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AGENERASE™
GlaxoSmithKline

Amprenavir

QUALITATIVE AND QUANTITATIVE COMPOSITION

Soft capsules: amprenavir 150 mg.
Oral Solution: amprenavir 15 mg/ml.

PHARMACEUTICAL FORM

Soft Capsules.
Oral Solution.

CLINICAL PARTICULARS

Indications

AGENERASE is indicated in combination with other antiretroviral agents for the treatment of Human Immunodeficiency Virus (HIV) infected patients.

Dosage and Administration

AGENERASE is administered orally and can be taken with or without food.

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

AGENERASE is also available as an oral solution for use in children or adults unable to swallow capsules. Amprenavir is 14% less bioavailable from the oral solution than from the capsules; therefore AGENERASE capsules and AGENERASE oral solution are not interchangeable on a mg per mg basis (see Pharmacokinetics).

Patients should discontinue AGENERASE oral solution as soon as they are able to take the capsule formulation (see Warnings and Precautions).

- **Adults and adolescents (from 13 years of age) greater than 50 kg body weight**

The recommended dose of AGENERASE capsules is 1200 mg twice daily in combination with other antiretroviral agents.

If AGENERASE capsules are used in combination with ritonavir in adults, reduced doses of AGENERASE (600 mg twice daily) and ritonavir (100 mg twice daily) are recommended.

The recommended dose of amprenavir oral solution is 1400 mg (93.3 ml) twice daily in combination with other antiretroviral agents.

- **Children (4 to 12 years) and subjects less than 50 kg body weight**

The recommended dose of AGENERASE capsules is 20 mg/kg body weight twice a day, or 15 mg/kg three times a day, in combination with other antiretroviral agents, without exceeding a total daily dose of 2400 mg.

The recommended dose of AGENERASE oral solution is 22.5 mg (1.5 ml)/kg body weight twice a day, or 17 mg (1.1 ml)/kg three times a day, in combination with other antiretroviral agents, without exceeding a total daily dose of 2800 mg.

The pharmacokinetic interactions between amprenavir and low doses of ritonavir or other protease inhibitors have not yet been evaluated in children. Therefore, such combinations should be avoided in children.

- **Children less than 4 years of age**

The safety and efficacy of AGENERASE capsules in children less than 4 years of age has not yet been established (see Pre-clinical Safety Data).

AGENERASE oral solution is contraindicated for use in children less than 4 years of age (see Contraindications and Pre-clinical Safety Data).

- **Elderly**

The pharmacokinetics of amprenavir have not been studied in patients over 65 years of age (see Pharmacokinetics).

- **Renal Impairment**

No initial dose adjustment of AGENERASE capsules is considered necessary in patients with renal impairment (see Pharmacokinetics).

AGENERASE oral solution should be used with caution in patients with renal impairment (see Warnings and Precautions).

• Hepatic Impairment

The principal route of metabolism and excretion of amprenavir is via the liver.

AGENERASE should be used with caution in patients with hepatic impairment (see Warnings and Precautions).

The dose of AGENERASE should be reduced to 450 mg (capsules) or 513 mg (34 ml oral solution) twice a day for patients with moderate hepatic impairment and to 300 mg (capsules) or 342 mg (23 ml oral solution) twice a day for patients with severe hepatic impairment (see Pharmacokinetics).

No dosage recommendation can be made in children with hepatic impairment.

Contraindications

- Known hypersensitivity to amprenavir or any ingredient of the formulation.
- AGENERASE must not be administered concurrently with medicinal products 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 medicinal products and create the potential for serious and/or life threatening adverse events such as cardiac arrhythmia (for example terfenadine, astemizole, cisapride, pimozide), prolonged sedation or respiratory depression (for example trizolam, midazolam) or peripheral vasospasm or ischaemia (for example ergot derivatives) (see Interactions).

- If AGENERASE is co-administered with ritonavir, the antiarrhythmic agents flecainide and propafenone are also contraindicated (see Interactions).
- Rifampicin must not be administered concurrently with AGENERASE. Rifampicin decreases the amprenavir plasma AUC by approximately 82% (see Interactions).

AGENERASE Oral Solution: there is a potential risk of toxicity from the excipient propylene glycol. The ability to metabolise propylene glycol may not be fully developed in children less than four years of age.Children below the age of four years should not receive AGENERASE oral solution (see Warnings and Precautions, and Pharmacokinetics).

Warnings and Precautions

The principal route of metabolism and excretion of amprenavir, and the propylene glycol excipient of AGENERASE oral solution, is via the liver. AGENERASE should be used with caution in patients with hepatic impairment. The dose of AGENERASE should be reduced in patients with moderate or severe hepatic impairment (see Dosage and Administration).

Children (4 years and above) and adults, particularly those with renal or hepatic impairment, or those with genetically lower levels of alcohol dehydrogenase (e.g. those of Japanese or Chinese origin) should be monitored for adverse reactions potentially related to the propylene glycol content (550 mg/ml) of AGENERASE oral solution such as seizures, stupor, tachycardia, hyperosmolarity, lactic acidosis, renal toxicity, haemolysis. For the same reason, the concomitant administration of AGENERASE oral solution with disulfiram or other medicinal products that reduce alcohol dehydrogenase activity (e.g. metronidazole) or preparations that contain alcohol or additional propylene glycol should be avoided (see Interactions).

The safety and efficacy of AGENERASE in children less than 4 years of age has not yet been established (see Pre-clinical Safety Data).

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 AGENERASE 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 serum concentrations

when administered concomitantly (see Interactions). Because of the potential for metabolic interactions with amprenavir, the efficacy of hormonal contraceptives may be modified, but there is insufficient information to predict the nature of the interactions. Therefore, alternative methods of contraception are recommended for women of childbearing potential (see Interactions).

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.

Immune Reconstitution Syndrome: In HIV-infected patients with severe immune deficiency at the time of initiation of anti-retroviral 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.

Patients should be advised that AGENERASE, 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 AGENERASE, 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.

AGENERASE capsules and oral solution contain vitamin E, therefore additional vitamin E supplementation is not recommended. Amprenavir, like other HIV protease inhibitors is an inhibitor of the cytochrome P450 CYP3A4 enzyme. AGENERASE should not be administered concurrently with medications with narrow therapeutic windows which are substrates of CYP3A4. There are also other agents that may result in serious and/or life-threatening drug interactions, therefore caution is advised whenever AGENERASE is co-administered with medicinal products that are inducers, inhibitors or substrates of CYP3A4 (see Contraindications and Interactions).

Pharmacokinetic studies with other CYP 3A4 inhibitors, including other protease inhibitors, indicate that amprenavir may significantly increase lovastatin and simvastatin concentrations, which have been associated with an increased incidence of myopathy, including rhabdomyolysis.

Pharmacokinetic studies with other CYP 3A4 inhibitors, including other protease inhibitors, indicate that amprenavir may increase atorvastatin concentrations. Use the lowest possible dose of atorvastatin with careful monitoring or consider the use of pravastatin or fluvastatin as alternative HMG-CoA reductase inhibitors in combination with AGENERASE.

Co-administration of AGENERASE with halofantrine is not recommended as halofantrine concentrations may be increased, potentially increasing the risk of serious adverse effects such as cardiac arrhythmia (see Interactions).

Concomitant use of amprenavir 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 Interactions).

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 is an inhibitor 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 AGENERASE and bepridil are coadministered.

• Fat redistribution

Redistribution / accumulation of body fat, including central obesity, dorsocervical fat enlargement (buffalo hump), peripheral wasting, facial wasting, breast enlargement elevated serum lipid and blood glucose levels, have been observed either separately or together in some patients receiving combination antiretroviral therapy (see Adverse Reactions).

Whilst all members of the PI and NRTI classes of medicinal products have been associated with one or more of these specific adverse events, linked to a general syndrome commonly referred to as lipodystrophy, data indicate that there are differences in the risk between individual members of the respective therapeutic classes.

In addition, the lipodystrophy syndrome has a multifactorial etiology; with for example HIV disease status, older age and duration of antiretroviral treatment all playing important, possibly synergistic roles.

The long-term consequences of these events are currently unknown.

Clinical examination should include evaluation for physical signs of fat redistribution. Consideration should be given to the measurement of serum lipids and blood glucose. Lipid disorders should be managed as clinically appropriate.

Interactions

Amprenavir is primarily metabolised in the liver by the cytochrome P450 CYP 3A4 enzyme. Therefore, drugs that either share this metabolic pathway or modify CYP3A4 activity may modify the pharmacokinetics of amprenavir. Similarly, amprenavir might also modify the pharmacokinetics of other drugs that share this metabolic pathway.

Terfenadine, cisapride, pimozide or astemizole are contraindicated in patients receiving AGENERASE. Co-administration may result in competitive inhibition of metabolism of these products, leading to serious life threatening cardiac arrhythmias. Although specific studies have not been performed, co-administration with potent sedatives metabolised by CYP3A4 (e.g. triazolam, midazolam) should be avoided due to the potential for prolonged sedation. AGENERASE should also not be co-administered with ergot derivatives (see Contraindications).

Amprenavir has a low potential for clinically significant drug–drug interactions due to binding displacement. It is primarily bound to the alpha1 acid glycoprotein and binding displacement interactions with this protein are rare.

Pharmacokinetics for amprenavir			Co-administered drug	Pharmacokinetics for amprenavir Co-administered drug		
Cmax	AUC	Cmin		Cmax	AUC	Cmin
↔	↔	N/A	zidovudine	↑ 40%	↑ 31%	N/A
↔	↔	N/A	lamivudine	↓ 16%	↓ 9%	N/A
↔	↔	↔	abacavir	↔	↔	↔
↑ 18%	↑ 33%	↑ 25%	indinavir	↓ 22%	↓ 38%	↓ 27%
↓ 37%	↓ 32%	↓ 14%	saquinavir	↑ 21%	↓ 19%	↓ 48%
↓ 14%	↑ 9%	↑ 189%	nelfinavir	↑ 12%	↑ 15%	↑ 14%
↓ 16%	↑ 32%	N/A	ketoconazole	↑ 19%	↑ 44%	N/A
↓ 70%	↓ 82%	↓ 92%	rifampicin	↔	↔	↔
↓ 7%	↓ 15%	↓ 15%	rifabutin	127%	204%	349%
N/A(1)	N/A(1)	N/A(1)	R-methadone (active)	↓ 25%	↓ 13%	↔
N/A(1)	N/A(1)	N/A(1)	S-methadone (inactive)	↓ 48%	↓ 40%	↓ 23%
↔	↓ 22%	↓ 20%	ethinyl estradiol	↔	↔	↑ 32%
			norethindrome	↔	↑ 18%	↑ 45%
↑ 15%	↑ 18%	↑ 39%	clarithromycin	↓ 10%	↔	↔

↑ = Increase; ↓ = Decrease; ↔ = no effect, N/A = Not available. (1) – see Other potential interactions, Methadone, below.

AGENERASE 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 Contraindications). The full prescribing information of ritonavir should be referred to prior to undertaking the dosing regimen of amprenavir with ritonavir.

Drug interaction studies with a range of drugs likely to be co-administered with AGENERASE have been performed and the results are shown in the following table.

When either zidovudine, lamivudine, abacavir, indinavir, saquinavir or nelfinavir are used in combination with amprenavir no dosage adjustments are considered necessary.

Where pharmacokinetic changes were observed, as with indinavir, saquinavir and nelfinavir, antiviral efficacy was shown in clinical studies to be maintained.

Rifampicin reduces trough plasma concentration of amprenavir by approximately 80% and must not be used concurrently with AGENERASE (see Contraindications).

Co-administration of AGENERASE with rifabutin results in a 200% increase in rifabutin plasma AUC, and an increase of rifabutin related adverse events. A dosage reduction of rifabutin of at least half the recommended dose is required, if it is clinically necessary to coadminister with AGENERASE.

No dosage adjustment is considered necessary when ketoconazole or clarithromycin is administered with AGENERASE.

• Ritonavir

Co-administration of ritonavir with AGENERASE results in a significant increase in the Cmin and AUC of amprenavir. When AGENERASE capsules are given in combination with ritonavir in adults, reduced doses of both medicinal products should be used (see Dosage and Administration). In clinical practice, doses of AGENERASE 600 mg twice daily and ritonavir 100 mg twice daily are being used: evaluation of the safety and efficacy of these regimens is ongoing. AGENERASE oral solution and ritonavir oral solution should not be co-administered (see Warnings and Precautions)

• Lopinavir/ritonavir

In an open-label, non-fasting pharmacokinetic study, the AUC, Cmax and Cmin of lopinavir were decreased by 38%, 28% and 52% respectively when AGENERASE (750 mg twice daily) was given in combination with 400 mg lopinavir + 100 mg ritonavir twice daily. In the same study, the AUC, Cmax, and Cmin of amprenavir were increased 72%, 12%, and 483%, respectively, when 400 mg lopinavir + 100 mg ritonavir twice daily was coadministered with AGENERASE (750 mg twice daily) compared to values after standard doses of AGENERASE (1200 mg twice daily).

The amprenavir plasma Cmin values achieved with the combination of AGENERASE (600 mg twice daily) in combination with 400 mg lopinavir + 100 mg ritonavir twice daily) are approximately 40-50% lower than when AGENERASE (600 mg twice daily) is given in combination with ritonavir (100 mg twice daily).

Adding additional ritonavir to an AGENERASE plus lopinavir / ritonavir regimen increase lopinavir Cmin values, but not amprenavir Cmin values.

No dose recommendations can be given for the co-administration of AGENERASE and lopinavir+ritonavir.

• Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs)

Efavirenz: Efavirenz has been seen to decrease the Cmax, AUC, and Cmin,ss of amprenavir by approximately 40% in adults. No dose recommendations can be given for the co-administration of AGENERASE, with or without another protease inhibitor, and efavirenz.

Nevirapine: Based on its effect on other HIV protease inhibitors, nevirapine may decrease the serum concentrations of amprenavir.

Delavirdine: The AUC, Cmax and Cmin of delavirdine were decreased by 61%, 47% and 88% respectively when given with AGENERASE. The AUC, Cmax and

Cmin of amprenavir were increased by 130%, 40% and 125% respectively.

No dose recommendations can be given for the co-administration of AGENERASE and delavirdine. If these medicinal products are used concomitantly care is advised, as delavirdine may be less effective due to decreased and potentially sub-therapeutic plasma concentrations.

• Other potential interactions

Other medications listed below are examples of substrates, inhibitors, or inducers of CYP3A4 that could have potential interactions, when used concomitantly with amprenavir. The clinical significance of these potential interactions are unknown and have not been studied. Patients should therefore be monitored for toxicities associated with such drugs when these are used in combination with AGENERASE.

Antibiotics: Dapsone and erythromycin may have their plasma concentrations increased by amprenavir. Erythromycin may also increase amprenavir serum concentrations.

Antifungals: Itraconazole may have its plasma concentrations increased by amprenavir.

Itraconazole may increase serum concentrations of amprenavir.

Benzodiazepines: Alprazolam, clorazepate, diazepam, and flurazepam may have their serum concentrations increased by amprenavir, which could increase their activity.

Calcium channel blockers: Diltiazem, nicardipine, nifedipine, and nimodipine may have their serum concentrations increased by amprenavir, which could increase their activity.

HMG-CoA reductase inhibitors: Lovastatin, simvastatin, atorvastatin and to a lesser extent pravastatin and fluvastatin may have their serum concentrations increased by amprenavir, which could increase their activity or toxicity (see Warnings and Precautions).

Erectile dysfunction agents: Based on data for other protease inhibitors, caution should be used when prescribing sildenafil to patients receiving AGENERASE. Co-administration of AGENERASE with sildenafil may substantially increase sildenafil plasma concentrations and may result in sildenafil-associated adverse events.

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 Warnings and Precautions).

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 AGENERASE and may result in an increase in halofantrine associated adverse events such as cardiac arrhythmia. Concomitant use is not recommended (see Warnings and Precautions).

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

Methadone: Co-administration of AGENERASE and methadone resulted in a 30%, 27% and 25% decrease in serum amprenavir AUC, Cmax, and Cmin, respectively, as compared to a non-matched historical control group.

Paroxetine: plasma concentrations of paroxetine may be significantly decreased when co-administered with AGENERASE and ritonavir. Any paroxetine dose

adjustment should be guided by clinical effect (tolerability and efficacy).

Steroids: Estrogens, progestogens, and some glucocorticoids may have an interaction with amprenavir but there is insufficient information to predict the nature of the interaction. Alternative methods of contraception are recommended for women of childbearing potential

St John's Wort: Co-administration of Hypericum perforatum (St John's Wort) may lead to decreased serum levels of amprenavir (see Warnings and Precautions).

Caution should be used when AGENERASE is coadministered with drugs known to

induce CYP 3A4, such as phenobarbital, phenytoin, carbamazepine and dexamethasone. Induction of amprenavir (CYP 3A4) metabolism may result in reduced serum amprenavir concentrations.

Other agents: 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.

There are other agents that may have their plasma concentrations increased by amprenavir and include but are not limited to: clozapine, cimetidine and loratadine. Cimetidine may increase amprenavir plasma concentrations.

Antacids (and didanosine because of its antacid content) have not been specifically studied. Based upon data with other protease inhibitors, it is advisable that antacids not be taken at the same time as AGENERASE because of potential interference with absorption. It is recommended that their administration be separated by at least an hour.

Alcohol and Alcohol Dehyrogenase Inhibitors: AGENERASE oral solution contains propylene glycol (550 mg/ml), which is primarily metabolised via alcohol dehydrogenase. Therefore, concomitant administration with disulfiram or other medicinal products that reduce alcohol dehydrogenase activity (e.g. metronidazole) or preparations that contain alcohol or propylene glycol should be avoided.

Pregnancy and Lactation

In pregnant rats and rabbits there were no major effects on embryo-foetal development. A number of minor changes, including thymic elongation and minor skeletal variations were seen, indicating developmental delay. Systemic plasma exposure (AUC) to amprenavir in pregnant rabbits was significantly lower at all doses compared to plasma exposure found in patients in clinical studies.

Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if the potential benefit justifies the potential risk to the foetus.

The safe use of AGENERASE in human pregnancy has not been established. Placental transfer of amprenavir and/or its related metabolites has been shown to occur in animals.

AGENERASE oral solution should not be used during pregnancy due to the potential risk of toxicity to the foetus from the propylene glycol content. If AGENERASE is used during pregnancy, AGENERASE capsules should be used.

Amprenavir related material was found in rat milk, but it is not known whether amprenavir is excreted in human milk. A reproduction study in pregnant rats dosed from the time of uterine implantation through lactation showed reduced body weights in the offspring. The systemic exposure to the dams associated with this finding, was approximately twice the exposure in humans, following administration of the recommended dose. The subsequent development of these offspring, including fertility and reproductive performance, were not affected by the maternal administration of amprenavir.

It is therefore recommended that mothers being treated with AGENERASE do not breast-feed their infants. Additionally, it is recommended by health experts that where possible, HIV infected women do not breast-feed their infants in order to avoid transmission of HIV.

Effects on Ability to Drive and Use Machines
No studies on the effects on ability to drive and use machines have been performed.

Adverse Reactions
Adverse events have been reported during treatment with AGENERASE. For many of these events it is unclear whether they are related to AGENERASE, to concomitant treatment with the wide range of drugs used in the management of HIV disease or as a result of the disease process.

AGENERASE was generally well tolerated. Most undesirable effects associated with AGENERASE therapy were mild to moderate in severity, early in onset, and rarely treatment limiting. In children the emerging safety profile is similar in nature to that seen in adults.

Adverse reactions are listed below by MedDRA body system organ class and by frequency. The frequency categories used are:

very common:	≥1 in 10
common:	≥1 in 100 and <1 in 10
uncommon:	≥1 in 1,000 and <1 in 100
rare:	≥1 in 10,000 and <1 in 1,000.

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

Most of the adverse events below come from two clinical trials (PROAB3001, PROAB3006) involving PI naïve subjects receiving AGENERASE 1200 mg twice daily.

Events (grade 2-4) reported by study investigators as attributable to study medication are included as well as grade 3-4 treatment emergent laboratory abnormalities. Note that the background rates in comparator groups were not taken into account.

Metabolism and Nutrition Disorders
Common: Elevated triglycerides, abnormal fat distribution (see Warnings and Precautions).
Uncommon: Hyperglycaemia, hypercholesterolaemia.

Elevated triglycerides and hyperglycaemia (grade 3-4) were reported primarily in patients with abnormal values at baseline.

Elevations in cholesterol were of grade 3-4 intensity.

In clinical studies involving antiretroviral naïve patients, abnormal fat distribution was uncommon, after a median duration of 36 weeks exposure.

Nervous system disorders
Very common:nHeadache.
Common: Oral/perioral paraesthesia.

Gastrointestinal disorders:
Very Common: Diarrhoea, nausea, flatulence, vomiting.

Hepatobiliary Disorders
Common: Elevated transaminases.

Elevated transaminases (grade 3-4) were reported primarily in patients with abnormal values at baseline.

Skin and subcutaneous tissue disorders
Very common: Rash.
Rare: Stevens Johnson syndrome.

Rash generally occurred during the second week of treatment and usually resolved spontaneously within two weeks, without stopping AGENERASE. However, occasionally the rash may be severe. Only 3% of patients discontinued AGENERASE due to a rash.

Angioedema has been reported rarely in patients taking fosamprenavir, which is the pro- drug of AGENERASE.

General disorders and administration site conditions
Very common: Fatigue.

Overdose
There are limited reports of overdosage with AGENERASE. If overdosage occurs the patient should be monitored for evidence of toxicity (see Adverse Reactions).

Standard supportive treatment should be provided as necessary. Since amprenavir is highly protein bound, dialysis is unlikely to be helpful in reducing blood levels.

PHARMACOLOGICAL PROPERTIES
Pharmacodynamics

Pharmacotherapeutic group – protease inhibitor; ATC Code: JO5A E05

Amprenavir is a non-peptidic competitive inhibitor of the HIV protease. It blocks the ability of the viral protease to cleave the precursor polyproteins necessary for viral replication. Protease inhibitors have exhibited greater potency against HIV in vitro, than the currently available nucleoside analogues that target HIV reverse transcriptase.

Amprenavir is a highly potent and selective inhibitor of HIV-1 and HIV-2 replication. It shows synergy in vitro in combination with nucleoside analogues including didanosine, zidovudine, abacavir and the protease inhibitor, saquinavir. It has been shown to be additive in combination with indinavir, ritonavir and nelfinavir.

Amprenavir resistant isolates of HIV have been selected in vitro. Under such conditions, at least three mutations were required at amino acid positions 46, 47 and 50 within the HIV protease, to produce a strain with a greater than 10 fold increase in IC50. The key mutation I50V, associated with resistance to amprenavir has not been observed as a natural variant or in protease inhibitor therapy experienced patients. Little cross-resistance has been observed between amprenavir selected resistant variants and other protease inhibitors, suggesting the potential for protease inhibitor salvage therapy. Other mutations associated with amprenavir resistance (I54V and I84V) have rarely been selected during AGENERASE therapy.

The resistance profile seen with AGENERASE is different from that observed with other protease inhibitors in clinical practice. In vitro, amprenavir-resistant isolates are highly susceptible to indinavir, saquinavir, and nelfinavir, but show reduced susceptibility to ritonavir. From 55 clinical isolates with mutations conferring resistance to the protease inhibitors in vivo, 55% were sensitive to amprenavir.

Cross-resistance should not occur between AGENERASE and reverse transcriptase inhibitors, because the enzyme targets are different.

Pharmacokinetics

Absorption

After oral administration, amprenavir is rapidly and well absorbed. The absolute bioavailability is unknown due to the lack of an acceptable i.v. formulation for use in man. Approximately 90% of an orally administered radiolabelled amprenavir dose was recovered in the urine and faeces, primarily as amprenavir metabolites. Following oral administration, the mean time (tmax) to maximal serum concentrations of amprenavir is between 1 to 2 h for the capsule and approximately 0.75 h for the oral solution. A second peak is observed after 10 to 12 h and may represent either delayed absorption or enterohepatic recirculation.

At therapeutic dosages (1200 mg twice daily), the mean steady state Cmax of amprenavir from capsules is 5.36 (0.92-9.81) micrograms/ml and the Cmin is 0.28 (0.12-0.51) micrograms/ml. The mean AUC over a dosing interval of 12 h is 18.46 (3.02 to 32.95) micrograms.h/ml. The 50 mg and 150 mg capsules have been shown to be bioequivalent. The oral solution at equivalent doses is less bioavailable compared to the capsules, with an AUC and Cmax approximately 14% and 19% lower, respectively. The clinical significance of this difference is likely to be minimal.

Administration of AGENERASE with food has a modest effect on overall plasma concentrations (AUC), reducing the AUC of amprenavir by between 14-25% and reducing Cmax by approximately 33%. This finding is not considered to be clinically significant therefore AGENERASE can be taken with or without food.

Distribution

The apparent volume of distribution is approximately 430 litres (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. The concentration of amprenavir in the cerebrospinal fluid is less than 1% of plasma concentration.

Amprenavir is approximately 90% protein bound. It is primarily bound to the alpha1 acid glycoprotein (AAG), but also to albumin. Concentrations of AAG have been shown to decrease during the course of

antiretroviral therapy. This change will decrease the total drug concentration in the plasma, however the amount of unbound amprenavir, which is the active moiety, is likely to be unchanged.

Clinically significant binding displacement interactions involving drugs primarily bound to AAG are generally not observed. Therefore, drug-drug interactions with AGENERASE due to protein binding displacement are highly unlikely.

Metabolism

Amprenavir is primarily metabolised by the liver with less than 3% excreted unchanged in the urine. The primary route of metabolism is via the cytochrome P450 CYP3A4 enzyme. Amprenavir is a substrate of and inhibits CYP3A4. Therefore drugs that are inducers, inhibitors or substrates of CYP3A4 must be used with caution when administered concurrently with AGENERASE (see Contraindications and Interactions).

Elimination

The plasma elimination half-life of amprenavir ranges from 7.1 to 10.6 h. Following multiple oral doses of AGENERASE 1200 mg twice a day, there is no significant drug accumulation. The primary route of elimination of amprenavir is via hepatic metabolism with less than 3% 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 Patient Populations

• Paediatrics

The pharmacokinetics of amprenavir in children (4 years of age and above) are similar to those in adults. Dosages of 20 mg/kg twice a day and 15 mg/kg three times a day of AGENERASE capsules, provided similar plasma concentrations compared to those obtained with 1200 mg twice a day in adults.

• Elderly

The pharmacokinetics of amprenavir have 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.

• Renal Impairment

Patients with renal impairment have not been specifically studied. Less than 3% of the therapeutic dose of amprenavir is excreted unchanged in the urine. The impact of renal impairment on amprenavir elimination should be minimal therefore, no initial dose adjustment is considered necessary.

• Hepatic Impairment

The pharmacokinetics of amprenavir are significantly altered in patients with moderate to severe hepatic impairment. The AUC increased nearly three fold in patients with moderate impairment and four fold in patients with severe hepatic impairment. Clearance also decreased in a corresponding manner to the AUC. The dosage should therefore be reduced in these patients (see Dosage and Administration).

Clinical Studies

AGENERASE in combination with other antiretroviral agents including nucleoside analogues, non-nucleoside analogues and protease inhibitors, has been shown to be effective in the treatment of HIV infection in adults. In clinical studies in naïve patients, the efficacy of amprenavir in combination with zidovudine and lamivudine was superior to this combination alone. Antiviral effects comparable to those seen in adults have been observed in children. The efficacy of AGENERASE has been demonstrated across the whole spectrum of HIV infection including early and late stage disease, in both antiretroviral naïve and experienced patients.

Pre-clinical Safety Data

• Carcinogenesis, mutagenesis

In long-term carcinogenicity studies with amprenavir, there were benign hepatocellular adenomas in males at the high dose of 500 mg/kg/day in mice or 750 mg/kg/day in rats. Exposures at these dose levels were equivalent to 2.0-fold (mice) or 3.8-fold (rats) those in humans given 1200 mg twice daily of amprenavir alone. Altered hepatocellular foci were seen in male mice at doses of 275 and 500 mg/kg/day (exposure at least 2.0 times human therapeutic exposure).

The significance of the observed effects for humans is uncertain, however there is no evidence from clinical trials or marketed use to suggest that these findings are of clinical significance. amprenavir was not mutagenic or genotoxic in a battery of in vivo and in vitro genetic toxicity assays, including bacterial reverse mutation (Ames Test), mouse lymphoma, rat micronucleus, and chromosome aberration in human peripheral lymphocytes.

• **Reproductive toxicology**
(See Pregnancy and Lactation)

• Animal toxicology and/or pharmacology In mature animals, amprenavir was generally well tolerated. The clinically relevant findings were restricted to the liver. Liver toxicity consisted of increases in liver enzymes, liver weights and microscopic findings including hepatocyte necrosis. This liver toxicity can be monitored for and detected in clinical use, with measurement of AST, ALT and alkaline phosphatase activity. However, significant liver toxicity has not been observed in patients treated in clinical studies, either during administration of amprenavir or after discontinuation.
Toxicity studies in young animals treated from four days old resulted in high mortality in both the control animals and those receiving amprenavir. These results show that young animals lack fully developed metabolic pathways, and could not metabolise or excrete amprenavir, or some components of the formulation. In clinical studies, amprenavir has been administered to children from four years of age and has been shown to be well tolerated. The safety and efficacy of amprenavir in children less than four years of age has not yet been established.

PHARMACEUTICAL PARTICULARS

List of Excipients

Capsule shell: gelatin, glycerol, d-sorbitol and sorbitans solution, titanium dioxide, red printing ink.

Capsule contents: D-alpha tocopheryl polyethylene glycol 1000 succinate (TPGS), macrogol 400, propylene glycol.

Oral solution: propylene glycol, macrogol 400, D-alpha tocopheryl polyethylene glycol 1000 succinate (TPGS), acesulfame potassium, saccharin sodium, sodium chloride, artificial grape bubblegum flavour, natural peppermint flavour menthol, anhydrous citric acid, sodium citrate dihydrate, purified water.

Incompatibilities
Not applicable.

Shelf Life
The expiry date is indicated on the packaging.

Special Precautions for Storage
Do not store capsules above 30oC. Keep the container tightly closed.
Do not store the oral solution above 25oC.

Nature and Contents of Container
AGENERASE Capsules are supplied in white HDPE bottles.

AGENERASE oral solution is supplied in white HDPE bottles; a 20 ml measuring cup is provided in the pack.

Instructions for Use/Handling
No special requirements.
Not all presentations are available in every country.
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GlaxoSmithKline group of companies