PRODUCT PROFILE

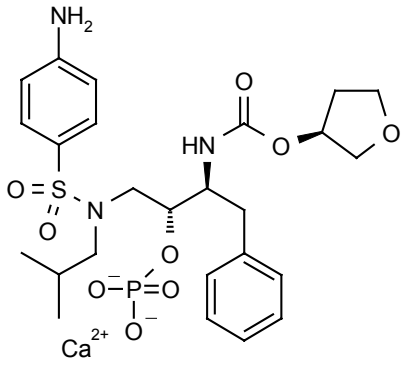
TYPE OF APPLICATION

This is a full Marketing Authorisation Application for fosamprenavir, which is a new active substance presented as two pharmaceutical forms:

Fosamprenavir film-coated tablets	(Each film-coated tablet contains 700 mg of fosamprenavir as fosamprenavir calcium)
Fosamprenavir Oral Suspension	(each mL of suspension contains 50mg of fosamprenavir as fosamprenavir calcium)

CHEMICAL AND PHARMACOKINETIC PROPERTIES

The chemical name of fosamprenavir calcium is (3*S*)-Tetrahydrofuran-3-yl (1*S*,2*R*)-3-[[(4-aminophenyl) sulphonyl](isobutyl)amino]-1-benzyl-2-(phosphonooxy) propylcarbamate monocalcium salt. Fosamprenavir calcium is a single stereoisomer with the (3*S*) (1*S*,2*R*) configuration. It has a molecular formula of $C_{25}H_{34}CaN_3O_9PS$ and a molecular weight of 623.7. Fosamprenavir calcium is a white to cream coloured solid. It has the following structural formula:



Fosamprenavir is almost entirely (99%) converted to the active moiety, amprenavir (APV), at or near the intestinal epithelium via alkaline phosphatase. Plasma fosamprenavir exposure is minimal (fosamprenavir AUC <0.6% of corresponding APV AUC). The absolute bioavailability of APV from fosamprenavir cannot be determined. Plasma APV concentrations can be quantified as early as 0.25 hours post dosing and maximum plasma APV concentrations are measured at approximately 1.5 to 2 hours following both single-dose and multiple-dose administration. APV has a large (430L) apparent oral volume of distribution in humans, suggesting that APV penetrates freely into tissues beyond the systemic circulation. The principal route of APV elimination is hepatic metabolism via CYP3A4; minimal APV (<1% of dose) is eliminated unchanged in urine. Fosamprenavir is recommended for coadministration with ritonavir (RTV) because RTV enhances plasma APV exposure primarily through inhibition of APV metabolism (CYP3A4), thus achieving plasma APV concentrations above the IC_{50} for APV against HIV from patients with various levels of HIV protease inhibitor experience, including PI-naïve and multiple-PI-experienced patients. Coadministration of

fosamprenavir with ritonavir (RTV) does not appear to alter the absorption of fosamprenavir or the conversion of fosamprenavir to APV based on achievement of similar low plasma fosamprenavir concentrations and a similar plasma APV $t_{max,ss}$. Steady-state plasma APV geometric mean PK parameter values following administration of each of the two recommended fosamprenavir tablet regimens are as follows: fosamprenavir 1400mg OD + RTV 200mg OD: $AUC_{24,ss}$: 69.4h*µg/mL, $C_{max,ss}$: 7.24µg/mL, $C_{\tau,ss}$: 1.45µg/mL, $t_{max,ss}$: 2.1h; fosamprenavir 700mg BID + RTV 100mg BID: $AUC_{24,ss}$: 79.2h*µg/mL, $C_{max,ss}$: 6.08µg/mL, $C_{\tau,ss}$: 2.12µg/mL, $t_{max,ss}$: 1.5h.

Fosamprenavir tablets may be taken without regard to food intake because plasma APV AUC_{∞} and C_{max} values were bioequivalent when 908 tablets were administered with a high-fat meal compared to fasting. However, administration of the fosamprenavir oral suspension formulation with a high-fat meal reduced plasma APV AUC_{∞} by 29% and C_{max} by 46%. Thus, for convenience the suspension formulation is recommended to be administered to adults with food at an increased dose of either 900mg BID + RTV 100mg BID or 1800mg OD + RTV 200mg OD.

MODE OF ACTION

Fosamprenavir is the phosphate ester prodrug of APV and requires *in vivo* metabolism to release the active moiety, APV, and has little or no antiviral activity in the absence of this metabolism. *In vitro* studies have been performed to investigate the activities and mechanisms of action of fosamprenavir and a comprehensive evaluation of the mechanism of action of APV was completed as part of the nonclinical development programme for that compound. APV has been shown to be a potent inhibitor of HIV-1 and HIV-2 proteases

In clinical studies, fosamprenavir in combination with low dose ritonavir once daily and twice daily used in combination with abacavir and lamivudine has been shown to be effective in the treatment of HIV infection in adults.

INDICATIONS AND POSOLOGY

Fosamprenavir in combination with low dose ritonavir is indicated for the treatment of Human Immunodeficiency Virus (HIV) infected adults for use in combination with other antiretroviral agents

Adults (greater than or equal to 18 years of age)*:* The recommended tablet dose is 1400 mg fosamprenavir once daily with 200 mg ritonavir once daily or 700 mg fosamprenavir twice daily with 100 mg ritonavir twice daily. The recommended dose for fosamprenavir oral suspension is 1800 mg once daily with 200 mg ritonavir once daily or 900 mg twice daily with 100 mg ritonavir twice daily Both regimens must be administered in combination with other antiretroviral agents.

Children (less than 12 years of age) and adolescents 12 to 17 years of age*:* The safety and efficacy of fosamprenavir in combination with ritonavir has not yet been established in this patient population

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

For convenience, fosamprenavir oral suspension should be taken with food.

Renal impairment*:* No initial dose adjustment is considered necessary in patients with renal impairment

Hepatic impairment*:* Fosamprenavir is converted in man to amprenavir. The principal route of amprenavir and ritonavir elimination is hepatic metabolism. There are limited data regarding the use of this combination in patients with hepatic impairment and therefore specific dosage recommendations cannot be made. Consequently, fosamprenavir in combination with ritonavir should be used with caution in patients with mild or moderate hepatitic impairment and must not be used in those with severe hepatic impairment

PRECAUTIONS

Patients should be advised that treatment with the fosamprenavir / 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. 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 / ritonavir versus those who received fosamprenavir / ritonavir and did not have a sulphonamide allergy. Yet, fosamprenavir in combination with ritonavir should be used with caution in patients with a known sulphonamide allergy.

Hepatic / Renal dysfunction: There are limited data on the pharmacokinetics and safety of the fosamprenavir / ritonavir combination in patients with significant hepatic or renal dysfunction. Amprenavir and ritonavir are both principally metabolised by the liver and thus caution should be exercised when administering the fosamprenavir / ritonavir combination to patients with mild or moderate hepatic impairment and should not be used in patients with severe hepatic impairment (see 4.3 Contraindications). 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.

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.

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.

The HMG-CoA reductase inhibitors lovastatin and simvastatin are highly dependent on CYP3A4 for metabolism, thus concomitant use of Telzir and ritonavir with simvastatin or lovastatin is not recommended due to an increased risk of myopathy, including rhabdomyolysis. Caution must also be exercised if Telzir and ritonavir are used concurrently with atorvastatin, which is metabolized to a lesser extent by CYP3A4. In this situation, a reduced dose of atorvastatin should be considered (see 4.5 Interactions with other medicinal products and other forms of interaction). If treatment with a HMG-CoA reductase inhibitor is indicated, pravastatin or fluvastatin are recommended (see 4.5 Interaction with other medicinal products and other forms of interaction).

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 CYP 3A4 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 fosamprenavir and ritonavir are coadministered with bepridil.

Serious and/or life-threatening drug interactions could occur between amprenavir or ritonavir 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.

Particular caution must be used when prescribing sildenafil in patients receiving fosamprenavir and ritonavir. Co-administration of fosamprenavir and ritonavir with sildenafil is expected to substantially increase sildenafil concentrations and may result in an increase in sildenafil-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 with fosamprenavir a larger increase in rifabutin concentrations is expected. A reduction of rifabutin dosage of at least 50 % the recommended dose is recommended when administered with fosamprenavir and ritonavir and patients should be clinically monitored.

Because of the potential for interactions with amprenavir and ritonavir, the efficacy of hormonal contraceptives may be modified but there is insufficient information to predict the nature of the interactions. Therefore, alternative reliable barrier methods of contraception are recommended for women of childbearing potential.

Amprenavir and ritonavir both decrease plasma concentrations of methadone. Therefore, when methadone is co-administered with fosamprenavir in combination with ritonavir, patients should be monitored for opiate abstinence syndrome. No recommendations can currently be made regarding adjustment of methadone dose when co-administered with fosamprenavir.

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. The full prescribing information of ritonavir should be referred to prior to undertaking the dosing regimen of Telzir and ritonavir with other medicinal products.

Rash/cutaneous reactions: Most patients with mild or moderate rash can continue the fosamprenavir / ritonavir combination. 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. The fosamprenavir / ritonavir combination should be permanently discontinued in case of severe rash, or in case of rash of moderate intensity with systemic or mucosal symptoms.

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 reintroduced if treatment had been discontinued. A causal relationship has been evoked, although the mechanism of action has not been elucidated. Haemophiliac patients should therefore be informed of the possibility of increased bleeding.

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

Redistribution of body fat : combination antiretroviral therapy, including regimens containing a protease inhibitor, is associated with redistribution of body fat in some patients. Protease inhibitors are also associated with metabolic abnormalities such as hypertriglyceridemia, hypercholesterolemia, insulin resistance and hyperglycaemia. Clinical examination should include evaluation for physical signs of fat redistribution. Consideration should be given to measurements of serum lipids and blood glucose. The mechanisms of these events and long term consequences, such as increased risk of cardiovascular disease, are currently unknown.

Pregnancy: In pregnant rats and rabbits there were no major effects on embryo-fetal development. Systemic plasma exposures (AUC) to amprenavir in these studies was 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.

Telzir is not indicated during pregnancy. It should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Lactation: Due to the possibility of transfer of the HIV virus in maternal milk, breast-feeding of infants is contra-indicated.

CLINICAL SAFETY DATA

Fosamprenavir was not mutagenic or genotoxic in a standard battery of *in vitro* and *in vivo* assays.

In toxicity studies in rats and dogs, fosamprenavir produced evidence of gastrointestinal intolerance (salivation, vomiting and soft to liquid faeces). Hepatic changes (raised serum liver enzyme activities and microscopic changes) were also observed. In humans, raised serum liver enzymes have also been seen, however these were more commonly observed in patients co-infected with Hepatitis B and/or C (see 4.4 Special warnings and special precautions for use).

Carcinogenicity studies of fosamprenavir in rats and mice have not been completed; however, results are available from the carcinogenicity studies in mice and rats with amprenavir. Lifetime carcinogenicity studies with amprenavir have shown benign heptocellular adenomas in males at the high dose of 500 mg/kg/day in mice or 750 mg/kg/day in rats. Exposures at these dosages were similar to those seen in humans in clinical studies with fosamprenavir in combination with ritonavir. Altered heptocellular foci were seen in male mice at doses of 275 and 500 mg/kg/day.

REGISTRATION STATUS

Fosamprenavir in combination with ritonavir is not yet registered in any country. Marketing Applications will be also submitted to the USA, Canada, Australia and other Licensing Authorities worldwide.