative non-hormonal methods of contraception are recommended for women of childbearing potential (see section 4.5).

No data are available on the co-administration of TELZIR and ritonavir with oestrogens and/or progestogens when used as hormonal replacement therapies. The efficacy and safety of these therapies with TELZIR and ritonavir has not been established.

Co-administration of TELZIR/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 medicines. Please refer to the relevant product information for these medications (see section 4.5).

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 (see section 4.5).

Hepatitis C virus (HCV) Direct-Acting Antivirals: When hepatitis C virus direct-acting antiviral (DAA) medicines, which are metabolised by CYP3A4 or are inducers/inhibitors of CYP3A4, are co-administered with TELZIR/ritonavir, altered plasma concentrations of medicines 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 medicines.
- Loss of therapeutic effect of fosamprenavir/ritonavir or concomitant medicines and possible development of resistance.

Therefore, co-administration of TELZIR/ritonavir is not recommended with HCV DAA medicines, 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 medicines.

Rhabdomyolysis:

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

Clinical chemistry abnormalities:

Severe 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 subjects, included: increased ALT (5-8 %); AST (4-6 %); serum lipase (4-6 %) and triglycerides (6 %). Total cholesterol elevations were observed in less than 1 % of subjects.

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

4.5 Interaction with other medicines and other forms of interaction:

When fosamprenavir and ritonavir are co-administered, the ritonavir metabolic medicine interaction profile may predominate because ritonavir is a more potent CYP3A4 inhibitor. The full prescribing information for ritonavir must therefore be consulted prior to initiation of therapy with TELZIR and ritonavir.

Interaction studies have only been performed in adults.

Ritonavir is a potent inhibitor of the cytochrome P450 isoform CYP3A. Ritonavir also inhibits CYP2D6 and induces CYP3A4, CYP1A2, CYP2C9 and glucuronosyl transferase. Amprenavir, the active metabolite of fosamprenavir, is a less potent CYP3A4 inhibitor than ritonavir.

Interactions involving CYP3A4: Amprenavir, the active metabolite of fosamprenavir, and ritonavir are primarily metabolised in the liver by CYP3A4. Therefore, medicines that either share this metabolic pathway or modify CYP3A4 activity may modify the pharmacokinetics of amprenavir and ritonavir. Similarly, administration of fosamprenavir in combination with ritonavir

may modify the pharmacokinetics of other medicines that share this metabolic pathway (see section 4.3 and section 4.4).

The medicines listed below include examples of substrates, inhibitors, or inducers of CYP3A4 that could interact with TELZIR 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 TELZIR and ritonavir.

Interactions involving CYP2D6:

Ritonavir is an inhibitor of CYP2D6. Therefore, the combination of ritonavir with fosamprenavir may result in increased plasma concentrations of medicines that are primarily metabolised by CYP2D6 (see section 4.3).

Associations contraindicated (see section 4.3*)*:

TELZIR in combination with ritonavir must not be administered concurrently with medicines with narrow therapeutic windows that are substrates of cytochrome P450 3A4 (CYP3A4). Co-administration may result in competitive inhibition of the metabolism of these medicines and create the potential for serious and/or life-threatening adverse events such as cardiac dysrhythmia (e.g. cisapride, pimozide, ketoconazole, itraconazole), hypotension (for example, the alpha blocker alfuzosin), prolonged sedation or respiratory depression (e.g. triazolam, midazolam, quetiapine) or peripheral vasospasm or ischaemia (e.g. ergot derivatives) or rhabdomyolysis (e.g. lovastatin and simvastatin) (see section 4.3).

TELZIR/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).

TELZIR in combination with ritonavir should not be co-administered with medicines that are highly dependent on CYP2D6 metabolism and for which elevated plasma concentrations are

associated with serious and/or life-threatening results. These medicines include flecainide and propafenone (see section 4.3).

Rifampicin reduces the amprenavir plasma AUC by approximately 82 %. Based on information for other protease inhibitors, it is expected that co-administration of TELZIR and ritonavir with rifampicin will also result in large decreases in plasma concentrations of amprenavir. Accordingly, TELZIR in combination with ritonavir should not be co-administered with rifampicin (see section 4.3).

Serum levels of amprenavir and ritonavir can be reduced by concomitant use of the herbal preparation St John's Wort (*Hypericum perforatum*). This is due to metabolising enzymes being induced by St John's Wort. Herbal preparations containing St John's Wort should therefore not be combined with TELZIR and ritonavir. If a patient is already taking St John's Wort, it should be stopped. Amprenavir and ritonavir levels may increase on stopping St John's Wort. The inducing effect may persist for at least 2 weeks after cessation of treatment with St John's Wort (see section 4.3).

There is no information on interaction with other herbal preparations, including spirulina, African potato and garlic. These products should therefore be avoided.

Ketoconazole/Itraconazole: amprenavir and ritonavir both significantly increase plasma concentrations of ketoconazole and are expected to increase itraconazole concentrations. Ketoconazole and itraconazole (> 200 mg/day) should not be used concomitantly with TELZIR and ritonavir (see section 4.3).

Rifampicin: rifampicin is a potent inducer of CYP3A4. Concomitant administration with amprenavir resulted in a reduction of amprenavir C_{min} and AUC by 92 % and 82 %, respectively. Rifampicin must not be used concomitantly with the TELZIR/ritonavir combination (see section 4.3).

Additional associations, precautions for use:

Antiretroviral medicines:

Non-nucleoside reverse transcriptase inhibitors:

Efavirenz: concurrent administration of efavirenz (600 mg once daily) with the fosamprenavir and ritonavir once daily regimen (fosamprenavir 1 400 mg once daily and ritonavir 200 mg once daily) decreased plasma amprenavir AUC by 13 % and C_{min} by 36 %. An increase in the ritonavir dose to 300 mg once daily is recommended in order to maintain plasma amprenavir concentrations.

When efavirenz (600 mg once daily) was co-administered with the fosamprenavir and ritonavir twice daily regimen (fosamprenavir 700 mg twice daily and ritonavir 100 mg twice daily) plasma amprenavir concentrations were not significantly changed.

Nevirapine: 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 TELZIR (700 mg twice daily) plus ritonavir (100 mg twice daily), no dose adjustment is necessary. The TELZIR with ritonavir once daily regimen has not been studied.

Delavirdine: no dose recommendations can be given for the co-administration of the TELZIR/ritonavir combination and delavirdine. If these medicines are used concomitantly care is advised, as delavirdine may be less effective due to decreased and potentially sub-therapeutic plasma concentrations.

Nucleoside/Nucleotide reverse transcriptase inhibitors: No dose adjustment is considered necessary when the following antiretroviral medicines are co-administered with fosamprenavir and ritonavir: 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 the following sections. Appropriate doses of these combinations with respect to safety and efficacy have not been established.

Lopinavir/ritonavir: the $C_{max,}$ AUC and C_{min} of lopinavir were increased by 30 %, 37 % and 52 % respectively when the lopinavir/ritonavir combination (400 mg/100 mg twice daily for 2 weeks) was given with fosamprenavir/ritonavir (700 mg/100 mg twice daily for two weeks). The C_{max}, AUC and C_{min} of amprenavir were decreased by 58 %, 63 % and 65 % respectively.

The C_{max}, AUC and C_{min} of lopinavir were unchanged (compared with values observed when lopinavir/ritonavir 400 mg/100 mg was administered twice daily for two weeks) when the lopinavir/ritonavir combination (533 mg/133 mg twice daily for 2 weeks) was given with fosamprenavir (1 400 mg twice daily for two weeks). The C_{max}, AUC and C_{min} of amprenavir were decreased by 13 %, 26 % and 42 % respectively compared to values obtained with fosamprenavir/ritonavir, 700/100 mg twice daily dosing for two weeks.

Indinavir: amprenavir (750 or 800 mg three times daily) was administered for 2 weeks to patients receiving concomitant indinavir (800 mg three times daily, fasted). Amprenavir steady state C_{max}, AUC, and C_{min} were significantly increased by 18 %, 33 %, and 25 %, respectively. Compared to historic data, indinavir steady state C_{max}, AUC, and C_{min} were decreased by 22 %, 38 %, and 27 %, respectively.

Saquinavir: amprenavir (750 or 800 mg three times daily) was administered for 2 weeks to patients receiving concomitant saquinavir (800 mg three times daily, fed state). Amprenavir steady state C_{max}, AUC and C_{min} were significantly decreased by 37 %, 32 % and 14 % respectively. Compared to historic data, the saquinavir steady state C_{max}, AUC, and C_{min} were significantly increased by 21 %, decreased 19 % and decreased 48 % respectively.

Nelfinavir: amprenavir (750 or 800 mg three times daily) was administered for 2 weeks to patients receiving concomitant nelfinavir (750 mg three times daily, fed state). Amprenavir steady state C_{max}, and C_{min} were significantly decreased by 14 % and increased 189 % respectively. Compared to historic data, the nelfinavir steady state C_{max}, AUC, and C_{min} were increased by 12 %, 15 %, and 14 %, respectively.

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-τ) decreased by 22 %, C_{max} by 24 % and C_{τ} remained unchanged relative to values obtained from atazanavir (300 mg once daily) plus ritonavir (100 mg once daily).

- ***Integrase inhibitors:***

Raltegravir: Reductions in amprenavir C_{min} of 19-33% and raltegravir C_{min} of 36-54% were observed following the co-administration of fosamprenavir/ritonavir 700/100mg twice daily and raltegravir 400 mg twice daily. Reductions in amprenavir C_{min} of 17-50% and raltegravir C_{min} of 25-41% were observed following the co-administration of fosamprenavir/ritonavir 1400/100 mg once daily and raltegravir 400 mg twice daily. The clinical significance of these reductions is unknown.

Dolutegravir: Amprenavir pharmacokinetics were unchanged following co-administration of fosamprenavir/ritonavir 700/100mg twice daily with dolutegravir 50 mg once daily. Dolutegravir $AUC_{(0-\tau)}$, C_{max}, and C_{τ} 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. Maraviroc exposures are increased by approximately 2-fold when administered with fosamprenavir/ritonavir. Clinical studies showed comparable efficacy between fosamprenavir/ritonavir with maraviroc 150 mg twice daily and other boosted PIs with maraviroc 150 mg twice daily; if TELZIR/ritonavir is co-administered with maraviroc, the recommended dose of maraviroc is 150 mg twice daily. No dosage adjustment is required for TELZIR with ritonavir.

Anti-hepatitis C medicinal products:

Telaprevir: Concomitant administration of TELZIR with ritonavir and telaprevir results in reduced steady state exposure to both amprenavir and telaprevir. The mechanism of interaction is unknown. Concomitant administration of TELZIR with ritonavir and telaprevir is not recommended.

Antibiotics/Antifungals:

Clarithromycin: ritonavir significantly increases plasma concentrations of clarithromycin. A reduction in the clarithromycin dose should be considered when co-administered with TELZIR 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 medicines are expected to be increased when co-administered.

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 in the rifabutin dosage by at least 75 % is recommended when administered with TELZIR with ritonavir. Further dose reduction may be necessary**.**

Other medicines:

Antacids: the AUC and C_{max} of amprenavir were decreased by 18 % and 35 % respectively, whilst the C_{min} (C12) was increased by 14 %, when a single 1 400 mg dose of fosamprenavir was co-administered with a single 30 ml dose of antacid suspension (equivalent to 3 g aluminium hydroxide and 1,5 g magnesium hydroxide). No dose adjustment for any of the respective medicines is considered necessary when administered concomitantly, however, there is no information on multiple doses of each medicine given together.

Antimalarials: The use of TELZIR concomitantly with halofantrine is not recommended because increased plasma halofantrine exposure may increase the risk of life-threatening dysrhythmia.

Histamine H_2 receptor antagonist: serum levels of amprenavir can be reduced by concomitant use of histamine H_2 receptor antagonists (e.g. ranitidine and cimetidine). Concurrent administration of ranitidine (300 mg single dose) with fosamprenavir (1 400 mg single dose) decreased plasma amprenavir AUC by 30 % and C_{max} by 51 %. There was, however, no change observed in the amprenavir C_{min} (C12). No dose adjustment for any of the respective medicines is considered necessary when administered concomitantly.

Proton pump inhibitors: Co-administration of esomeprazole (20 mg once daily) with TELZIR (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 medicines is considered necessary when administered concomitantly.

Medicines with a narrow therapeutic window: For some substances that can cause serious or life-threatening adverse experiences, such as amiodarone, quinidine, lidocaine (by systemic route), tricyclic antidepressants (e.g. desipramine and nortriptyline), plasma concentration monitoring should be done. When warfarin or other oral anticoagulants are co-administered with TELZIR a re-inforced monitoring of INR (International Normalised Ratio) is recommended (see section 4.3).

Anticonvulsant medicines:

Phenytoin: The AUC and C_{min} of amprenavir were increased by 20 % and 19 % respectively, with C_{max} unchanged when TELZIR (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 TELZIR plus ritonavir is given in combination with phenytoin, no change to the TELZIR 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 anticonvulsant medicines: concomitant administration of other anticonvulsant medicines known to be enzymatic inducers (e.g. phenobarbital, carbamazepine) has not been studies 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).

Bepridil: 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 medicine metabolism, and because increased plasma bepridil exposure may increase the risk of life-threatening dysrhythmia, caution is warranted when TELZIR and ritonavir are co-administered with bepridil.

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, tadalafil and vardenafil) are expected to substantially increase when co-administered with TELZIR and ritonavir and may result in an increase in PDE5 inhibitor associated adverse events including hypotension, visual changes and priapism. Concomitant use of PDE5 inhibitors for the treatment of erectile dysfunction or pulmonary arterial hypertension is not recommended (see section 4.4). Concomitant use of TELZIR/ritonavir is contraindicated in patients being treated with sildenafil for pulmonary arterial hypertension (see section 4.3).

Fluticasone propionate (interaction with ritonavir): in a clinical study where ritonavir 100 mg capsules twice daily were co-administered with 200 μg intranasal fluticasone propionate (once daily) for seven days in healthy subjects, the fluticasone propionate plasma levels increased significantly, whereas the intrinsic cortisol levels decreased by approximately 86 %. Greater

risks of systemic effects are expected when fluticasone propionate is administered via the orally inhaled route.

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).

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.

HMG-CoA reductase inhibitors: HMG-CoA reductase inhibitors taken in combination with HIV protease inhibitors may result in an increase in the blood levels of the HMG-CoA reductase inhibitor, with an increase in the risk of myopathy. HMG-CoA reductase inhibitors which are highly dependent on CYP3A4 for metabolism, such as lovastatin and simvastatin, are expected to have markedly increased plasma concentrations when co-administered with TELZIR and ritonavir. Since increased concentrations of HMG-CoA reductase inhibitors may cause myopathy, including rhabdomyolysis, the combination of lovastatin or simvastatin with TELZIR and ritonavir must not be used (see section 4.3).

The C_{max}, AUC and C_{min} of atorvastatin were increased by 184 %, 153 % and 73 % respectively when atorvastatin (10 mg once daily for 4 days) was given with TELZIR/ritonavir (700 mg/100 mg twice daily for two weeks). The C_{max}, AUC and C_{min} of amprenavir were unchanged. When used with TELZIR in combination with ritonavir, doses of atorvastatin no greater than 20 mg/day should be administered, with careful monitoring of liver function and CPK, for atorvastatin toxicity. No adjustment of the TELZIR/ritonavir dose is required when co-administered with atorvastatin. 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.

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

Methadone: co-administration of TELZIR 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 % respectively. 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. On the basis of these data no dose adjustment is necessary when TELZIR with ritonavir is co-administered with methadone.

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

Steroids: co-administration of TELZIR 700 mg twice daily + ritonavir 100 mg twice daily with ethinyl 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_{τ} by 34 %, 38 %, and 26 %, respectively. Steady state plasma amprenavir pharmacokinetic (PK) parameters were not significantly affected by co-administration with EE 0,035 mg/NE 0,5 mg; however, ritonavir $AUC_{(0-\tau)}$ and C_{max} were 45 % and 63 % higher, respectively, compared to historical data in female subjects dosed with TELZIR/ritonavir alone. In addition to the decreased hormonal contraceptive exposures, co-administration of TELZIR with ritonavir and EE 0,035 mg/NE 0,5 mg 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).

Antineoplastic medicines:

When antineoplastic medicines (for example dasatinib, nilotinib, ibrutinib, vinblastine and everolimus) that are metabolised by CYP3A are co-administered with TELZIR 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 nes. In

case of concomitant administration with antineoplastic medicines metabolized by CYP3A, please refer to the relevant product information for these medicines.

Antipsychotics:

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

Lurasidone: Concomitant administration of TELZIR/ritonavir with lurasidone is contraindicated due to the potential for serious and/or life-threatening reactions (see section 4.3).

4.6 Fertility, pregnancy and lactation:

The safety of TELZIR in pregnancy has not been established. TELZIR should not be used during pregnancy as there is no information on the use of TELZIR in pregnancy.

Pregnancy: In pregnant rats and rabbits there were no major effects on embryo-foetal development. However systemic plasma exposures (AUC) to amprenavir in these studies were similar (rats) or lower (rabbits) than exposure in patients in clinical studies with TELZIR. In view of the low exposure in rabbits, the potential developmental toxicity of TELZIR has not been fully determined.

Breastfeeding: The safety of TELZIR in breastfeeding has not been established. Due to the possibility of transfer of the HIV virus in maternal milk, breastfeeding of infants is not recommended.

Fertility: No human data on the effect of fosamprenavir on fertility are available. In rats, there was no major effect on fertillty or reproductive performance with fosamprenavir (see section 5.3).

4.7 Effects on ability to drive and use machines:

TELZIR can cause dizziness which may affect the ability to drive and use machines.

4.8 Undesirable effects:

Adverse reactions are listed by MedDRA system organ class and absolute frequency.

Frequencies are defined as very common (≥1/10), common (≥1/100, <1/10), uncommon (≥1/1 000, <100) and rare (≥1/10 000, <1/1 000).

Frequency categories for the events listed below have been based on clinical trials data.

Most the adverse events below come from two large clinical studies in adults.

The most frequent clinical adverse event related to study medicine, of at least moderate intensity (Grade 2 or more) and occuring in at least 2 % of patients are included.

Metabolism and nutrition disorders:

Common: hypertriglyceridaemia (see section 4.4)

Nervous system disorders:

Common: headache

Gastrointestinal disorders:

Very common: diarrhoea

Common: loose stools, nausea, vomiting, abdominal pain

Skin and subcutaneous tissue disorders:

Common: rash

Rare: Stevens-Johnson Syndrome

Erythematous or maculopapular cutaneous eruptions, with or without pruritus, may occur during therapy. The rash most generally will resolve spontaneously without the necessity of discontinuing of treatment with the TELZIR/ritonavir combination. TELZIR/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)

Renal and urinary disorders:

Uncommon**:** renal stones.

General disorders and administration site conditions:

Common: fatigue

Investigations:

Very common: blood cholesterol increased

Common: Blood triglycerides increased, alanine aminotransferase increased, aspartate aminotransferase increased, lipase increased.

Post-Marketing:

In addition to adverse reactions reported from clinical trials, the following reactions have been reported post-approval use of TELZIR. The frequencies of the following adverse events are unknown.

Cardiac disorders: myocardial infarction

Immune system disorders: angioedema

Metabolism and nutritional disorders: hypercholesterolaemia (see section 4.4)

Nervous system disorders: dizziness, oral paraesthesia.

Reporting of side effects:

If you get side effects, talk to your doctor or pharmacist or nurse. You can also report side effects to SAHPRA via the "**6.04 Adverse Drug Reaction Reporting Form**", found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8. By reporting side effects, you can help provide more information on the safety of TELZIR.

4.9 Overdose:

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

5. PHARMACOLOGICAL PROPERTIES:

A 20.2.8 Antiviral agents

5.1 Pharmacodynamic Properties:

Fosamprenavir requires metabolism *in vivo* to generate the active moiety, amprenavir. In the absence of *in vivo* metabolism, fosamprenavir has negligible activity *in vitro.* Amprenavir is a competitive inhibitor of the HIV protease. It blocks the ability of the viral protease to cleave the precursor polyproteins necessary for viral replication.

Amprenavir is a 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 additive anti-HIV-1 activity in combination with the non-nucleoside reverse transcriptase inhibitor (NNRTI) nevirapine and protease inhibitors (PIs) indinavir, lopinavir, ritonavir and nelfinavir *in vitro*.

Administration of fosamprenavir/ritonavir combination regimens (700/100 mg twice daily and 1 400/200 mg once daily) results in 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 μg/ml) to heavily PI-experienced (mean protein-binding adjusted IC_{50} = 0,90 μg/ml).

Resistance *in vivo*: protease inhibitor naïve subjects:

Development of resistance to amprenavir during therapy may involve mainly mutations I50V or I54L/M or V32I+I47V or, rarely, I84V. Each of these four genetic patterns may be accompanied by additional secondary mutations, in particular M46I/I, and produces viruses with reduced susceptibility to amprenavir, some cross resistance to ritonavir, but susceptibility to indinavir, nelfinavir and saquinavir is retained.

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. In the PI-experienced population, it is not certain that mutations which emerge during therapy are always attributable to the study regimen. There is the possibility that mutations were present or archived as minority species following a prior PI regimen, and initiation of the subsequent regimen results in their re-appearance, particularly in the early weeks following the initiation of the new regimen. However, mutations that emerged post-week 8 with fosamprenavir/ritonavir in previously PI experienced subjects in study APV30003 were generally substitutions that have been associated with the emergence of resistance to amprenavir.

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

5.2 Pharmacokinetic Properties:

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

The pharmacokinetic properties of amprenavir following co-administration of fosamprenavir and ritonavir in healthy adult subjects and HIV-infected patients showed no substantial differences. Co-administration of ritonavir with fosamprenavir increases plasma amprenavir concentrations primarily through inhibition of amprenavir metabolism.

Fosamprenavir tablet and oral suspension formulations, when given fasted, delivered equivalent plasma amprenavir AUC_{∞} values and the fosamprenavir oral suspension formulation delivered a 14 % higher plasma amprenavir C_{max} as compared to the oral tablet formulation.

To aid palatability and assist compliance, the dosing recommendations are to administer the TELZIR oral suspension with food in children and adolescents. The dose recommendations for this population were based on the paediatric studies where the TELZIR oral suspension was administered with food, and therefore take into account the observed food effect (see section 4.2).

Absorption:

After multiple dose oral administration of fosamprenavir 1 400 mg once daily and ritonavir 200 mg once daily, amprenavir was absorbed with a geometric mean (95 % CI) steady state peak plasma amprenavir concentration (C_{max}) of 7,24 (6,32-8,28) μg/ml occurring approximately 2 (0,8-5,0) hours after dosing (t_{max}). The mean steady state plasma amprenavir trough concentration (C_{min}) was 1,45 (1,16-1,81) μg/ml and $AUC_{24,ss}$ was 69,4 (59,7-80,8) h.μg/ml. After multiple dose oral administration of fosamprenavir 700 mg twice daily and ritonavir 100 mg twice daily, amprenavir was absorbed with a geometric mean (95 % CI) steady state peak plasma amprenavir concentration (C_{max}) of 6,08 (5,38-6,86) μg/ml occurring approximately 1,5 (0,75-5,0) hours after dosing (t_{max}). The mean steady state plasma amprenavir trough concentration (C_{min}) was 2,12 (1,77-2,54) μg/ml and $AUC_{24,ss}$ was 79,2 (69,0-90,6) h.μg/ml. Administration of the fosamprenavir tablet formulation with a high fat meal did not alter plasma amprenavir pharmacokinetics (C_{max}, t_{max} or $AUC_{0-\infty}$) compared to the administration of this formulation in the fasted state. TELZIR tablets may be taken without regard to food intake. Administration of the fosamprenavir oral suspension formulation with a high fat meal reduced plasma amprenavir AUC by approximately 29 % and C_{max} by approximately 46 % as compared to the administration of this formulation in the fasted state. For adult patients the fosamprenavir oral suspension should be taken without food and on an empty stomach. In children and adolescents, the fosamprenavir oral suspension should be taken with food. The dose recommendations for this population therefore take into account the observed food effect (see section 4.2).

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

Distribution:

The apparent volume of distribution of amprenavir following administration of fosamprenavir is approximately 430 ℓ (6 ℓ/kg assuming a 70 kg body weight), suggesting a large volume of distribution, with penetration of amprenavir freely into tissues beyond the systemic circulation. 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:

Fosamprenavir is almost completely hydrolysed to amprenavir and inorganic phosphate as it is absorbed through the gut epithelium, following oral administration. Amprenavir is primarily metabolised by the liver with less than 1 % excreted unchanged in the urine. The primary route of metabolism is via the cytochrome P450 3A4 enzyme. Amprenavir metabolism is inhibited by ritonavir, via inhibition of CYP3A4, resulting in increased plasma concentrations of amprenavir. Amprenavir in addition is also an inhibitor of the CYP3A4 enzyme, although to a lesser extent than ritonavir.

Therefore, medicines that are inducers, inhibitors or substrates of CYP3A4 must be used with caution when administered concurrently with fosamprenavir and ritonavir (see section 4.3 and section 4.5).

Elimination:

Following administration of fosamprenavir, the mean 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 and unchanged amprenavir 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 TELZIR (oral suspension or tablets) plus ritonavir (oral suspension or tablets) 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 the table below.

Table 1: Pharmacokinetic parameters in paediatric patients receiving TELZIR with ritonavir twice daily

Parameter	**6–11 years**		**12–18 years**	
	n	TELZIR 18 mg/kg plus Ritonavir 3 mg/kg Twice daily	n	TELZIR 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_{τ} (µg/ml)	17	2,69 (2,15, 3,36)	24	1,61 (1,21, 2,15)

Elderly: The pharmacokinetics of fosamprenavir 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 medicine therapy.

Renal impairment: Patients with renal impairment have not been specifically studied. Less than 1 % of the therapeutic dose of amprenavir is excreted unchanged in the urine.

Hepatic impairment*:* Fosamprenavir is converted in humans 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 mild or moderate hepatic impairment receiving fosamprenavir with ritonavir compared to matched control subjects with normal hepatic function.

For subjects with mild hepatic impairment (Child-Pugh 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) based on slightly higher plasma amprenavir C_{max} (17 %), slightly higher plasma amprenavir $AUC_{(0-\tau)}$ (22 %), and similar C_{τ} 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 (Child-Pugh 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). 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_{τ} values, plasma unbound amprenavir C_{τ} 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_{τ}, and approximately 42 % lower unbound C_{τ} 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 (Child-Pugh score of 10-13), a reduced dose of fosamprenavir 300 mg twice daily with a reduced dosing frequency of ritonavir 100 mg once daily delivered 19 % lower plasma amprenavir C_{max}, 23 % lower $AUC_{(0-\tau)}$, and 38 % lower C_{τ}

values, but similar unbound plasma amprenavir C_τ 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_τ than achieved in subjects with normal hepatic function receiving the standard fosamprenavir with ritonavir 700 mg/100 mg twice daily regimen.

6. PHARMACEUTICAL PARTICULARS:

6.1 List of Excipients:

TELZIR TABLETS:

The tablets also contain the following excipients: hypromellose, titanium dioxide (E171), triacetin, iron oxide red (E172), microcrystalline cellulose, croscarmellose sodium, povidone K30, magnesium stearate and colloidal silicon dioxide.

TELZIR ORAL SUSPENSION:

Preservatives:

Methyl parahydroxybenzoate

Propyl parahydroxybenzoate

The oral suspension also contains the following excipients: hypromellose, sucralose, propylene glycol, polysorbate 80, calcium chloride dihydrate, artificial grape bubblegum flavour, natural peppermint flavour and purified water.

6.2. Incompatibilities:

TELZIR TABLETS:

Not applicable.

TELZIR ORAL SUSPENSION:

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

6.3 Shelf life:

TELZIR TABLETS: 24 months

TELZIR ORAL SUSPENSION: 24 months

6.4 Special precautions for storage:

TELZIR TABLETS:

Store at or below 30 °C.

TELZIR ORAL SUSPENSION:

Store at or below 30 °C. Do not freeze.

Discard 28 days after first opening.

6.5 Nature and contents of container:

TELZIR TABLETS:

White HDPE bottles with a child-resistant closure containing 60 tablets.

TELZIR ORAL SUSPENSION:

White HDPE bottle with a child-resistant closure containing 225 ml oral suspension. A 10 ml dosing syringe is provided in the pack.

6.6 Special precautions for disposal:

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

7. HOLDER OF CERTIFICATE OF REGISTRATION:

GlaxoSmithKline South Africa (Pty) Ltd

39 Hawkins Avenue

Epping Industria 1, 7460

8. REGISTRATION NUMBER:

TELZIR TABLETS: A38/20.2.8/0378

TELZIR ORAL SUSPENSION: A38/20.2.8/0379

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

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