

**ANNEX I**

**SUMMARY OF PRODUCT CHARACTERISTICS**

Medicinal product no longer authorised

## **1. NAME OF THE MEDICINAL PRODUCT**

Agenerase 50 mg soft capsules.

## **2. QUALITATIVE AND QUANTITATIVE COMPOSITION**

Each capsule contains 50 mg of amprenavir.

Excipients:  
d-sorbitol (E420)

For a full list of excipients, see section 6.1.

## **3. PHARMACEUTICAL FORM**

Soft capsule.

Oblong, opaque, off-white to cream coloured, printed with 'GX CC1'.

## **4. CLINICAL PARTICULARS**

### **4.1 Therapeutic indications**

Agenerase, in combination with other antiretroviral agents, is indicated for the treatment of protease inhibitor (PI) experienced HIV-1 infected adults and children above the age of 4 years. Agenerase capsules should normally be administered with low dose ritonavir as a pharmacokinetic enhancer of amprenavir (see sections 4.2 and 4.5). The choice of amprenavir should be based on individual viral resistance testing and treatment history of patients (see section 5.1).

The benefit of Agenerase boosted with ritonavir has not been demonstrated in PI naïve patients (see section 5.1)

### **4.2 Posology and method of administration**

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

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

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

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 milligram per milligram basis (see section 5.2).

Adults and adolescents of 12 years of age and older (greater than 50 kg body weight): the recommended dose of Agenerase capsules is 600 mg twice daily with ritonavir, 100 mg twice daily, in combination with other antiretroviral agents.

If Agenerase capsules are used without the boosting effect of ritonavir higher doses of Agenerase (1200 mg twice daily) should be used.

Children (4 to 12 years) and patients less than 50 kg body weight: the recommended dose of Agenerase capsules is 20 mg/kg body weight twice a day, in combination with other antiretroviral agents, without exceeding a total daily dose of 2400 mg (see section 5.1).

The pharmacokinetics, efficacy and safety of Agenerase in combination with 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: Agenerase is not recommended in children below 4 years due to lack of data on safety and efficacy (see section 5.2).

Elderly: the pharmacokinetics, efficacy and safety of amprenavir have not been studied in patients over 65 years of age (see section 5.2).

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

Hepatic impairment: the principal route of metabolism of amprenavir is via the liver. Agenerase capsules should be used with caution in patients with hepatic impairment. Clinical efficacy and safety have not been determined in this patient group. For subjects with hepatic impairment, pharmacokinetic data are available for the use of Agenerase capsules without the boosting effect of ritonavir. Based on pharmacokinetic data, the dose of Agenerase capsules should be reduced to 450 mg twice a day for adult patients with moderate hepatic impairment and to 300 mg twice a day for adult patients with severe hepatic impairment. No dose recommendation can be made in children with hepatic impairment (see section 5.2).

The use of amprenavir in combination with ritonavir has not been studied in patients with hepatic impairment. No dose recommendations can be made regarding this combination. Concomitant administration should be used with caution in patients with mild and moderate hepatic impairment and is contraindicated in patients with severe hepatic impairment (see section 4.3).

### **4.3 Contraindications**

Hypersensitivity to the active substance or to any of the excipients.

Agenerase must not be administered concurrently with medicinal products with narrow therapeutic windows that are substrates of cytochrome P450 3A4 (CYP3A4). Co-administration may result in competitive inhibition of the metabolism of these medicinal products and create the potential for serious and/or life-threatening adverse events such as cardiac arrhythmia (e.g. amiodarone, bepridil, quinidine, terfenadine, astemizole, cisapride, pimozide), respiratory depression and /or prolonged sedation (e.g. oral triazolam and oral midazolam (for caution on parenterally administered midazolam, see section 4.5)) or peripheral vasospasm or ischaemia and ischaemia of other tissues, including cerebral or myocardial ischaemia (e.g. ergot derivatives).

Agenerase in combination with ritonavir is contraindicated in patients with severe hepatic impairment.

Combination of rifampicin with Agenerase with concomitant low-dose ritonavir is contraindicated. (see section 4.5).

Agenerase with ritonavir must not be co-administered with medicinal products with narrow therapeutic windows that are highly dependent on CYP2D6 metabolism, e.g. flecainide and propafenone (see section 4.5).

Herbal preparations containing St John's wort (*Hypericum perforatum*) must not be used while taking amprenavir due to the risk of decreased plasma concentrations and reduced clinical effects of amprenavir (see section 4.5).

#### 4.4 Special warnings and precautions for use

Patients should be advised that Agenerase, 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 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.

On the basis of current pharmacodynamic data, amprenavir should be used in combination with at least two other antiretrovirals. When amprenavir is administered as monotherapy, resistant viruses rapidly emerge (see section 5.1). Agenerase capsules should normally be given in combination with low dose ritonavir and in combination with other antiretroviral agents (see section 4.2).

**Liver Disease:** The safety and efficacy of amprenavir has not been established in patients with significant underlying liver disorders. Agenerase capsules are contraindicated in patients with severe hepatic impairment when used in combination with ritonavir (see section 4.3). Patients with chronic hepatitis B or C and treated with combination antiretroviral therapy are at an increased risk of severe and potentially fatal hepatic adverse events. In case of concomitant antiviral therapy for hepatitis B or C, please refer also to the relevant product information for these medicinal products.

Patients with pre-existing liver dysfunction, including chronic active hepatitis, have an increased frequency of liver function abnormalities during combination antiretroviral therapy and should be monitored according to standard practice. If there is evidence of worsening liver disease in such patients, interruption or discontinuation of treatment must be considered.

##### Medicinal products – interactions

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

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

For some medicinal products that can cause serious or life-threatening undesirable effects, such as carbamazepine, phenobarbital, phenytoin, tricyclic antidepressants and warfarin (monitor International Normalised Ratio), concentration monitoring is available; this should minimise the risk of potential safety problems with concomitant use.

The use of Agenerase concomitantly with halofantrine or lidocaine (systemic) is not recommended (see section 4.5).

Anticonvulsants (carbamazepine, phenobarbital, phenytoin) should be used with caution. Agenerase may be less effective due to decreased amprenavir plasma concentrations in patients taking these medicinal products concomitantly (see section 4.5).

Therapeutic concentration monitoring is recommended for immunosuppressant medicinal products (cyclosporine, tacrolimus, rapamycin) when co-administered with Agenerase (see section 4.5).

Caution is advised when Agenerase is used concomitantly with PDE5 inhibitors (e.g. sildenafil and vardenafil) (see section 4.5).

Caution is advised when Agenerase is used concomitantly with delavirdine (see section 4.5).

A reduction of rifabutin dosage of at least 50 % is recommended when administered with Agenerase. When ritonavir is co-administered further dose reduction may be necessary (see section 4.5).

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 reliable methods of contraception are recommended for women of childbearing potential (see section 4.5).

Co-administration of amprenavir with methadone leads to a decrease of methadone concentrations. Therefore, when methadone is co-administered with amprenavir, patients should be monitored for opiate abstinence syndrome, in particular if low-dose ritonavir is also given. No recommendations can currently be made regarding adjustment of amprenavir dose when amprenavir is co-administered with methadone.

Agenerase capsules contain vitamin E (36 IU/50 mg capsule), therefore additional vitamin E supplementation is not recommended.

Agenerase capsules also contain sorbitol (E420). Patients with rare hereditary problems of fructose intolerance should not take this medicine.

Due to the potential risk of toxicity from the high propylene glycol content of Agenerase oral solution, this formulation is contraindicated in children below the age of four years and should be used with caution in certain other patient populations. The Summary of Product Characteristics of Agenerase oral solution should be consulted for full prescribing information.

#### Rash / cutaneous reactions

Most patients with mild or moderate rash can continue Agenerase. Appropriate antihistamines (e.g. cetirizine dihydrochloride) may reduce pruritus and hasten the resolution of rash. Agenerase should be permanently discontinued when rash is accompanied with systemic symptoms or allergic symptoms or mucosal involvement (see section 4.8).

#### 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.

#### Lipodystrophy

Combination antiretroviral therapy has been associated with the redistribution of body fat (lipodystrophy) in HIV patients. The long-term consequences of these events are currently unknown. Knowledge about the mechanism is incomplete. A connection between visceral lipomatosis and protease inhibitors and lipodystrophy and nucleoside reverse transcriptase inhibitors has been hypothesised. A higher risk of lipodystrophy has been associated with individual factors such as older age, and with drug related factors such as longer duration of antiretroviral treatment and associated metabolic disturbances. Clinical examination should include evaluation for physical signs of fat redistribution. Consideration should be given to the measurement of fasting serum lipids and blood glucose. Lipid disorders should be managed as clinically appropriate (see section 4.8).

### Haemophilic patients

There have been reports of increased bleeding, including spontaneous skin haematomas and haemarthroses, in haemophilic 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. Haemophilic patients should therefore be made aware of the possibility of increased bleeding.

### Immune Reactivation Syndrome

In HIV-infected patients with severe immune deficiency at the time of institution of combination antiretroviral therapy (CART), an inflammatory reaction to asymptomatic or residual opportunistic pathogens may arise and cause serious clinical conditions, or aggravation of symptoms. Typically, such reactions have been observed within the first few weeks or months of initiation of CART. Relevant examples are cytomegalovirus retinitis, generalised and/or focal mycobacterium infections, and *Pneumocystis carinii* pneumonia. Any inflammatory symptoms should be evaluated and treatment instituted when necessary.

### Osteonecrosis

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

## **4.5 Interaction with other medicinal products and other forms of interaction**

Interaction studies have been performed with amprenavir as the sole protease inhibitor. When amprenavir and ritonavir are co-administered, the ritonavir metabolic drug interaction profile may predominate because ritonavir is a more potent CYP3A4 inhibitor. Ritonavir also inhibits CYP2D6 and induces CYP3A4, CYP1A2, CYP2C9 and glucuronosyl transferase. The full prescribing information for ritonavir must therefore be consulted prior to initiation of therapy with Agenerase and ritonavir.

Amprenavir and ritonavir are primarily metabolised in the liver by CYP3A4. Therefore, medicinal products that either share this metabolic pathway or modify CYP3A4 activity may modify the pharmacokinetics of amprenavir. Similarly, amprenavir and ritonavir might also modify the pharmacokinetics of other medicinal products that share this metabolic pathway.

### **Associations contraindicated (see section 4.3)**

#### CYP3A4 substrates with narrow therapeutic index

Agenerase must not be administered concurrently with medicinal products with narrow therapeutic windows containing active substances that are substrates of cytochrome P450 3A4 (CYP3A4). Co-administration may result in competitive inhibition of the metabolism of these active substances thus increasing their plasma level and leading to serious and / or life-threatening adverse reactions such as cardiac arrhythmia (e.g. amiodarone, astemizole, bepridil, cisapride, pimozide, quinidine, terfenadine) or peripheral vasospasm or ischaemia (e.g. ergotamine, dihydroergotamine).

#### CYP2D6 substrates with narrow therapeutic index

Agenerase with ritonavir must not be co-administered with medicinal products containing active substances that are highly dependent on CYP2D6 metabolism and for which elevated plasma concentrations are associated with serious and / or life-threatening adverse reactions. These active substances include flecainide and propafenone.

#### Rifampicin

Rifampicin is a strong CYP3A4 inducer and has been shown to cause an 82% decrease in amprenavir AUC, which can result in virological failure and resistance development. During attempts to overcome the decreased exposure by increasing the dose of other protease inhibitors with ritonavir, a high frequency of liver reactions was seen. The combination of rifampicin and Agenerase with concomitant low-dose ritonavir is contraindicated (see section 4.3).

#### St John's wort (*Hypericum perforatum*)

Serum levels of amprenavir can be reduced by concomitant use of the herbal preparation St John's wort (*Hypericum perforatum*). This is due to induction of drug metabolising enzymes by St John's wort. Herbal preparations containing St John's wort should therefore not be combined with Agenerase. If a patient is already taking St John's wort, check amprenavir and if possible viral levels and stop St John's wort. Amprenavir levels may increase on stopping St John's wort. The dose of amprenavir may need adjusting. The inducing effect may persist for at least 2 weeks after cessation of treatment with St John's wort.

- Other combinations

Of note, the following interaction data was obtained in adults.

#### Antiretroviral agents

- **Protease inhibitors (PIs):**

Indinavir: the AUC,  $C_{\min}$  and  $C_{\max}$  of indinavir were decreased by 38 %, 27 %, and 22 %, respectively, when given with amprenavir. The clinical relevance of these changes is unknown. The AUC,  $C_{\min}$  and  $C_{\max}$  of amprenavir were increased by 33 %, 25 %, and 18 %, respectively. No dose adjustment is necessary for either medicinal product when indinavir is administered in combination with amprenavir.

Saquinavir: the AUC,  $C_{\min}$  and  $C_{\max}$  of saquinavir were decreased by 19 % and 48 % and increased by 21 %, respectively, when given with amprenavir. The clinical relevance of these changes is unknown. The AUC,  $C_{\min}$  and  $C_{\max}$  of amprenavir were decreased by 32 %, 14 %, and 37 %, respectively. No dose adjustment is necessary for either medicinal product when saquinavir is administered in combination with amprenavir.

Nelfinavir: the AUC,  $C_{\min}$  and  $C_{\max}$  of nelfinavir were increased by 15 %, 14 %, and 12 %, respectively, when given with amprenavir. The  $C_{\max}$  of amprenavir was decreased by 14 % whilst the AUC and  $C_{\min}$  were increased by 9 % and 189 %, respectively. No dose adjustment is necessary for either medicinal product when nelfinavir is administered in combination with amprenavir (see also efavirenz below).

Ritonavir: the AUC and  $C_{\min}$  of amprenavir were increased by 64% and 508% respectively and the  $C_{\max}$  decreased by 30% when ritonavir (100 mg twice daily) was co-administered with amprenavir capsule (600 mg twice daily) compared to values achieved after 1200 mg twice daily doses of amprenavir capsules. In clinical trials, doses of amprenavir 600 mg twice daily and ritonavir 100 mg twice daily have been used; confirming the safety and efficacy of this regimen.

Lopinavir / ritonavir (Kaletra): in an open-label, non-fasting pharmacokinetic study, the AUC,  $C_{\max}$  and  $C_{\min}$  of lopinavir were decreased by 38%, 28% and 52% respectively when amprenavir (750 mg twice daily) was given in combination with Kaletra (400 mg lopinavir + 100 mg ritonavir twice daily). In the same study, the AUC,  $C_{\max}$ , and  $C_{\min}$  of amprenavir were increased 72%, 12%, and 483%, respectively, when compared to values after standard doses of amprenavir (1200 mg twice daily).

The amprenavir plasma  $C_{\min}$  values achieved with the combination of amprenavir (600 mg twice daily) in combination with Kaletra (400 mg lopinavir + 100 mg ritonavir twice daily) are approximately 40-50% lower than when amprenavir (600 mg twice daily) is given in combination with ritonavir 100 mg twice daily. Adding additional ritonavir to an amprenavir plus Kaletra regimen increase lopinavir  $C_{\min}$  values, but not amprenavir  $C_{\min}$  values. No dose recommendation can be given for the co-

administration of amprenavir and Kaletra, but close monitoring is advised because the safety and efficacy of this combination is unknown.

- ***Nucleoside analogue reverse transcriptase inhibitors (NRTIs):***

Zidovudine: the AUC and  $C_{max}$  of zidovudine were increased by 31 % and 40 %, respectively, when given with amprenavir. The AUC and the  $C_{max}$  of amprenavir were unaltered. No dose adjustment for either medicinal product is necessary when zidovudine is administered in combination with amprenavir.

Lamivudine: the AUC and  $C_{max}$  of lamivudine and amprenavir, respectively, were both unaltered when these two medicinal products were given concomitantly. No dose adjustment is necessary for either medicinal product when lamivudine is administered in combination with amprenavir.

Abacavir: the AUC,  $C_{min}$  and  $C_{max}$  of abacavir were unaltered when given with amprenavir. The AUC,  $C_{min}$  and  $C_{max}$  of amprenavir were increased by 29 %, 27 %, and 47 %, respectively. No dose adjustment is necessary for either medicinal product when abacavir is administered in combination with amprenavir.

Didanosine: no pharmacokinetic study has been performed with Agenerase in combination with didanosine, however, due to its antacid component, it is recommended that didanosine and Agenerase should be administered at least one hour apart (see Antacids below).

- ***Non-nucleoside reverse transcriptase inhibitors (NNRTIs):***

Efavirenz: efavirenz has been seen to decrease the  $C_{max}$ , AUC and  $C_{min,ss}$  of amprenavir by approximately 40 % in adults. When amprenavir is combined with ritonavir, the effect of efavirenz is compensated by the pharmacokinetic booster effect of ritonavir. Therefore, if efavirenz is given in combination with amprenavir (600 mg twice daily) and ritonavir (100 mg twice daily), no dose adjustment is necessary.

Further, if efavirenz is given in combination with amprenavir and nelfinavir, no dosage adjustment is necessary for any of the medicinal products.

Treatment with efavirenz in combination with amprenavir and saquinavir is not recommended, as the exposure to both protease inhibitors would be decreased.

No dose recommendation can be given for the co-administration of amprenavir with another protease inhibitor and efavirenz in children. Such combinations should be avoided in patients with hepatic impairment.

Nevirapine: The effect of nevirapine on other protease inhibitors and the limited evidence available suggest that nevirapine may decrease the serum concentrations of amprenavir.

Delavirdine: the AUC,  $C_{max}$  and  $C_{min}$  of delavirdine were decreased by 61%, 47% and 88% respectively when given with amprenavir. The AUC,  $C_{max}$  and  $C_{min}$  of amprenavir were increased by 130%, 40% and 125% respectively.

No dose recommendations can be given for the co-administration of amprenavir 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.

No dose recommendations can be given for the co-administration of amprenavir and low dose ritonavir with delavirdine. If these medicinal products are used concomitantly care is advised, and close clinical and virological monitoring should be performed since it is difficult to predict the effect of the combination of amprenavir and ritonavir on delavirdine.

## **Antibiotics/antifungals**

**Rifabutin:** co-administration of amprenavir with rifabutin resulted in a 193 % increase in rifabutin AUC and an increase of rifabutin-related adverse events. The increase in rifabutin plasma concentration is likely to result from inhibition of rifabutin CYP3A4 mediated metabolism by amprenavir. When it is clinically necessary to co-administer rifabutin with Agenerase, a dosage reduction of at least half the recommended dose of rifabutin is advised, although no clinical data are available. When ritonavir is co-administered a larger increase in rifabutin concentration may occur.

**Clarithromycin:** the AUC and  $C_{min}$  of clarithromycin were unaltered and the  $C_{max}$  decreased by 10 % when given with amprenavir. The AUC,  $C_{min}$  and  $C_{max}$  of amprenavir were increased by 18 %, 39 % and 15 %, respectively. No dose adjustment is necessary for either medicinal product when clarithromycin is administered in combination with amprenavir. When ritonavir is co-administered an increase in clarithromycin concentrations may occur.

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

**Ketoconazole / Itraconazole:** the AUC and  $C_{max}$  of ketoconazole were increased by 44 % and 19 %, respectively when given with amprenavir alone. The AUC and  $C_{max}$  of amprenavir were increased by 31 % and decreased by 16 %, respectively. Itraconazole concentrations are expected to increase in the same manner as ketoconazole. No dose adjustment for any of the medicinal products is necessary when either ketoconazole or itraconazole is administered in combination with amprenavir. Co-administration of fosamprenavir 700 mg with ritonavir 100 mg twice daily and ketoconazole 200 mg once daily increased plasma ketoconazole  $C_{max}$  by 25 % and increased AUC(0- $\tau$ ) to values 2.69-fold those observed on administration of ketoconazole 200 mg once daily without concurrent fosamprenavir with ritonavir. The  $C_{max}$ , AUC and  $C_{min}$  of amprenavir were unchanged. When used with Agenerase with ritonavir, high doses (>200 mg/day) of ketoconazole or itraconazole are not recommended.

## **Other possible interactions**

Other medicinal products, listed below, including examples of substrates, inhibitors or inducers of CYP3A4, may lead to interactions when administered with Agenerase. The clinical significance of these possible interactions is not known and has not been investigated. Patients should therefore be monitored for toxic reactions associated with these medicinal products when these are administered in combination with Agenerase.

**Antacids:** on the basis of the data for other protease inhibitors, it is advisable not to take antacids at the same time as Agenerase, since its absorption may be impaired. It is recommended that antacids and Agenerase should be administered at least one hour apart.

**Anticonvulsant active substances:** concomitant administration of anticonvulsant active substances known as enzymatic inductors (phenytoin, phenobarbital, carbamazepine) with amprenavir may lead to a decrease in the plasma concentrations of amprenavir. These combinations should be used with caution and therapeutic concentration monitoring is recommended (see section 4.4).

**Calcium-channel blockers:** amprenavir may lead to increased serum concentrations of calcium channel blockers such as amlodipine, diltiazem, felodipine, isradipine, nicardipine, nifedipine, nimodipine, nisoldipine and verapamil, possibly resulting in enhanced activity and toxicity of these medicinal products.

**Erectile dysfunction agents:** based on data for other protease inhibitors caution should be used when prescribing PDE5 inhibitors (e.g. sildenafil and vardenafil) to patients receiving Agenerase. Co-administration with Agenerase may substantially increase PDE5 inhibitor plasma concentrations and associated adverse events, including hypotension, visual changes and priapism (see section 4.4).

Fluticasone propionate (interaction with ritonavir): in a clinical study where ritonavir 100 mg capsules bid were co-administered with 50 µg intranasal fluticasone propionate (4 times daily) for 7 days in healthy subjects, the fluticasone propionate plasma levels increased significantly, whereas the intrinsic cortisol levels decreased by approximately 86 % (90 % confidence interval 82-89 %). Greater effects may be expected when fluticasone propionate is inhaled. 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 could also occur with other corticosteroids metabolised via the P450 3A pathway e.g. budesonide. Consequently, concomitant administration of Agenerase with ritonavir and these glucocorticoids is not recommended unless the potential benefit of treatment outweighs the risk of systemic corticosteroid effects (see section 4.4). A dose reduction of the glucocorticoid should be considered with close monitoring of local and systemic effects or a switch to a glucocorticoid, which is not a substrate for CYP3A4 (e.g. beclomethasone). Moreover, in case of withdrawal of glucocorticoids progressive dose reduction may have to be performed over a longer period. The effects of high fluticasone systemic exposure on ritonavir plasma levels is yet unknown.

HMG-CoA reductase inhibitors: 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 Agenerase. Since increased concentrations of HMG-CoA reductase inhibitors may cause myopathy, including rhabdomyolysis, the combination of these medicinal products with Agenerase is not recommended. Atorvastatin is less dependent on CYP3A4 for metabolism. When used with Agenerase, the lowest possible dose of atorvastatin should be administered. The metabolism of pravastatin and fluvastatin is not dependent on CYP3A4, and interactions are not expected with protease inhibitors. If treatment with a HMG-CoA reductase inhibitor is indicated, pravastatin or fluvastatin is recommended.

Immunosuppressants: frequent therapeutic concentration monitoring of immunosuppressant levels is recommended until levels have stabilised as plasma concentrations of cyclosporin, rapamycin and tacrolimus may be increased when co-administered with amprenavir (see section 4.4).

Midazolam: midazolam is extensively metabolized by CYP3A4. Coadministration with Agenerase with or without ritonavir may cause a large increase in the concentration of this benzodiazepine. No drug interaction study has been performed for the co-administration of Agenerase with benzodiazepines. Based on data for other CYP3A4 inhibitors, plasma concentrations of midazolam are expected to be significantly higher when midazolam is given orally. Therefore Agenerase should not be co-administered with orally administered midazolam (see section 4.3), whereas caution should be used with co-administration of Agenerase and parenteral midazolam. Data from concomitant use of parenteral midazolam with other protease inhibitors suggest a possible 3-4 fold increase in midazolam plasma levels. If Agenerase with or without ritonavir is co-administered with parenteral midazolam, it should be done in an intensive care unit (ICU) or similar setting which ensures close clinical monitoring and appropriate medical management in case of respiratory depression and/or prolonged sedation. Dosage adjustment for midazolam should be considered, especially if more than a single dose of midazolam is administered.

Methadone and opiate derivatives: co-administration of methadone with amprenavir resulted in a decrease in the  $C_{max}$  and AUC of the active methadone enantiomer (R-enantiomer) of 25% and 13% respectively, whilst the  $C_{max}$ , AUC and  $C_{min}$  of the inactive methadone enantiomer (S-enantiomer) were decreased by 48%, 40% and 23% respectively. When methadone is co-administered with amprenavir, patients should be monitored for opiate abstinence syndrome, in particular if low-dose ritonavir is also given.

As compared to a non-matched historical control group, co-administration of methadone and amprenavir resulted in a 30%, 27% and 25% decrease in serum amprenavir AUC,  $C_{max}$  and  $C_{min}$  respectively. No recommendations can currently be made regarding adjustment of amprenavir dose when amprenavir is co-administered with methadone due to the inherent low reliability of non-matched historical controls.

*Oral anticoagulants:* a reinforced monitoring of the International Normalised Ratio is recommended in case of administration of Agenerase with warfarin or other oral anticoagulants, due to a possible decrease or increase of their antithrombotic effect (see section 4.4).

*Steroids:* oestrogens and progestogens may interact with amprenavir. However, the information currently available is not sufficient for determining the nature of the interaction. Co-administration of 0.035 mg ethinyl estradiol plus 1.0 mg norethindrone resulted in a decrease of the amprenavir AUC and  $C_{\min}$  of 22% and 20% respectively,  $C_{\max}$  being unchanged. The  $C_{\min}$  of ethinyl estradiol was increased by 32%, whilst the AUC and  $C_{\min}$  of norethindrone were increased by 18% and 45% respectively. Alternative methods of contraception are recommended for women of childbearing potential. When ritonavir is co-administered, the effect on hormonal contraceptive concentrations cannot be predicted, therefore, alternative methods of contraception are also recommended.

*Tricyclic antidepressants:* careful monitoring of the therapeutic and adverse reactions of tricyclic antidepressants is recommended when they (for example desipramine and nortriptyline) are concomitantly administered with Agenerase (see section 4.4).

*Paroxetine:* plasma concentrations of paroxetine may be significantly decreased when co-administered with amprenavir and ritonavir. The mechanism of this interaction remains unknown. Based on historical comparison, amprenavir pharmacokinetic parameters were not altered by paroxetine. Therefore, if paroxetine is co-administered with Agenerase and ritonavir, the recommended approach is a dose titration of paroxetine based on a clinical assessment of antidepressant response. In addition, patients on stable dose of paroxetine who start treatment with Agenerase and ritonavir should be monitored for antidepressant response.

*Other substances:* plasma concentrations of other substances may be increased by amprenavir. These include substances such as: clozapine, cimetidine, dapsone and loratadine. Some substances (e.g. lidocaine (by systemic route) and halofantrine) given with Agenerase may cause serious adverse reactions. Concomitant use is not recommended (see section 4.4).

#### **4.6 Pregnancy and lactation**

*Pregnancy:* there are no adequate data from the use of amprenavir in pregnant women. Studies in animals have shown reproductive toxicity (see section 5.3). The potential risk for humans is unknown.

This medicinal product should be used during pregnancy only after careful weighing of the potential benefits compared to the potential risk to the foetus.

*Lactation:* 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 weight gains in the offspring during the nursing period. The systemic exposure to the dams associated with this finding was similar to exposure in humans, following administration of the recommended dose. The subsequent development of the offspring, including fertility and reproductive performance, was 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 that HIV infected women do not breast feed their infants in order to avoid transmission of HIV.

#### **4.7 Effects on ability to drive and use machines**

No studies on the effects on ability to drive and use machines have been performed (see section 4.8).

#### **4.8 Undesirable effects**

The safety of Agenerase has been studied in adults and children at least 4 years of age, in controlled clinical trials, in combination with various other antiretroviral agents. Adverse events considered associated with the use of Agenerase are gastro-intestinal symptoms, rash and oral/peri-oral paraesthesia. Most undesirable effects associated with Agenerase therapy were mild to moderate in severity, early in onset, and rarely treatment limiting. For many of these events, it is unclear whether they are related to Agenerase, to concomitant treatment used in the management of HIV disease or to the disease process.

In children, the nature of the safety profile is similar 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 1200mg twice daily. Events (grade 2-4) reported by study investigators as attributable to study medication and occurring in >1% of patients, 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, elevated amylase, abnormal fat redistribution, anorexia  
Uncommon: Hyperglycaemia, hypercholesterolaemia

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

Elevations in cholesterol were of grade 3-4 intensity.

Combination antiretroviral therapy has been associated with redistribution of body fat (lipodystrophy) in HIV patients including the loss of peripheral and facial subcutaneous fat, increased intra-abdominal and visceral fat, breast hypertrophy and dorsocervical fat accumulation (buffalo hump).

Symptoms of abnormal fat redistribution were infrequent in PROAB3001 with amprenavir. Only one case (a buffalo hump) was reported in 113 (< 1 %) antiretroviral naïve subjects treated with amprenavir in combination with lamivudine/zidovudine for a median duration of 36 weeks. In study PROAB3006, seven cases (3 %) were reported in 245 NRTI-experienced subjects treated with amprenavir and in 27 (11 %) of 241 subjects treated with indinavir, in combination with various NRTIs for a median duration of 56 weeks (p< 0.001).

Combination antiretroviral therapy has been associated with metabolic abnormalities such as hypertriglyceridaemia, hypercholesterolaemia, insulin resistance, hyperglycaemia and hyperlactataemia (see section 4.4).

#### Psychiatric disorders

Common: Mood disorders, depressive disorders

#### Nervous system disorders

Very Common: Headache  
Common: Oral/perioral paraesthesia, tremors, sleep disorders

#### Gastrointestinal disorders

Very Common: Diarrhoea, nausea, flatulence, vomiting  
Common: Abdominal pain, abdominal discomfort, dyspeptic symptoms, loose stools

#### Hepatobiliary disorders

Common: Elevated transaminases  
Uncommon: Hyperbilirubinaemia

Elevated transaminases and hyperbilirubinaemia (grade 3-4) were reported primarily in patients with abnormal values at baseline. Almost all subjects with abnormal liver function tests were co-infected with Hepatitis B or C virus.

#### Skin and subcutaneous tissue disorders

Very Common: Rash  
Uncommon: Angioedema  
Rare: Stevens Johnson syndrome

Rashes were usually mild to moderate, erythematous or maculopapular cutaneous eruptions, with or without pruritus, occurring during the second week of therapy and resolving spontaneously within two weeks, without discontinuation of treatment with amprenavir. A higher incidence of rash was reported in patients treated with amprenavir in combination with efavirenz. Severe or life-threatening skin reactions have also occurred in patients treated with amprenavir (see section 4.4).

#### Musculoskeletal and connective tissue disorders

Increased CPK, myalgia, myositis, and rarely rhabdomyolysis have been reported with protease inhibitors, particularly in combination with nucleoside analogues.

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

#### General disorders and administration site conditions

Very Common: Fatigue

In HIV-infected patients with severe immune deficiency at the time of initiation of combination antiretroviral therapy (CART), an inflammatory reaction to asymptomatic or residual opportunistic infections may arise (see section 4.4).

In PI experienced patients receiving Agenerase capsules 600 mg twice daily and low dose ritonavir, 100 mg twice daily, the nature and frequency of adverse events (grade 2-4) and Grade 3/4 laboratory abnormalities were similar to those observed with Agenerase alone, with the exception of elevated triglyceride levels, and elevated CPK levels which were very common in patients receiving Agenerase and low dose ritonavir.

### **4.9 Overdose**

There are limited reports of overdose with Agenerase. If overdose occurs, the patient should be monitored for evidence of toxicity (see section 4.8) and standard supportive treatment provided as

necessary. Since amprenavir is highly protein bound, dialysis is unlikely to be helpful in reducing blood levels of amprenavir.

## 5. PHARMACOLOGICAL PROPERTIES

### 5.1 Pharmacodynamic properties

Pharmacotherapeutic group; protease inhibitor; ATC Code: J05A E05

#### Mechanism of Action

Amprenavir is a competitive inhibitor of HIV-1 protease. Amprenavir binds to the active site of HIV-1 protease and thereby prevents the processing of viral gag and gag-pol polyprotein precursors, resulting in the formation of immature non-infectious viral particles. The *in vitro* antiviral activity observed with fosamprenavir is due to the presence of trace amounts of amprenavir.

#### Antiviral activity *in vitro*

The *in vitro* antiviral activity of amprenavir was evaluated against HIV-1 III<sub>B</sub> in both acutely and chronically infected lymphoblastic cell lines (MT-4, CEM-CCRF, H9) and in peripheral blood lymphocytes. The 50% inhibitory concentration (IC<sub>50</sub>) of amprenavir ranged from 0.012 to 0.08 µM in acutely infected cells and was 0.41 µM in chronically infected cells (1 µM = 0.50 µg/ml). The relationship between *in vitro* anti-HIV-1 activity of amprenavir and the inhibition of HIV-1 replication in humans has not been defined.

#### Resistance

##### *In vitro*

HIV-1 isolates with decreased susceptibility to amprenavir have been selected during *in vitro* serial passage experiments. Reduced susceptibility to amprenavir was associated with virus that had developed I50V or I84V or V32I+I47V or I54M mutations.

##### *In vivo*

###### a) ART-naïve or PI-naïve patients

(Note: Agenerase is not approved in ART-naïve or PI-naïve patients).

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

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

Genotypic analysis of isolates from 13 of 14 paediatric patients exhibiting virological failure among the 59 PI-naïve patients enrolled, demonstrated resistance patterns similar to those observed in adults.

## b) PI-experienced patients

### Amprenavir

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

### Fosamprenavir

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

In the paediatric studies APV20003 and APV29005, 67 PI-experienced patients were treated with fosamprenavir / ritonavir and of 22 virological failure isolates genotyped, nine patients were found with treatment-emergent protease mutations. The mutational profiles were similar to those described for PI-experienced adults treated with fosamprenavir / ritonavir.

### **Analyses based on genotypic resistance testing.**

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

### **Analyses based on phenotypic resistance testing.**

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

### **Cross-Resistance**

HIV-1 isolates with a decreased susceptibility to amprenavir have been selected during in vitro serial passage experiments. Reduced susceptibility to amprenavir was associated with virus that had developed I50V or I84V or V32I+I47V or I54M mutations. Each of these four genetic patterns associated with reduced susceptibility to amprenavir produces some cross-resistance to ritonavir but susceptibility to indinavir, nelfinavir and saquinavir is generally retained. There are currently data on cross-resistance between amprenavir and other protease inhibitors for all 4 fosamprenavir resistance pathways, either alone or in combination with other mutations. Based on data from twenty-five antiretroviral naïve patients failing a fosamprenavir containing regimen (one of whom showed Baseline resistance to lopinavir and saquinavir and another to tipranavir) the resistance pathways associated with amprenavir produce limited cross-resistance to atazanavir/ritonavir (three of 25

isolates), darunavir/ritonavir (four of 25 isolates), indinavir/ritonavir (one of 25 isolates), lopinavir/ritonavir (three of 24 isolates), saquinavir (three of 24 isolates) and tipranavir/ritonavir (four of 24 isolates).. Conversely amprenavir retains activity against some isolates with resistance to other PIs and this retained activity would depend on the number and type of protease resistance mutations present in the isolates

The number of key PI-resistance mutations increases markedly the longer a failing PI-containing regimen is continued. Early discontinuation of failing therapies is recommended in order to limit the accumulation of multiple mutations, which may be detrimental to a subsequent rescue regimen.

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

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

### ***Clinical experience:***

#### **PI-experienced adults, boosted Agenerase capsules**

The evidence of efficacy of Agenerase in combination with ritonavir 100 mg twice daily is based on study PRO30017, a randomized, open-label study, in which PI-experienced adults experiencing virological failure (viral load  $\geq 1000$  copies/ml) received either Agenerase (600 mg twice daily) in combination with ritonavir (100 mg twice daily) and nucleoside analogues (NRTI) or a standard of care (SOC) PI, predominantly boosted with low-dose RTV.

One hundred and sixty-three (163) patients with virus sensitive to Agenerase, at least one other PI, and at least one NRTI were included in PRO30017 substudy A. The primary analysis assessed the non-inferiority of APV/r to the SOC PI group with respect to time-weighted average change from baseline (AAUCMB) in plasma viral load (HIV-1 RNA) at week 16 using a non-inferiority margin of 0.4 log<sub>10</sub> copies/ml.

Results at week 16

	<b>Amprenavir / ritonavir (n = 80)</b>	<b>SOC PI (n = 83): Indinavir / RTV (29%) Lopinavir / RTV (36%) Saquinavir / RTV(20%)</b>	<b>Treatment difference</b>
<i>Baseline characteristics</i>			
Median HIV-1 RNA (log <sub>10</sub> copies/ml) (range)	4.11 (2.51–5.97)	4.10 (2.34–6.07)	
Median CD4 (cells/ml) (range)	265 (8–837)	322 (36–955)	
Prior number of PIs taken [n (%)]			
1	27 (34)	25 (30)	
2	18 (23)	29 (35)	
≥ 3	35 (44)	29 (35)	
Median number of PI primary mutations <sup>1</sup>	1.0 (range 0-2)	1.0 (range 0-2)	
Prior number of NRTIs taken [n (%)]	49 (61)	40 (48)	
≥ 4			
<i>Outcomes<sup>a</sup></i>			
Mean plasma HIV-1 RNA AAUCMB (log <sub>10</sub> copies/ml)	- 1.315	- 1.343	0.043 <sup>b</sup> (-0.250, 0.335) <sup>c</sup>
Plasma HIV-1 RNA below 400 copies/ml (%)	66	70	6 (-21, 9) <sup>c</sup>

<sup>a</sup> Intent To Treat (Exposed) Population; Observed analysis

<sup>b</sup> Mean stratified difference

<sup>c</sup> 95% confidence interval

<sup>1</sup> Primary mutations were as defined by the IAS USA at the time of the original analysis, 2002 D30N, M46I/L, G48V, I50V, V82A/F/T/S, I84V, L90M.

Heavily pre-treated children, unboosted Agenerase

The evidence of efficacy of unboosted Agenerase was based on two uncontrolled clinical studies involving 288 HIV infected children aged between 2 and 18 years, 152 of whom were PI experienced. The studies evaluated Agenerase oral solution and capsules at doses of 15 mg/kg three times daily, 20 mg/kg three times daily, 20 mg/kg twice daily and 22.5 mg/kg twice daily although the majority received 20 mg/kg twice daily. Those of at least 13 years of age and weighing at least 50 kg received 1200 mg Agenerase twice daily. Concomitant low dose ritonavir was not administered and the majority of the PI experienced subjects had prior exposure to at least one (78 %) or two (42 %) of the NRTIs co-administered with Agenerase. At Week 48, approximately 25 % of those enrolled had plasma HIV-1 RNA < 10,000 copies/ml and 9 % < 400 copies/ml with a median change from baseline in CD4+ cells of 26 cells/mm<sup>3</sup> (n=74).

Based on these data, careful consideration should be given to the expected benefit of unboosted Agenerase when optimising therapy for PI experienced children.

There is no data on the efficacy of boosted Agenerase in children.

## 5.2 Pharmacokinetic properties

**Absorption:** after oral administration, amprenavir is rapidly and well absorbed. The absolute bioavailability is unknown due to the lack of an acceptable intravenous formulation for use in man. Approximately 90 % of an orally administered radiolabelled amprenavir dose was recovered in the urine and the faeces, primarily as amprenavir metabolites. Following oral administration, the mean time ( $t_{max}$ ) to maximal serum concentrations of amprenavir is between 1-2 hours for the capsule and 0.5 to 1 hour for the oral solution. A second peak is observed after 10 to 12 hours and may represent either delayed absorption or enterohepatic recirculation.

At therapeutic dosages (1200 mg twice daily), the mean maximum steady state concentration ( $C_{max,ss}$ ) of amprenavir capsules is 5.36  $\mu\text{g/ml}$  (0.92-9.81) and the minimum steady state concentration ( $C_{min,ss}$ ) is 0.28  $\mu\text{g/ml}$  (0.12-0.51). The mean AUC over a dosing interval of 12 hours is 18.46  $\mu\text{g.h/ml}$  (3.02-32.95). The 50 mg and 150 mg capsules have been shown to be bioequivalent. The bioavailability of the oral solution at equivalent doses is lower than that of the capsules, with an AUC and  $C_{max}$  approximately 14 % and 19 % lower, respectively (see section 4.2).

The AUC and  $C_{min}$  of amprenavir were increased by 64% and 508% respectively and the  $C_{max}$  decreased by 30% when ritonavir (100 mg twice daily) was coadministered with amprenavir (600 mg twice daily) compared to values achieved after 1200 mg twice daily doses of amprenavir.

While administration of amprenavir with food results in a 25 % reduction in AUC, it had no effect on the concentration of amprenavir 12 hours after dosing ( $C_{12}$ ). Therefore, although food affects the extent and rate of absorption, the steady-state trough concentration ( $C_{min,ss}$ ) was not affected by food intake.

**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.

In *in vitro* studies, the protein binding of amprenavir is approximately 90 %. Amprenavir is primarily bound to the alpha-1-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 active substance concentration in the plasma, however the amount of unbound amprenavir, which is the active moiety, is likely to be unchanged. While absolute free active substance concentrations remain constant, the percent of free active substance will fluctuate directly with total active substance concentrations at steady-state go from  $C_{max,ss}$  to  $C_{min,ss}$  over the course of the dosing interval. This will result in a fluctuation in the apparent volume of distribution of total active substance, but the volume of distribution of free active substance does not change.

Clinically significant binding displacement interactions involving medicinal products primarily bound to AAG are generally not observed. Therefore, interactions with amprenavir 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, medicinal products that are inducers, inhibitors or substrates of CYP3A4 must be used with caution when administered concurrently with Agenerase (see sections 4.3, 4.4 and 4.5).

**Elimination:** the plasma elimination half-life of amprenavir ranges from 7.1 to 10.6 hours. The plasma amprenavir half-life is increased when Agenerase capsules are co-administered with ritonavir. Following multiple oral doses of amprenavir (1200 mg twice a day), there is no significant active substance 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 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 with Agenerase capsules provided similar daily amprenavir exposure to 1200 mg twice a day in adults. 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 milligram per milligram basis.

**Elderly:** the pharmacokinetics of amprenavir have not been studied in patients over 65 years of age.

**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. Renal clearance of ritonavir is also negligible; therefore the impact of renal impairment on amprenavir and ritonavir elimination should be minimal.

**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 section 4.2). These dosing regimens will provide plasma amprenavir levels comparable to those achieved in healthy subjects given a 1200 mg dose twice daily without concomitant administration of ritonavir.

### **5.3 Preclinical safety data**

In long-term carcinogenicity studies with amprenavir in mice and rats, there were benign hepatocellular adenomas in males at exposure levels equivalent to 2.0-fold (mice) or 3.8-fold (rats) those in humans given 1200 mg twice daily of amprenavir alone. In male mice altered hepatocellular foci were seen at doses that were at least 2.0 times human therapeutic exposure.

A higher incidence of hepatocellular carcinoma was seen in all amprenavir male mouse treatment groups. However, this increase was not statistically significantly different from male control mice by appropriate tests. The mechanism for the hepatocellular adenomas and carcinomas found in these studies has not been elucidated and the significance of the observed effects for humans is uncertain. However, there is little evidence from the exposure data in humans, both in clinical trials and from 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.

In toxicological studies with mature animals, the clinically relevant findings were mostly confined to the liver and gastrointestinal disturbances. 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 measurements 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 Agenerase or after discontinuation.

Amprenavir did not affect fertility.

Local toxicity and sensitising potential was absent in animal studies, but slight irritating properties to the rabbit eye were identified.

Toxicity studies in young animals, treated from four days of age, resulted in high mortality in both the control animals and those receiving amprenavir. These results imply that young animals lack fully developed metabolic pathways enabling them to excrete amprenavir or some critical components of the formulation (e.g. propylene glycol, PEG 400). However, the possibility of anaphylactic reaction related to PEG 400 cannot be excluded. In clinical studies, the safety and efficacy of amprenavir have not yet been established in children below four years of age.

In pregnant mice, rabbits and rats there were no major effects on embryo-foetal development. However, at systemic plasma exposures significantly below (rabbits) or not significantly higher (rat) than the expected human exposures during therapeutic dosing, a number of minor changes, including thymic elongation and minor skeletal variations were seen, indicating developmental delay. A dose-dependent increase in placental weight was found in the rabbit and rat which may indicate effects on placental function. It is therefore recommended that women of child-bearing potential taking Agenerase should practice effective contraception (e.g. barrier methods).

## **6. PHARMACEUTICAL PARTICULARS**

### **6.1 List of excipients**

*Capsule shell:*

gelatin,  
glycerol,  
d-sorbitol (E420) and sorbitans solution,  
titanium dioxide,  
red printing ink.

*Capsule contents:*

d-alpha tocopheryl polyethylene glycol 1000 succinate (TPGS),  
macrogol 400 (PEG 400),  
propylene glycol.

### **6.2 Incompatibilities**

Not applicable.

### **6.3 Shelf life**

3 years.

### **6.4 Special precautions for storage**

Do not store above 30°C.

Keep the container tightly closed.

### **6.5 Nature and contents of container**

White High Density Polyethylene (HDPE) bottles containing 480 capsules.

### **6.6 Special precautions for disposal**

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

**7. MARKETING AUTHORISATION HOLDER**

Glaxo Group Ltd  
Glaxo Wellcome House  
Berkeley Avenue  
Greenford  
Middlesex UB6 0NN  
United Kingdom

**8. MARKETING AUTHORISATION NUMBER**

EU/1/00/148/001

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

Date of first authorisation: 20 October 2000  
Date of last renewal: 17 November 2005

**10. DATE OF THE REVISION OF THE TEXT**

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

Medicinal product no longer authorised

## **1. NAME OF THE MEDICINAL PRODUCT**

Agenerase 150 mg soft capsules.

## **2. QUALITATIVE AND QUANTITATIVE COMPOSITION**

Each capsule contains 150 mg amprenavir.

Excipients:

Sorbitol (E420)

For a full list of excipients, see section 6.1.

## **3. PHARMACEUTICAL FORM**

Soft capsule.

Oblong, opaque, off-white to cream coloured, printed with 'GX CC2'.

## **4. CLINICAL PARTICULARS**

### **4.1 Therapeutic indications**

Agenerase, in combination with other antiretroviral agents, is indicated for the treatment of protease inhibitor (PI) experienced HIV-1 infected adults and children above the age of 4 years. Agenerase capsules should normally be administered with low dose ritonavir as a pharmacokinetic enhancer of amprenavir (see sections 4.2 and 4.5). The choice of amprenavir should be based on individual viral resistance testing and treatment history of patients (see section 5.1).

The benefit of Agenerase boosted with ritonavir has not been demonstrated in PI naïve patients (see section 5.1)

### **4.2 Posology and method of administration**

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

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

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

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 milligram per milligram basis (see section 5.2).

Adults and adolescents of 12 years of age and older (greater than 50 kg body weight): the recommended dose of Agenerase capsules is 600 mg twice daily with ritonavir, 100 mg twice daily, in combination with other antiretroviral agents.

If Agenerase capsules are used without the boosting effect of ritonavir higher doses of Agenerase (1200 mg twice daily) should be used.

Children (4 to 12 years) and patients less than 50 kg body weight: the recommended dose of Agenerase capsules is 20 mg/kg body weight twice a day, in combination with other antiretroviral agents, without exceeding a total daily dose of 2400 mg (see section 5.1).

The pharmacokinetics, efficacy and safety of Agenerase in combination with 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: Agenerase is not recommended in children below 4 years due to lack of data on safety and efficacy (see section 5.2).

Elderly: the pharmacokinetics, efficacy and safety of amprenavir have not been studied in patients over 65 years of age (see section 5.2).

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

Hepatic impairment: the principal route of metabolism of amprenavir is via the liver. Agenerase capsules should be used with caution in patients with hepatic impairment. Clinical efficacy and safety have not been determined in this patient group. For subjects with hepatic impairment, pharmacokinetic data are available for the use of Agenerase capsules without the boosting effect of ritonavir. Based on pharmacokinetic data, the dose of Agenerase capsules should be reduced to 450 mg twice a day for adult patients with moderate hepatic impairment and to 300 mg twice a day for adult patients with severe hepatic impairment. No dose recommendation can be made in children with hepatic impairment (see section 5.2).

The use of amprenavir in combination with ritonavir has not been studied in patients with hepatic impairment. No dose recommendations can be made regarding this combination. Concomitant administration should be used with caution in patients with mild and moderate hepatic impairment and is contraindicated in patients with severe hepatic impairment (see section 4.3).

### **4.3 Contraindications**

Hypersensitivity to the active substance or to any of the excipients.

Agenerase must not be administered concurrently with medicinal products with narrow therapeutic windows that are substrates of cytochrome P450 3A4 (CYP3A4). Co-administration may result in competitive inhibition of the metabolism of these medicinal products and create the potential for serious and/or life-threatening adverse events such as cardiac arrhythmia (e.g. amiodarone, bepridil, quinidine, terfenadine, astemizole, cisapride, pimozide), respiratory depression and /or prolonged sedation (e.g. oral triazolam and oral midazolam (for caution on parenterally administered midazolam, see section 4.5)) or peripheral vasospasm or ischaemia and ischaemia of other tissues, including cerebral or myocardial ischaemia (e.g. ergot derivatives).

Agenerase in combination with ritonavir is contraindicated in patients with severe hepatic impairment.

Combination of rifampicin with Agenerase with concomitant low-dose ritonavir is contraindicated. (see section 4.5).

Agenerase with ritonavir must not be co-administered with medicinal products with narrow therapeutic windows that are highly dependent on CYP2D6 metabolism, e.g. flecainide and propafenone (see section 4.5).

Herbal preparations containing St John's wort (*Hypericum perforatum*) must not be used while taking amprenavir due to the risk of decreased plasma concentrations and reduced clinical effects of amprenavir (see section 4.5).

#### 4.4 Special warnings and precautions for use

Patients should be advised that Agenerase, 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 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.

On the basis of current pharmacodynamic data, amprenavir should be used in combination with at least two other antiretrovirals. When amprenavir is administered as monotherapy, resistant viruses rapidly emerge (see section 5.1). Agenerase capsules should normally be given in combination with low dose ritonavir and in combination with other antiretroviral agents (see section 4.2).

**Liver Disease:** The safety and efficacy of amprenavir has not been established in patients with significant underlying liver disorders. Agenerase capsules are contraindicated in patients with severe hepatic impairment when used in combination with ritonavir (see section 4.3). Patients with chronic hepatitis B or C and treated with combination antiretroviral therapy are at an increased risk of severe and potentially fatal hepatic adverse events. In case of concomitant antiviral therapy for hepatitis B or C, please refer also to the relevant product information for these medicinal products.

Patients with pre-existing liver dysfunction, including chronic active hepatitis, have an increased frequency of liver function abnormalities during combination antiretroviral therapy and should be monitored according to standard practice. If there is evidence of worsening liver disease in such patients, interruption or discontinuation of treatment must be considered.

##### Medicinal products – interactions

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

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

For some medicinal products that can cause serious or life-threatening undesirable effects, such as carbamazepine, phenobarbital, phenytoin, tricyclic antidepressants and warfarin (monitor International Normalised Ratio), concentration monitoring is available; this should minimise the risk of potential safety problems with concomitant use.

The use of Agenerase concomitantly with halofantrine or lidocaine (systemic) is not recommended (see section 4.5).

Anticonvulsants (carbamazepine, phenobarbital, phenytoin) should be used with caution. Agenerase may be less effective due to decreased amprenavir plasma concentrations in patients taking these medicinal products concomitantly (see section 4.5).

Therapeutic concentration monitoring is recommended for immunosuppressant medicinal products (cyclosporine, tacrolimus, rapamycin) when co-administered with Agenerase (see section 4.5).

Caution is advised when Agenerase is used concomitantly with PDE5 inhibitors (e.g. sildenafil and vardenafil) (see section 4.5).

Caution is advised when Agenerase is used concomitantly with delavirdine (see section 4.5).

A reduction of rifabutin dosage of at least 50 % is recommended when administered with Agenerase. When ritonavir is co-administered further dose reduction may be necessary (see section 4.5).

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 reliable methods of contraception are recommended for women of childbearing potential (see section 4.5).

Co-administration of amprenavir with methadone leads to a decrease of methadone concentrations. Therefore, when methadone is co-administered with amprenavir, patients should be monitored for opiate abstinence syndrome, in particular if low-dose ritonavir is also given. No recommendations can currently be made regarding adjustment of amprenavir dose when amprenavir is co-administered with methadone.

Agenerase capsules contain vitamin E (109 IU/150 mg capsule), therefore additional vitamin E supplementation is not recommended.

Agenerase capsules also contain sorbitol (E420). Patients with rare hereditary problems of fructose intolerance should not take this medicine.

Due to the potential risk of toxicity from the high propylene glycol content of Agenerase oral solution, this formulation is contraindicated in children below the age of four years and should be used with caution in certain other patient populations. The Summary of Product Characteristics of Agenerase oral solution should be consulted for full prescribing information.

#### Rash / cutaneous reactions

Most patients with mild or moderate rash can continue Agenerase. Appropriate antihistamines (e.g. cetirizine dihydrochloride) may reduce pruritus and hasten the resolution of rash. Agenerase should be permanently discontinued when rash is accompanied with systemic symptoms or allergic symptoms or mucosal involvement (see section 4.8).

#### 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.

#### Lipodystrophy

Combination antiretroviral therapy has been associated with the redistribution of body fat (lipodystrophy) in HIV patients. The long-term consequences of these events are currently unknown. Knowledge about the mechanism is incomplete. A connection between visceral lipomatosis and protease inhibitors and lipodystrophy and nucleoside reverse transcriptase inhibitors has been hypothesised. A higher risk of lipodystrophy has been associated with individual factors such as older age, and with drug related factors such as longer duration of antiretroviral treatment and associated metabolic disturbances. Clinical examination should include evaluation for physical signs of fat redistribution. Consideration should be given to the measurement of fasting serum lipids and blood glucose. Lipid disorders should be managed as clinically appropriate (see section 4.8).

#### Haemophilic patients

There have been reports of increased bleeding, including spontaneous skin haematomas and haemarthroses, in haemophilic 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. Haemophilic patients should therefore be made aware of the possibility of increased bleeding.

#### Immune Reactivation Syndrome

In HIV-infected patients with severe immune deficiency at the time of institution of combination antiretroviral therapy (CART), an inflammatory reaction to asymptomatic or residual opportunistic pathogens may arise and cause serious clinical conditions, or aggravation of symptoms. Typically, such reactions have been observed within the first few weeks or months of initiation of CART. Relevant examples are cytomegalovirus retinitis, generalised and/or focal mycobacterium infections, and *Pneumocystis carinii* pneumonia. Any inflammatory symptoms should be evaluated and treatment instituted when necessary.

#### Osteonecrosis

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

#### **4.5 Interaction with other medicinal products and other forms of interaction**

Interaction studies have been performed with amprenavir as the sole protease inhibitor. When amprenavir and ritonavir are co-administered, the ritonavir metabolic drug interaction profile may predominate because ritonavir is a more potent CYP3A4 inhibitor. Ritonavir also inhibits CYP2D6 and induces CYP3A4, CYP1A2, CYP2C9 and glucuronosyl transferase. The full prescribing information for ritonavir must therefore be consulted prior to initiation of therapy with Agenerase and ritonavir.

Amprenavir and ritonavir are primarily metabolised in the liver by CYP3A4. Therefore, medicinal products that either share this metabolic pathway or modify CYP3A4 activity may modify the pharmacokinetics of amprenavir. Similarly, amprenavir and ritonavir might also modify the pharmacokinetics of other medicinal products that share this metabolic pathway.

#### **Associations contraindicated (see section 4.3)**

##### CYP3A4 substrates with narrow therapeutic index

Agenerase must not be administered concurrently with medicinal products with narrow therapeutic windows containing active substances that are substrates of cytochrome P450 3A4 (CYP3A4). Co-administration may result in competitive inhibition of the metabolism of these active substances thus increasing their plasma level and leading to serious and / or life-threatening adverse reactions such as cardiac arrhythmia (e.g. amiodarone, astemizole, bepridil, cisapride, pimozone, quinidine, terfenadine) or peripheral vasospasm or ischaemia (e.g. ergotamine, dihydroergotamine) (see section 4.3).

##### CYP2D6 substrates with narrow therapeutic index

Agenerase with ritonavir must not be co-administered with medicinal products containing active substances that are highly dependent on CYP2D6 metabolism and for which elevated plasma concentrations are associated with serious and / or life-threatening adverse reactions. These active substances include flecainide and propafenone (see section 4.3).

### Rifampicin

Rifampicin is a strong CYP3A4 inducer and has been shown to cause an 82% decrease in amprenavir AUC, which can result in virological failure and resistance development. During attempts to overcome the decreased exposure by increasing the dose of other protease inhibitors with ritonavir, a high frequency of liver reactions was seen. The combination of rifampicin and Agenerase with concomitant low-dose ritonavir is contraindicated (see section 4.3).

### St John's wort (*Hypericum perforatum*)

Serum levels of amprenavir can be reduced by concomitant use of the herbal preparation St John's wort (*Hypericum perforatum*). This is due to induction of drug metabolising enzymes by St John's wort. Herbal preparations containing St John's wort should therefore not be combined with Agenerase. If a patient is already taking St John's wort, check amprenavir and if possible viral levels and stop St John's wort. Amprenavir levels may increase on stopping St John's wort. The dose of amprenavir may need adjusting. The inducing effect may persist for at least 2 weeks after cessation of treatment with St John's wort (see section 4.3).

- Other combinations

Of note, the following interaction data was obtained in adults.

### Antiretroviral agents

- ***Protease inhibitors (PIs):***

Indinavir: the AUC,  $C_{\min}$  and  $C_{\max}$  of indinavir were decreased by 38 %, 27 %, and 22 %, respectively, when given with amprenavir. The clinical relevance of these changes is unknown. The AUC,  $C_{\min}$  and  $C_{\max}$  of amprenavir were increased by 33 %, 25 %, and 18 %, respectively. No dose adjustment is necessary for either medicinal product when indinavir is administered in combination with amprenavir.

Saquinavir: the AUC,  $C_{\min}$  and  $C_{\max}$  of saquinavir were decreased by 19 % and 48 % and increased by 21 %, respectively, when given with amprenavir. The clinical relevance of these changes is unknown. The AUC,  $C_{\min}$  and  $C_{\max}$  of amprenavir were decreased by 32 %, 14 %, and 37 %, respectively. No dose adjustment is necessary for either medicinal product when saquinavir is administered in combination with amprenavir.

Nelfinavir: the AUC,  $C_{\min}$  and  $C_{\max}$  of nelfinavir were increased by 15 %, 14 %, and 12 %, respectively, when given with amprenavir. The  $C_{\max}$  of amprenavir was decreased by 14 % whilst the AUC and  $C_{\min}$  were increased by 9 % and 189 %, respectively. No dose adjustment is necessary for either medicinal product when nelfinavir is administered in combination with amprenavir (see also efavirenz below).

Ritonavir: the AUC and  $C_{\min}$  of amprenavir were increased by 64% and 508% respectively and the  $C_{\max}$  decreased by 30% when ritonavir (100 mg twice daily) was coadministered with amprenavir capsules (600 mg twice daily) compared to values achieved after 1200 mg twice daily doses of amprenavir capsules. In clinical trials, doses of amprenavir 600 mg twice daily and ritonavir 100 mg twice daily have been used; confirming the safety and efficacy of this regimen.

Lopinavir / ritonavir (Kaletra): in an open-label, non-fasting pharmacokinetic study, the AUC,  $C_{\max}$  and  $C_{\min}$  of lopinavir were decreased by 38%, 28% and 52% respectively when amprenavir (750 mg twice daily) was given in combination with Kaletra (400 mg lopinavir + 100 mg ritonavir twice daily). In the same study, the AUC,  $C_{\max}$ , and  $C_{\min}$  of amprenavir were increased 72%, 12%, and 483%, respectively, when compared to values after standard doses of amprenavir (1200 mg twice daily).

The amprenavir plasma  $C_{\min}$  values achieved with the combination of amprenavir (600 mg twice daily) in combination with Kaletra (400 mg lopinavir + 100 mg ritonavir twice daily) are approximately 40-50% lower than when amprenavir (600 mg twice daily) is given in combination with ritonavir 100 mg

twice daily. Adding additional ritonavir to an amprenavir plus Kaletra regimen increase lopinavir  $C_{\min}$  values, but not amprenavir  $C_{\min}$  values. No dose recommendation can be given for the co-administration of amprenavir and Kaletra, but close monitoring is advised because the safety and efficacy of this combination is unknown.

- ***Nucleoside analogue reverse transcriptase inhibitors (NRTIs):***

Zidovudine: the AUC and  $C_{\max}$  of zidovudine were increased by 31 % and 40 %, respectively, when given with amprenavir. The AUC and the  $C_{\max}$  of amprenavir were unaltered. No dose adjustment for either medicinal product is necessary when zidovudine is administered in combination with amprenavir.

Lamivudine: the AUC and  $C_{\max}$  of lamivudine and amprenavir, respectively, were both unaltered when these two medicinal products were given concomitantly. No dose adjustment is necessary for either medicinal product when lamivudine is administered in combination with amprenavir.

Abacavir: the AUC,  $C_{\min}$ , and  $C_{\max}$  of abacavir were unaltered when given with amprenavir. The AUC,  $C_{\min}$ , and  $C_{\max}$  of amprenavir were increased by 29 %, 27 %, and 47 %, respectively. No dose adjustment is necessary for either medicinal product when abacavir is administered in combination with amprenavir.

Didanosine: no pharmacokinetic study has been performed with Agenerase in combination with didanosine, however, due to its antacid component, it is recommended that didanosine and Agenerase should be administered at least one hour apart (see Antacids below).

- ***Non-nucleoside reverse transcriptase inhibitors (NNRTIs):***

Efavirenz: efavirenz has been seen to decrease the  $C_{\max}$ , AUC, and  $C_{\min,ss}$  of amprenavir by approximately 40 % in adults. When amprenavir is combined with ritonavir, the effect of efavirenz is compensated by the pharmacokinetic booster effect of ritonavir. Therefore, if efavirenz is given in combination with amprenavir (600 mg twice daily) and ritonavir (100 mg twice daily), no dose adjustment is necessary.

Further, if efavirenz is given in combination with amprenavir and nelfinavir, no dosage adjustment is necessary for any of the medicinal products.

Treatment with efavirenz in combination with amprenavir and saquinavir is not recommended as the exposure to both protease inhibitors would be decreased.

No dose recommendation can be given for co-administration of amprenavir with another protease inhibitor and efavirenz in children. Such combinations should be avoided in patients with hepatic impairment.

Nevirapine : The effect of nevirapine on other protease inhibitors and the limited evidence available suggest that nevirapine may decrease the serum concentrations of amprenavir.

Delavirdine: the AUC,  $C_{\max}$  and  $C_{\min}$  of delavirdine were decreased by 61%, 47% and 88% respectively when given with amprenavir. The AUC,  $C_{\max}$  and  $C_{\min}$  of amprenavir were increased by 130%, 40% and 125% respectively.

No dose recommendations can be given for the co-administration of amprenavir 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.

No dose recommendations can be given for the co-administration of amprenavir and low dose ritonavir with delavirdine. If these medicinal products are used concomitantly care is advised, and

close clinical and virological monitoring should be performed since it is difficult to predict the effect of the combination of amprenavir and ritonavir on delavirdine.

### **Antibiotics/antifungals**

**Rifabutin:** co-administration of amprenavir with rifabutin resulted in a 193 % increase in rifabutin AUC and an increase of rifabutin-related adverse events. The increase in rifabutin plasma concentration is likely to result from inhibition of rifabutin CYP3A4 mediated metabolism by amprenavir. When it is clinically necessary to co-administer rifabutin with Agenerase, a dosage reduction of at least half the recommended dose of rifabutin is advised, although no clinical data are available. When ritonavir is co-administered a larger increase in rifabutin concentration may occur.

**Clarithromycin:** the AUC and  $C_{min}$  of clarithromycin were unaltered and the  $C_{max}$  decreased by 10 % when given with amprenavir. The AUC,  $C_{min}$  and  $C_{max}$  of amprenavir were increased by 18 %, 39 %, and 15 % respectively. No dose adjustment is necessary for either medicinal product when clarithromycin is administered in combination with amprenavir. When ritonavir is co-administered an increase in clarithromycin concentrations may occur.

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

**Ketoconazole / Itraconazole:** the AUC and  $C_{max}$  of ketoconazole were increased by 44 % and 19 % respectively when given with amprenavir alone. The AUC and  $C_{max}$  of amprenavir were increased by 31 % and decreased by 16 %, respectively. Itraconazole concentrations are expected to increase in the same manner as ketoconazole. No dose adjustment for any of the medicinal products is necessary when either ketoconazole or itraconazole administered in combination with amprenavir. Co-administration of fosamprenavir 700 mg with ritonavir 100 mg twice daily and ketoconazole 200 mg once daily increased plasma ketoconazole  $C_{max}$  by 25 % and increased AUC(0- $\tau$ ) to values 2.69-fold those observed on administration of ketoconazole 200 mg once daily without concurrent fosamprenavir with ritonavir. The  $C_{max}$ , AUC and  $C_{min}$  of amprenavir were unchanged. When used with Agenerase with ritonavir, high doses (>200 mg/day) of ketoconazole or itraconazole are not recommended.

### **Other possible interactions**

Other medicinal products, listed below, including examples of substrates, inhibitors or inducers of CYP3A4, may lead to interactions when administered with Agenerase. The clinical significance of these possible interactions is not known and has not been investigated. Patients should therefore be monitored for toxic reactions associated with these medicinal products when these are administered in combination with Agenerase.

**Antacids:** on the basis of the data for other protease inhibitors, it is advisable not to take antacids at the same time as Agenerase, since its absorption may be impaired. It is recommended that antacids and Agenerase should be administered at least one hour apart.

**Anticonvulsant active substances:** concomitant administration of anticonvulsant active substances known as enzymatic inductors (phenytoin, phenobarbital, carbamazepine) with amprenavir may lead to a decrease in the plasma concentrations of amprenavir. These combinations should be used with caution and therapeutic concentration monitoring is recommended (see section 4.4).

**Calcium-channel blockers:** amprenavir may lead to increased serum concentrations of calcium channel blockers such as amlodipine, diltiazem, felodipine, isradipine, nifedipine, nimodipine, nisoldipine and verapamil, possibly resulting in enhanced activity and toxicity of these medicinal products.

*Erectile dysfunction agents:* based on data for other protease inhibitors caution should be used when prescribing PDE5 inhibitors (e.g. sildenafil and vardenafil) to patients receiving Agenerase. Co-administration with Agenerase may substantially increase PDE5 inhibitor plasma concentrations and associated adverse events, including hypotension, visual changes and priapism (see section 4.4).

*Fluticasone propionate (interaction with ritonavir):* in a clinical study where ritonavir 100 mg capsules bid were co-administered with 50 µg intranasal fluticasone propionate (4 times daily) for 7 days in healthy subjects, the fluticasone propionate plasma levels increased significantly, whereas the intrinsic cortisol levels decreased by approximately 86 % (90 % confidence interval 82-89 %). Greater effects may be expected when fluticasone propionate is inhaled. 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 could also occur with other corticosteroids metabolised via the P450 3A pathway e.g. budesonide. Consequently, concomitant administration of Agenerase with ritonavir and these glucocorticoids is not recommended unless the potential benefit of treatment outweighs the risk of systemic corticosteroid effects (see section 4.4). A dose reduction of the glucocorticoid should be considered with close monitoring of local and systemic effects or a switch to a glucocorticoid, which is not a substrate for CYP3A4 (e.g. beclomethasone). Moreover, in case of withdrawal of glucocorticoids progressive dose reduction may have to be performed over a longer period. The effects of high fluticasone systemic exposure on ritonavir plasma levels is yet unknown.

*HMG-CoA reductase inhibitors:* 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 Agenerase. Since increased concentrations of HMG-CoA reductase inhibitors may cause myopathy, including rhabdomyolysis, the combination of these medicinal products with Agenerase is not recommended. Atorvastatin is less dependent on CYP3A4 for metabolism. When used with Agenerase, the lowest possible dose of atorvastatin should be administered. The metabolism of pravastatin and fluvastatin is not dependent on CYP3A4, and interactions are not expected with protease inhibitors. If treatment with a HMG-CoA reductase inhibitor is indicated, pravastatin or fluvastatin is recommended.

*Immunosuppressants:* frequent therapeutic concentration monitoring of immunosuppressant levels is recommended until levels have stabilised as plasma concentrations of cyclosporin, rapamycin and tacrolimus may be increased when co-administered with amprenavir (see section 4.4).

*Midazolam:* midazolam is extensively metabolized by CYP3A4. Coadministration with Agenerase with or without ritonavir may cause a large increase in the concentration of this benzodiazepine. No drug interaction study has been performed for the co-administration of Agenerase with benzodiazepines. Based on data for other CYP3A4 inhibitors, plasma concentrations of midazolam are expected to be significantly higher when midazolam is given orally. Therefore Agenerase should not be co-administered with orally administered midazolam (see section 4.3), whereas caution should be used with co-administration of Agenerase and parenteral midazolam. Data from concomitant use of parenteral midazolam with other protease inhibitors suggest a possible 3-4 fold increase in midazolam plasma levels. If Agenerase with or without ritonavir is co-administered with parenteral midazolam, it should be done in an intensive care unit (ICU) or similar setting which ensures close clinical monitoring and appropriate medical management in case of respiratory depression and/or prolonged sedation. Dosage adjustment for midazolam should be considered, especially if more than a single dose of midazolam is administered.

*Methadone and opiate derivatives:* co-administration of methadone with amprenavir resulted in a decrease in the  $C_{max}$  and AUC of the active methadone enantiomer (R-enantiomer) of 25% and 13% respectively, whilst the  $C_{max}$ , AUC and  $C_{min}$  of the inactive methadone enantiomer (S-enantiomer) were decreased by 48%, 40% and 23% respectively. When methadone is co-administered with amprenavir, patients should be monitored for opiate abstinence syndrome, in particular if low-dose ritonavir is also given.

As compared to a non-matched historical control group, co-administration of methadone and amprenavir resulted in a 30%, 27% and 25% decrease in serum amprenavir AUC,  $C_{max}$  and  $C_{min}$  respectively. No recommendations can currently be made regarding adjustment of amprenavir dose when amprenavir is co-administered with methadone due to the inherent low reliability of non-matched historical controls.

*Oral anticoagulants:* a reinforced monitoring of the International Normalised Ratio is recommended in case of administration of Agenerase with warfarin or other oral anticoagulants, due to a possible decrease or increase of their antithrombotic effect (see section 4.4).

*Steroids:* oestrogens and progestogens may interact with amprenavir. However, the information currently available is not sufficient for determining the nature of the interaction. Co-administration of 0.035 mg ethinyl estradiol plus 1.0 mg norethindrone resulted in a decrease of the amprenavir AUC and  $C_{min}$  of 22% and 20% respectively,  $C_{max}$  being unchanged. The  $C_{min}$  of ethinyl estradiol was increased by 32%, whilst the AUC and  $C_{min}$  of norethindrone were increased by 18% and 45% respectively. Alternative methods of contraception are recommended for women of childbearing potential. When ritonavir is co-administered, the effect on hormonal contraceptive concentrations cannot be predicted, therefore, alternative methods of contraception are also recommended.

*Tricyclic antidepressants:* careful monitoring of the therapeutic and adverse reactions of tricyclic antidepressants is recommended when they (for example desipramine and nortriptyline) are concomitantly administered with Agenerase (see section 4.4).

*Paroxetine:* plasma concentrations of paroxetine may be significantly decreased when co-administered with amprenavir and ritonavir. The mechanism of this interaction remains unknown. Based on historical comparison, amprenavir pharmacokinetic parameters were not altered by paroxetine. Therefore, if paroxetine is co-administered with Agenerase and ritonavir, the recommended approach is a dose titration of paroxetine based on a clinical assessment of antidepressant response. In addition, patients on stable dose of paroxetine who start treatment with Agenerase and ritonavir should be monitored for antidepressant response.

*Other substances:* plasma concentrations of other substances may be increased by amprenavir. These include substances such as: clozapine, cimetidine, dapsone and loratadine.

Some substances (e.g. lidocaine (by systemic route) and halofantrine) given with Agenerase may cause serious adverse reactions. Concomitant use is not recommended (see section 4.4).

#### 4.6 Pregnancy and lactation

*Pregnancy:* there are no adequate data from the use of amprenavir in pregnant women. Studies in animals have shown reproductive toxicity (see section 5.3). The potential risk for humans is unknown.

This medicinal product should be used during pregnancy only after careful weighing of the potential benefits compared to the potential risk to the foetus.

*Lactation:* 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 weight gains in the offspring during the nursing period. The systemic exposure to the dams associated with this finding was similar to exposure in humans, following administration of the recommended dose. The subsequent development of the offspring, including fertility and reproductive performance, was 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 that HIV infected women do not breast-feed their infants in order to avoid transmission of HIV.

#### 4.7 Effects on ability to drive and use machines

No studies on the effects on ability to drive and use machines have been performed (see section 4.8).

#### 4.8 Undesirable effects

The safety of Agenerase has been studied in adults and children of at least 4 years of age, in controlled clinical trials, in combination with various other antiretroviral agents. Adverse events considered associated with the use of Agenerase are gastro-intestinal symptoms, rash and oral/peri-oral paraesthesia. Most undesirable effects associated with Agenerase therapy were mild to moderate in severity, early in onset, and rarely treatment-limiting. For many of these events, it is unclear whether they are related to Agenerase, to concomitant treatment used in the management of HIV disease or to the disease process.

In children, the nature of the safety profile is similar 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 1200mg twice daily. Events (grade 2-4) reported by study investigators as attributable to study medication and occurring in >1% of patients, 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, elevated amylase, abnormal fat redistribution, anorexia  
Uncommon: Hyperglycaemia, hypercholesterolaemia

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

Elevations in cholesterol were of grade 3-4 intensity.

Combination antiretroviral therapy has been associated with redistribution of body fat (lipodystrophy) in HIV patients including the loss of peripheral and facial subcutaneous fat, increased intra-abdominal and visceral fat, breast hypertrophy and dorsocervical fat accumulation (buffalo hump).

Symptoms of abnormal fat redistribution were infrequent in PROAB3001 with amprenavir. Only one case (a buffalo hump) was reported in 113 (< 1 %) antiretroviral naïve subjects treated with amprenavir in combination with lamivudine/zidovudine for a median duration of 36 weeks. In study PROAB3006, seven cases (3 %) were reported in 245 NRTI-experienced subjects treated with amprenavir and in 27 (11 %) of 241 subjects treated with indinavir, in combination with various NRTIs for a median duration of 56 weeks (p< 0.001).

Combination antiretroviral therapy has been associated with metabolic abnormalities such as hypertriglyceridaemia, hypercholesterolaemia, insulin resistance, hyperglycaemia and hyperlactataemia (see section 4.4).

### Psychiatric disorders

Common: Mood disorders, depressive disorders

### Nervous system disorders

Very Common: Headache

Common: Oral/perioral paraesthesia, tremors, sleep disorders

### Gastrointestinal disorders

Very Common: Diarrhoea, nausea, flatulence, vomiting

Common: Abdominal pain, abdominal discomfort, dyspeptic symptoms, loose stools

### Hepatobiliary disorders

Common: Elevated transaminases

Uncommon: Hyperbilirubinaemia

Elevated transaminases and hyperbilirubinaemia (grade 3-4) were reported primarily in patients with abnormal values at baseline. Almost all subjects with abnormal liver function tests were co-infected with Hepatitis B or C virus.

### Skin and subcutaneous tissue disorders

Very Common: Rash

Uncommon: Angioedema

Rare: Stevens Johnson syndrome

Rashes were usually mild to moderate, erythematous or maculopapular cutaneous eruptions, with or without pruritus, occurring during the second week of therapy and resolving spontaneously within two weeks, without discontinuation of treatment with amprenavir. A higher incidence of rash was reported in patients treated with amprenavir in combination with efavirenz. Severe or life-threatening skin reactions have also occurred in patients treated with amprenavir (see section 4.4).

### Musculoskeletal and connective tissue disorders

Increased CPK, myalgia, myositis, and rarely rhabdomyolysis have been reported with protease inhibitors, particularly in combination with nucleoside analogues.

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

### General disorders and administration site conditions

Very Common: Fatigue

In HIV-infected patients with severe immune deficiency at the time of initiation of combination antiretroviral therapy (CART), an inflammatory reaction to asymptomatic or residual opportunistic infections may arise (see section 4.4).

In PI experienced patients receiving Agenerase capsules 600 mg twice daily and low dose ritonavir, 100 mg twice daily, the nature and frequency of adverse events (grade 2-4) and Grade 3/4 laboratory abnormalities were similar to those observed with Agenerase alone, with the exception of elevated triglyceride levels, and elevated CPK levels which were very common in patients receiving Agenerase and low dose ritonavir.

## 4.9 Overdose

There are limited reports of overdose with Agenerase. If overdose occurs, the patient should be monitored for evidence of toxicity (see section 4.8), and standard supportive treatment provided as necessary. Since amprenavir is highly protein bound, dialysis is unlikely to be helpful in reducing blood levels of amprenavir.

## 5. PHARMACOLOGICAL PROPERTIES

### 5.1 Pharmacodynamic properties

Pharmacotherapeutic group; protease inhibitor; ATC Code: J05A E05

#### Mechanism of Action

Amprenavir is a competitive inhibitor of HIV-1 protease. Amprenavir binds to the active site of HIV-1 protease and thereby prevents the processing of viral gag and gag-pol polyprotein precursors, resulting in the formation of immature non-infectious viral particles. The *in vitro* antiviral activity observed with fosamprenavir is due to the presence of trace amounts of amprenavir.

#### Antiviral activity *in vitro*

The *in vitro* antiviral activity of amprenavir was evaluated against HIV-1 IIIB in both acutely and chronically infected lymphoblastic cell lines (MT-4, CEM-CCRF, H9) and in peripheral blood lymphocytes. The 50% inhibitory concentration (IC<sub>50</sub>) of amprenavir ranged from 0.012 to 0.08 µM in acutely infected cells and was 0.41 µM in chronically infected cells (1 µM = 0.50 µg/ml). The relationship between *in vitro* anti-HIV-1 activity of amprenavir and the inhibition of HIV-1 replication in humans has not been defined.

#### Resistance

##### *In vitro*

HIV-1 isolates with decreased susceptibility to amprenavir have been selected during *in vitro* serial passage experiments. Reduced susceptibility to amprenavir was associated with virus that had developed I50V or I84V or V32I+I47V or I54M mutations.

##### *In vivo*

- a) ART-naïve or PI-naïve patients

(Note: Agenerase is not approved in ART-naïve or PI-naïve patients).

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

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

Genotypic analysis of isolates from 13 of 14 paediatric patients exhibiting virological failure among the 59 PI-naïve patients enrolled, demonstrated resistance patterns similar to those observed in adults.

#### b) PI-experienced patients

##### Amprenavir

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

##### Fosamprenavir

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

In the paediatric studies APV20003 and APV29005, 67 PI-experienced patients were treated with fosamprenavir / ritonavir and of 22 virological failure isolates genotyped, nine patients were found with treatment-emergent protease mutations. The mutational profiles were similar to those described for PI-experienced adults treated with fosamprenavir / ritonavir.

##### **Analyses based on genotypic resistance testing.**

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

##### **Analyses based on phenotypic resistance testing.**

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

##### **Cross-Resistance**

HIV-1 isolates with a decreased susceptibility to amprenavir have been selected during in vitro serial passage experiments. Reduced susceptibility to amprenavir was associated with virus that had developed I50V or I84V or V32I+I47V or I54M mutations. Each of these four genetic patterns associated with reduced susceptibility to amprenavir produces some cross-resistance to ritonavir but susceptibility to indinavir, nelfinavir and saquinavir is generally retained. There are currently data on cross-resistance between amprenavir and other protease inhibitors for all 4 fosamprenavir resistance pathways, either alone or in combination with other mutations. Based on data from twenty-five antiretroviral naïve patients failing a fosamprenavir containing regimen (one of whom showed Baseline resistance to lopinavir and saquinavir and another to tipranavir) the resistance pathways associated with amprenavir produce limited cross-resistance to atazanavir/ritonavir (three of 25 isolates), darunavir/ritonavir (four of 25 isolates), indinavir/ritonavir (one of 25 isolates), lopinavir/ritonavir (three of 24 isolates), saquinavir (three of 24 isolates) and tipranavir/ritonavir (four

of 24 isolates).. Conversely amprenavir retains activity against some isolates with resistance to other PIs and this retained activity would depend on the number and type of protease resistance mutations present in the isolates.

The number of key PI-resistance mutations increases markedly the longer a failing PI-containing regimen is continued. Early discontinuation of failing therapies is recommended in order to limit the accumulation of multiple mutations, which may be detrimental to a subsequent rescue regimen.

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

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

***Clinical experience:***

PI-experienced adults, boosted Agenerase capsules

The evidence of efficacy of Agenerase in combination with ritonavir 100 mg twice daily is based on study PRO30017, a randomized, open-label study, in which PI-experienced adults experiencing virological failure (viral load  $\geq 1000$  copies/ml) received either Agenerase (600 mg twice daily) in combination with ritonavir (100 mg twice daily) and nucleoside analogues (NRTI) or a standard of care (SOC) PI, predominantly boosted with low-dose RTV.

One hundred and sixty-three (163) patients with virus sensitive to Agenerase, at least one other PI, and at least one NRTI were included in PRO30017 substudy A. The primary analysis assessed the non-inferiority of APV/r to the SOC PI group with respect to time-weighted average change from baseline (AAUCMB) in plasma viral load (HIV-1 RNA) at week 16 using a non-inferiority margin of 0.4 log<sub>10</sub> copies/ml.

Results at week 16

	<b>Amprenavir / ritonavir (n = 80)</b>	<b>SOC PI (n = 83): Indinavir / RTV (29%) Lopinavir / RTV (36%) Saquinavir / RTV(20%)</b>	<b>Treatment difference</b>
<i>Baseline characteristics</i>			
Median HIV-1 RNA (log <sub>10</sub> copies/ml) (range)	4.11 (2.51–5.97)	4.10 (2.34–6.07)	
Median CD4 (cells/ml) (range)	265 (8–837)	322 (36–955)	
Prior number of PIs taken [n (%)]			
1	27 (34)	25 (30)	
2	18 (23)	29 (35)	
$\geq 3$	35 (44)	29 (35)	
Median number of PI primary mutations <sup>1</sup>	1.0 (range 0-2)	1.0 (range 0-2)	
Prior number of NRTIs taken [n (%)]			
$\geq 4$	49 (61)	40 (48)	
<i>Outcomes</i> <sup>a</sup>			

Mean plasma HIV-1 RNA AAUCMB (log <sub>10</sub> copies/ml)	- 1.315	- 1.343	0.043 <sup>b</sup> (-0.250, 0.335) <sup>c</sup>
Plasma HIV-1 RNA below 400 copies/ml (%)	66	70	6 (-21, 9) <sup>c</sup>

<sup>a</sup> Intent To Treat (Exposed) Population: Observed analysis

<sup>b</sup> Mean stratified difference

<sup>c</sup> 95% confidence interval

<sup>1</sup> Primary mutations were as defined by the IAS USA at the time of the original analysis, 2002 D30N, M46I/L, G48V, I50V, V82A/F/T/S, I84V, L90M.

### Heavily pre-treated children, unboosted Agenerase

The evidence of efficacy of unboosted Agenerase was based on two uncontrolled clinical studies involving 288 HIV infected children aged between 2 and 18 years, 152 of whom were PI experienced. The studies evaluated Agenerase oral solution and capsules at doses of 15 mg/kg three times daily, 20 mg/kg three times daily, 20 mg/kg twice daily and 22.5 mg/kg twice daily although the majority received 20 mg/kg twice daily. Those of at least 13 years of age and weighing at least 50 kg received 1200 mg Agenerase twice daily. Concomitant low dose ritonavir was not administered and the majority of the PI experienced subjects had prior exposure to at least one (78 %) or two (42 %) of the NRTIs co-administered with Agenerase. At Week 48, approximately 25 % of those enrolled had plasma HIV-1 RNA < 10,000 copies/ml and 9 % < 400 copies/ml with a median change from baseline in CD4+ cells of 26 cells/mm<sup>3</sup> (n=74).

Based on these data, careful consideration should be given to the expected benefit of unboosted Agenerase when optimising therapy for PI experienced children.

There is no data on the efficacy of boosted Agenerase in children.

## **5.2 Pharmacokinetic properties**

**Absorption:** after oral administration, amprenavir is rapidly and well absorbed. The absolute bioavailability is unknown due to the lack of an acceptable intravenous formulation for use in man. Approximately 90 % of an orally administered radiolabelled amprenavir dose was recovered in the urine and the faeces, primarily as amprenavir metabolites. Following oral administration, the mean time ( $t_{max}$ ) to maximal serum concentrations of amprenavir is between 1-2 hours for the capsule and 0.5 to 1 hour for the oral solution. A second peak is observed after 10 to 12 hours and may represent either delayed absorption or enterohepatic recirculation.

At therapeutic dosages (1200 mg twice daily), the mean maximum steady state concentration ( $C_{max,ss}$ ) of amprenavir capsules is 5.36 µg/ml (0.92-9.81) and the minimum steady state concentration ( $C_{min,ss}$ ) is 0.28 µg/ml (0.12-0.51). The mean AUC over a dosing interval of 12 hours is 18.46 µg.h/ml (3.02-32.95). The 50 mg and 150 mg capsules have been shown to be bioequivalent. The bioavailability of the oral solution at equivalent doses is lower than that of the capsules, with an AUC and  $C_{max}$  approximately 14 % and 19 % lower, respectively (see section 4.2).

The AUC and  $C_{min}$  of amprenavir were increased by 64% and 508% respectively and the  $C_{max}$  decreased by 30% when ritonavir (100 mg twice daily) was coadministered with amprenavir (600 mg twice daily) compared to values achieved after 1200 mg twice daily doses of amprenavir.

While administration of amprenavir with food results in a 25 % reduction in AUC, it had no effect on the concentration of amprenavir 12 hours after dosing ( $C_{12}$ ). Therefore, although food affects the extent and rate of absorption, the steady-state trough concentration ( $C_{min,ss}$ ) was not affected by food intake.

**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.

In *in vitro* studies, the protein binding of amprenavir is approximately 90 %. Amprenavir is primarily bound to the alpha-1-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 active substance concentration in the plasma, however the amount of unbound amprenavir, which is the active moiety, is likely to be unchanged. While absolute free active substance concentrations remain constant, the percent of free active substance will fluctuate directly with total active substance concentrations at steady-state go from  $C_{\max,ss}$  to  $C_{\min,ss}$  over the course of the dosing interval. This will result in a fluctuation in the apparent volume of distribution of total active substance but the volume of distribution of free active substance does not change.

Clinically significant binding displacement interactions involving medicinal products primarily bound to AAG are generally not observed. Therefore, interactions with amprenavir 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 medicinal products that are inducers, inhibitors or substrates of CYP3A4 must be used with caution when administered concurrently with Agenerase (see sections 4.3, 4.4 and 4.5).

**Elimination:** the plasma elimination half-life of amprenavir ranges from 7.1 to 10.6 hours. The plasma amprenavir half-life is increased when Agenerase capsules are co-administered with ritonavir. Following multiple oral doses of amprenavir (1200 mg twice a day), there is no significant active substance 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 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 with Agenerase capsules provided similar daily amprenavir exposure to 1200 mg twice a day in adults. 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 milligram per milligram basis.

**Elderly:** the pharmacokinetics of amprenavir have not been studied in patients over 65 years of age.

**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. Renal clearance of ritonavir is also negligible; therefore the impact of renal impairment on amprenavir and ritonavir elimination should be minimal.

**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 section 4.2). These dosing regimens will provide plasma amprenavir levels comparable to those achieved in healthy subjects given a 1200 mg dose twice daily without concomitant administration of ritonavir.

### 5.3 Preclinical safety data

In long-term carcinogenicity studies with amprenavir in mice and rats, there were benign hepatocellular adenomas in males at exposure levels equivalent to 2.0-fold (mice) or 3.8-fold (rats) those in humans given 1200 mg twice daily of amprenavir alone. In male mice altered hepatocellular foci were seen at doses that were at least 2.0 times human therapeutic exposure.

A higher incidence of hepatocellular carcinoma was seen in all amprenavir male mouse treatment groups. However, this increase was not statistically significantly different from male control mice by appropriate tests. The mechanism for the hepatocellular adenomas and carcinomas found in these studies has not been elucidated and the significance of the observed effects for humans is uncertain. However, there is little evidence from the exposure data in humans, both in clinical trials and from 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.

In toxicological studies with mature animals, the clinically relevant findings were mostly confined to the liver and gastrointestinal disturbances. 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 measurements 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 Agenerase or after discontinuation.

Amprenavir did not affect fertility. Local toxicity and sensitising potential was absent in animal studies, but slight irritating properties to the rabbit eye were identified.

Toxicity studies in young animals, treated from four days of age, resulted in high mortality in both the control animals and those receiving amprenavir. These results imply that young animals lack fully developed metabolic pathways enabling them to excrete amprenavir or some critical components of the formulation (e.g. propylene glycol, PEG400). However, the possibility of anaphylactic reaction related to PEG400 cannot be excluded. In clinical studies, the safety and efficacy of amprenavir have not yet been established in children below four years of age.

In pregnant mice, rabbits and rats there were no major effects on embryo-foetal development. However, at systemic plasma exposures significantly below (rabbits) or not significantly higher (rat) than the expected human exposures during therapeutic dosing, a number of minor changes, including thymic elongation and minor skeletal variations were seen, indicating developmental delay. A dose-dependent increase in placental weight was found in the rabbit and rat which may indicate effects on placental function. It is therefore recommended that women of child-bearing potential taking Agenerase should practice effective contraception (e.g. barrier methods).

## 6. PHARMACEUTICAL PARTICULARS

### 6.1 List of excipients

*Capsule shell:*

gelatin,  
glycerol,  
d-sorbitol (E420) and sorbitans solution,  
titanium dioxide,  
red printing ink.

*Capsule contents:*

d-alpha tocopheryl polyethylene glycol 1000 succinate (TPGS),

macrogol 400 (PEG 400),  
propylene glycol.

## **6.2 Incompatibilities**

Not applicable.

## **6.3 Shelf life**

3 years.

## **6.4 Special precautions for storage**

Do not store above 30°C.

Keep the container tightly closed.

## **6.5 Nature and contents of container**

One or two white High Density Polyethylene (HDPE) bottles, each containing 240 capsules.

## **6.6 Special precautions for disposal**

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

## **7. MARKETING AUTHORISATION HOLDER**

Glaxo Group Ltd  
Glaxo Wellcome House  
Berkeley Avenue  
Greenford  
Middlesex UB6 0NN  
United Kingdom

## **8. MARKETING AUTHORISATION NUMBERS**

EU/1/00/148/002  
EU/1/00/148/003

## **9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**

Date of first authorisation: 20 October 2000  
Date of last renewal: 17 November 2005

## **10. DATE OF THE REVISION OF THE TEXT**

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

## **1. NAME OF THE MEDICINAL PRODUCT**

Agenerase 15 mg/ml oral solution.

## **2. QUALITATIVE AND QUANTITATIVE COMPOSITION**

Agenerase oral solution contains 15 mg/ml of amprenavir.

Excipients:

For a full list of excipients, see section 6.1.

## **3. PHARMACEUTICAL FORM**

Oral solution.

The oral solution is clear, pale yellow to yellow with grape, bubblegum and peppermint flavouring.

## **4. CLINICAL PARTICULARS**

### **4.1 Therapeutic indications**

Agenerase oral solution, in combination with other antiretroviral agents, is indicated for the treatment of protease inhibitor (PI) experienced HIV-1 infected adults and children above the age of 4 years. The choice of amprenavir should be based on individual viral resistance testing and treatment history of patients (see section 5.1).

The benefit of Agenerase oral solution boosted with ritonavir has not been demonstrated either in PI naïve patients or in PI experienced patients.

### **4.2 Posology and method of administration**

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

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

Agenerase oral solution is administered orally and can be taken with or without food.

Agenerase is also available as capsules. Amprenavir is 14 % less bioavailable from the Agenerase oral solution than from the capsules; therefore, Agenerase capsules and Agenerase oral solution are not interchangeable on a milligram per milligram basis (see section 5.2).

Patients should discontinue Agenerase oral solution as soon as they are able to swallow the capsule formulation (see section 4.4).

Patients of 4 years and older unable to swallow Agenerase capsules: the recommended dose of Agenerase oral solution is 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 (see section 5.1).

The pharmacokinetic interactions between amprenavir and low doses of ritonavir or other protease inhibitors have not yet been evaluated in children. Additionally, as no dosing recommendations can be made regarding the concomitant use of Agenerase oral solution and low dose ritonavir, the use of this combination must be avoided in these patient populations.

Children less than 4 years of age: Agenerase oral solution is contraindicated in children less than 4 years of age. (see sections 4.3 and 5.3 ).

Elderly: the pharmacokinetics, efficacy and safety of amprenavir have not been studied in patients over 65 years of age. (see section 5.2).

Renal impairment: although no dose adjustment is considered necessary for amprenavir, Agenerase oral solution is contraindicated in patients with renal failure (see section 4.3).

Hepatic impairment: Agenerase oral solution is contraindicated in patients with hepatic impairment or failure (see section 4.3) (see Summary of Product Characteristics of Agenerase Capsules for prescribing information)

### 4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients

Because of the potential risk of toxicity from the large amount of the excipient propylene glycol, Agenerase oral solution is contraindicated in infants and children below the age of 4 years, pregnant women, patients with hepatic impairment or failure and patients with renal failure. Agenerase oral solution is also contraindicated in patients treated with disulfiram or other medicinal products that reduce alcohol metabolism (e.g. metronidazole) and preparations that contain alcohol (e.g. ritonavir oral solution) or additional propylene glycol (see section 4.4 and 5.1).

Agenerase must not be administered concurrently with medicinal products with narrow therapeutic windows that are substrates of cytochrome P450 3A4 (CYP3A4). Co-administration may result in competitive inhibition of the metabolism of these medicinal products and create the potential for serious and/or life-threatening adverse events such as cardiac arrhythmia (e.g. amiodarone, bepridil, quinidine, terfenadine, astemizole, cisapride, pimozide), respiratory depression and /or prolonged sedation (e.g. oral triazolam and oral midazolam (for caution on parenterally administered midazolam, see section 4.5)) or peripheral vasospasm or ischaemia and ischaemia of other tissues, including cerebral or myocardial ischaemia (e.g. ergot derivatives).

Combination of rifampicin with Agenerase with concomitant low-dose ritonavir is contraindicated. (see section 4.5).

Herbal preparations containing St John's wort (*Hypericum perforatum*) must not be used while taking amprenavir due to the risk of decreased plasma concentrations and reduced clinical effects of amprenavir (see section 4.5).

### 4.4 Special warnings and precautions for use

Patients should be advised that Agenerase, 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 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.

On the basis of current pharmacodynamic data amprenavir should be used in combination with at least two other antiretrovirals. When amprenavir is administered as monotherapy, resistant viruses rapidly emerge (see section 5.1).

**Liver Disease:** The principal route of metabolism of amprenavir and the propylene glycol excipient is via the liver, Agenerase oral solution is contraindicated in patients with hepatic impairment or failure (see section 4.3).

Patients taking the oral solution of Agenerase, particularly those with renal impairment or those with decreased ability to metabolise propylene glycol (e.g. those of Asian origin), should be monitored for adverse reactions potentially related to the high propylene glycol content (550 mg/ml), such as seizures, stupor, tachycardia, hyperosmolarity, lactic acidosis, renal toxicity, haemolysis. For patients with renal failure, hepatic impairment or failure, children and pregnant women, see section 4.3. The concomitant administration of Agenerase oral solution with disulfiram or other medicinal products that reduce alcohol metabolism (e.g. metronidazole), or preparations that contain alcohol (e.g. ritonavir oral solution) or additional propylene glycol is contraindicated (see sections 4.3 and 4.5).

#### Medicinal products – interactions

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

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

For some medicinal products that can cause serious or life-threatening undesirable effects, such as carbamazepine, phenobarbital, phenytoin, tricyclic antidepressants and warfarin (monitor International Normalised Ratio), concentration monitoring is available; this should minimise the risk of potential safety problems with concomitant use.

The use of Agenerase concomitantly with halofantrine or lidocaine (systemic) is not recommended (see section 4.5).

Anticonvulsants (carbamazepine, phenobarbital, phenytoin) should be used with caution. Agenerase may be less effective due to decreased amprenavir plasma concentrations in patients taking these medicinal products concomitantly (see section 4.5).

Therapeutic concentration monitoring is recommended for immunosuppressant medicinal products (cyclosporine, tacrolimus, rapamycin) when co-administered with Agenerase (see section 4.5).

Caution is advised when Agenerase is used concomitantly with PDE5 inhibitors (e.g. sildenafil and vardenafil) (see section 4.5).

Caution is advised when Agenerase is used concomitantly with delavirdine (see section 4.5).

A reduction of rifabutin dosage of at least 50 % is recommended when administered with Agenerase (see section 4.5).

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 reliable methods of contraception are recommended for women of childbearing potential (see section 4.5).

Co-administration of amprenavir with methadone leads to a decrease of methadone concentrations. Therefore, when methadone is co-administered with amprenavir, patients should be monitored for opiate abstinence syndrome, in particular if low-dose ritonavir is also given. No recommendations can currently be made regarding adjustment of amprenavir dose when amprenavir is co-administered with methadone.

Agenerase oral solution contains vitamin E (46 IU/ml), therefore additional vitamin E supplementation is not recommended.

Agenerase oral solution contains 1 mg potassium per ml. This must be considered when prescribing to patients with reduced kidney function or patients on a controlled potassium diet.

Agenerase oral solution also contains 4 mg sodium per ml. This must be taken into consideration when prescribing to patients on a controlled sodium diet.

#### Rash / cutaneous reactions

Most patients with mild or moderate rash can continue Agenerase. Appropriate antihistamines (e.g. cetirizine dihydrochloride) may reduce pruritus and hasten the resolution of rash. Agenerase should be permanently discontinued when rash is accompanied with systemic symptoms or allergic symptoms or mucosal involvement (see section 4.8).

#### 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.

#### Lipodystrophy

Combination antiretroviral therapy has been associated with the redistribution of body fat (lipodystrophy) in HIV patients. The long-term consequences of these events are currently unknown. Knowledge about the mechanism is incomplete. A connection between visceral lipomatosis and protease inhibitors and lipodystrophy and nucleoside reverse transcriptase inhibitors has been hypothesised. A higher risk of lipodystrophy has been associated with individual factors such as older age, and with drug related factors such as longer duration of antiretroviral treatment and associated metabolic disturbances. Clinical examination should include evaluation for physical signs of fat redistribution. Consideration should be given to the measurement of fasting serum lipids and blood glucose. Lipid disorders should be managed as clinically appropriate (see section 4.8).

#### Haemophilic patients

There have been reports of increased bleeding, including spontaneous skin haematomas and haemarthroses in haemophilic 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. Haemophilic patients should therefore be made aware of the possibility of increased bleeding.

#### Immune Reactivation Syndrome

In HIV-infected patients with severe immune deficiency at the time of institution of combination antiretroviral therapy (CART), an inflammatory reaction to asymptomatic or residual opportunistic pathogens may arise and cause serious clinical conditions, or aggravation of symptoms. Typically, such reactions have been observed within the first few weeks or months of initiation of CART. Relevant examples are cytomegalovirus retinitis, generalised and/or focal mycobacterium infections, and *Pneumocystis carinii* pneumonia. Any inflammatory symptoms should be evaluated and treatment instituted when necessary.

## Osteonecrosis

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

## **4.5 Interaction with other medicinal products and other forms of interaction**

Amprénavir is primarily metabolised in the liver by CYP3A4. Therefore, medicinal products that either share this metabolic pathway or modify CYP3A4 activity may modify the pharmacokinetics of amprénavir. Similarly, amprénavir might also modify the pharmacokinetics of other medicinal products that share this metabolic pathway.

### **Associations contraindicated (see section 4.3)**

#### CYP3A4 substrates with narrow therapeutic index

Agenerase must not be administered concurrently with medicinal products with narrow therapeutic windows containing active substances that are substrates of cytochrome P450 3A4 (CYP3A4). Co-administration may result in competitive inhibition of the metabolism of these active substances thus increasing their plasma level and leading to serious and / or life-threatening adverse reactions such as cardiac arrhythmia (e.g. amiodarone, astemizole, bepridil, cisapride, pimozide, quinidine, terfenadine) or peripheral vasospasm or ischaemia (e.g. ergotamine, dihydroergotamine) (see section 4.3).

#### Rifampicin

Rifampicin is a strong CYP3A4 inducer and has been shown to cause an 82% decrease in amprénavir AUC, which can result in virological failure and resistance development. During attempts to overcome the decreased exposure by increasing the dose of other protease inhibitors with ritonavir, a high frequency of liver reactions was seen. The combination of rifampicin and Agenerase with concomitant low-dose ritonavir is contraindicated (see section 4.3).

#### St John's wort (*Hypericum perforatum*)

Serum levels of amprénavir can be reduced by concomitant use of the herbal preparation St John's wort (*Hypericum perforatum*). This is due to induction of drug metabolising enzymes by St John's wort. Herbal preparations containing St John's wort should therefore not be combined with Agenerase. If a patient is already taking St John's wort, check amprénavir and if possible viral levels and stop St John's wort. Amprénavir levels may increase on stopping St John's wort. The dose of amprénavir may need adjusting. The inducing effect may persist for at least 2 weeks after cessation of treatment with St John's wort (see section 4.3).

- Other combinations

Of note, the following interaction data was obtained in adults.

### **Antiretroviral agents**

- ***Protease inhibitors (PIs)***

Indinavir: the AUC,  $C_{min}$  and  $C_{max}$  of indinavir were decreased by 38 %, 27 %, and 22 %, respectively, when given with amprénavir. The clinical relevance of these changes is unknown. The AUC,  $C_{min}$  and  $C_{max}$  of amprénavir were increased by 33 %, 25 %, and 18 %, respectively. No dose adjustment is necessary for either medicinal product when indinavir is administered in combination with amprénavir.

Saquinavir: the AUC,  $C_{\min}$  and  $C_{\max}$  of saquinavir were decreased by 19 % and 48 % and increased by 21 %, respectively, when given with amprenavir. The clinical relevance of these changes is unknown. The AUC,  $C_{\min}$  and  $C_{\max}$  of amprenavir were decreased by 32 %, 14 % and 37 %, respectively. No dose adjustment is necessary for either medicinal product when saquinavir is administered in combination with amprenavir.

Nelfinavir: the AUC,  $C_{\min}$  and  $C_{\max}$  of nelfinavir were increased by 15 %, 14 %, and 12 % respectively when given with amprenavir. The  $C_{\max}$  of amprenavir was decreased by 14 % whilst the AUC and  $C_{\min}$  were increased by 9 % and 189 %, respectively. No dose adjustment is necessary for either medicinal product when nelfinavir is administered in combination with amprenavir (see also efavirenz below).

Ritonavir: the AUC and  $C_{\min}$  of amprenavir were increased by 64% and 508% respectively and the  $C_{\max}$  decreased by 30% when ritonavir (100 mg twice daily) was co-administered with amprenavir capsules (600 mg twice daily) compared to values achieved after 1200 mg twice daily doses of amprenavir capsules. In clinical trials, doses of amprenavir 600 mg twice daily and ritonavir 100 mg twice daily have been used; confirming the safety and efficacy of this regimen.

Agenerase oral solution and ritonavir oral solution should not be co-administered (see section 4.3).

Lopinavir / ritonavir (Kaletra): in an open-label, non-fasting pharmacokinetic study, the AUC,  $C_{\max}$  and  $C_{\min}$  of lopinavir were decreased by 38%, 28% and 52% respectively when amprenavir (750 mg twice daily) was given in combination with Kaletra (400 mg lopinavir + 100 mg ritonavir twice daily). In the same study, the AUC,  $C_{\max}$ , and  $C_{\min}$  of amprenavir were increased 72%, 12%, and 483%, respectively, when compared to values after standard doses of amprenavir (1200 mg twice daily).

The amprenavir plasma  $C_{\min}$  values achieved with the combination of amprenavir (600 mg twice daily) in combination with Kaletra (400 mg lopinavir + 100 mg ritonavir twice daily) are approximately 40-50% lower than when amprenavir (600 mg twice daily) is given in combination with ritonavir 100 mg twice daily. Adding additional ritonavir to an amprenavir plus Kaletra regimen increase lopinavir  $C_{\min}$  values, but not amprenavir  $C_{\min}$  values. No dose recommendation can be given for the co-administration of amprenavir and Kaletra, but close monitoring is advised because the safety and efficacy of this combination is unknown.

- **Nucleoside analogue reverse transcriptase inhibitors (NRTIs):**

Zidovudine: the AUC and  $C_{\max}$  of zidovudine were increased by 31 % and 40 %, respectively, when given with amprenavir. The AUC and the  $C_{\max}$  of amprenavir were unaltered. No dose adjustment for either medicinal product is necessary when zidovudine is administered in combination with amprenavir.

Lamivudine: the AUC and  $C_{\max}$  of lamivudine and amprenavir, respectively, were both unaltered when these two medicinal products were given concomitantly. No dose adjustment is necessary for either medicinal product when lamivudine is administered in combination with amprenavir.

Abacavir: the AUC,  $C_{\min}$  and  $C_{\max}$  of abacavir were unaltered when given with amprenavir. The AUC,  $C_{\min}$ , and  $C_{\max}$  of amprenavir were increased by 29 %, 27 %, and 47 % respectively. No dose adjustment is necessary for either medicinal product when abacavir is administered in combination with amprenavir.

Didanosine: no pharmacokinetic study has been performed with Agenerase in combination with didanosine, however, due to its antacid component, it is recommended that didanosine and Agenerase should be administered at least one hour apart (see Antacids below).

- **Non-nucleoside reverse transcriptase inhibitors (NNRTIs):**

Efavirenz: efavirenz has been seen to decrease the  $C_{\max}$ , AUC, and  $C_{\min,ss}$  of amprenavir by approximately 40 % in adults. When amprenavir is combined with ritonavir, the effect of efavirenz is

compensated by the pharmacokinetic booster effect of ritonavir. Therefore, if efavirenz is given in combination with amprenavir (600 mg twice daily) and ritonavir (100 mg twice daily), no dose adjustment is necessary.

Further, if efavirenz is given in combination with amprenavir and nelfinavir, no dosage adjustment is necessary for any of the medicinal products.

Treatment with efavirenz in combination with amprenavir and saquinavir is not recommended, as the exposure to both protease inhibitors would be decreased.

No dose recommendation can be given for the co-administration of amprenavir with another protease inhibitor and efavirenz in children.

Nevirapine: The effect of nevirapine on other protease inhibitors and the limited evidence available suggest that nevirapine may decrease the serum concentrations of amprenavir.

Delavirdine: the AUC,  $C_{max}$  and  $C_{min}$  of delavirdine were decreased by 61%, 47% and 88% respectively when given with amprenavir. The AUC,  $C_{max}$  and  $C_{min}$  of amprenavir were increased by 130%, 40% and 125% respectively.

No dose recommendations can be given for the co-administration of amprenavir 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.

### **Antibiotics/antifungals**

Rifabutin: co-administration of amprenavir with rifabutin resulted in a 193 % increase in rifabutin AUC and an increase of rifabutin-related adverse events. The increase in rifabutin plasma concentration is likely to result from inhibition of rifabutin CYP3A4 mediated metabolism by amprenavir. When it is clinically necessary to co-administer rifabutin with Agenerase, a dosage reduction of at least half the recommended dose of rifabutin is advised, although no clinical data are available.

Clarithromycin: the AUC and  $C_{min}$  of clarithromycin were unaltered and the  $C_{max}$  decreased by 10 % when given with amprenavir. The AUC,  $C_{min}$  and  $C_{max}$  of amprenavir were increased by 18 %, 39 %, and 15 % respectively. No dose adjustment is necessary for either medicinal product when clarithromycin is administered in combination with amprenavir.

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

Ketoconazole / Itraconazole: the AUC and  $C_{max}$  of ketoconazole were increased by 44 % and 19 % respectively when given with amprenavir. The AUC and  $C_{max}$  of amprenavir were increased by 31 % and decreased by 16 % respectively. Itraconazole concentrations are expected to increase in the same manner as ketoconazole. No dose adjustment for any of the medicinal products is necessary when either ketoconazole or itraconazole is administered in combination with amprenavir.

Metronidazole: Agenerase oral solution is contraindicated in patients treated with metronidazole (see section 4.3).

### **Other possible interactions**

Other medicinal products, listed below, including examples of substrates, inhibitors or inducers of CYP3A4, may lead to interactions when administered with Agenerase. The clinical significance of these possible interactions is not known and has not been investigated. Patients should therefore be

monitored for toxic reactions associated with these medicinal products when these are administered in combination with Agenerase.

***Alcohol and inhibitors of alcohol metabolism:*** 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 metabolism (e.g. metronidazole) or preparations that contain alcohol (e.g. ritonavir oral solution) or propylene glycol is contraindicated (see sections 4.3 and 4.4).

***Antacids:*** on the basis of the data for other protease inhibitors, it is advisable not to take antacids at the same time as Agenerase, since its absorption may be impaired. It is recommended that antacids and Agenerase should be administered at least one hour apart.

***Anticonvulsant active substances:*** concomitant administration of anticonvulsant active substances known as enzymatic inductors (phenytoin, phenobarbital, carbamazepine) with amprenavir may lead to a decrease in the plasma concentrations of amprenavir. These combinations should be used with caution and therapeutic concentration monitoring is recommended (see section 4.4).

***Calcium-channel blockers:*** amprenavir may lead to increased serum concentrations of calcium channel blockers such as amlodipine, diltiazem, felodipine, isradipine, nifedipine, nimodipine, nisoldipine and verapamil, possibly resulting in enhanced activity and toxicity of these medicinal products.

***Erectile dysfunction agents:*** based on data for other protease inhibitors caution should be used when prescribing PDE5 inhibitors (e.g. sildenafil and vardenafil) to patients receiving Agenerase. Co-administration with Agenerase may substantially increase PDE5 inhibitor plasma concentrations and associated adverse events, including hypotension, visual changes and priapism (see section 4.4).

***Fluticasone propionate (interaction with ritonavir):*** in a clinical study where ritonavir 100 mg capsules bid were co-administered with 50 µg intranasal fluticasone propionate (4 times daily) for 7 days in healthy subjects, the fluticasone propionate plasma levels increased significantly, whereas the intrinsic cortisol levels decreased by approximately 86 % (90 % confidence interval 82-89 %). Greater effects may be expected when fluticasone propionate is inhaled. 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 could also occur with other corticosteroids metabolised via the P450 3A pathway e.g. budesonide. Consequently, concomitant administration of Agenerase with ritonavir and these glucocorticoids is not recommended unless the potential benefit of treatment outweighs the risk of systemic corticosteroid effects (see section 4.4). A dose reduction of the glucocorticoid should be considered with close monitoring of local and systemic effects or a switch to a glucocorticoid, which is not a substrate for CYP3A4 (e.g. beclomethasone). Moreover, in case of withdrawal of glucocorticoids progressive dose reduction may have to be performed over a longer period. The effects of high fluticasone systemic exposure on ritonavir plasma levels is yet unknown.

***HMG-CoA reductase inhibitors:*** 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 Agenerase. Since increased concentrations of HMG-CoA reductase inhibitors may cause myopathy, including rhabdomyolysis, the combination of these medicinal products with Agenerase is not recommended. Atorvastatin is less dependent on CYP3A4 for metabolism. When used with Agenerase, the lowest possible dose of atorvastatin should be administered. The metabolism of pravastatin and fluvastatin is not dependent on CYP3A4, and interactions are not expected with protease inhibitors. If treatment with a HMG-CoA reductase inhibitor is indicated, pravastatin or fluvastatin is recommended.

***Immunosuppressants:*** frequent therapeutic concentration monitoring of immunosuppressant levels is recommended until levels have stabilised as plasma concentrations of cyclosporin, rapamycin and tacrolimus may be increased when co-administered with amprenavir (see section 4.4).

**Midazolam:** midazolam is extensively metabolized by CYP3A4. Coadministration with Agenerase with or without ritonavir may cause a large increase in the concentration of this benzodiazepine. No drug interaction study has been performed for the co-administration of Agenerase with benzodiazepines. Based on data for other CYP3A4 inhibitors, plasma concentrations of midazolam are expected to be significantly higher when midazolam is given orally. Therefore Agenerase should not be co-administered with orally administered midazolam (see section 4.3), whereas caution should be used with co-administration of Agenerase and parenteral midazolam. Data from concomitant use of parenteral midazolam with other protease inhibitors suggest a possible 3-4 fold increase in midazolam plasma levels. If Agenerase with or without ritonavir is co-administered with parenteral midazolam, it should be done in an intensive care unit (ICU) or similar setting which ensures close clinical monitoring and appropriate medical management in case of respiratory depression and/or prolonged sedation. Dosage adjustment for midazolam should be considered, especially if more than a single dose of midazolam is administered.

**Methadone and opiate derivatives:** co-administration of methadone with amprenavir resulted in a decrease in the  $C_{max}$  and AUC of the active methadone enantiomer (R-enantiomer) of 25% and 13% respectively, whilst the  $C_{max}$ , AUC and  $C_{min}$  of the inactive methadone enantiomer (S-enantiomer) were decreased by 48%, 40% and 23% respectively. When methadone is co-administered with amprenavir, patients should be monitored for opiate abstinence syndrome, in particular if low-dose ritonavir is also given.

As compared to a non-matched historical control group, co-administration of methadone and amprenavir resulted in a 30%, 27% and 25% decrease in serum amprenavir AUC,  $C_{max}$  and  $C_{min}$  respectively. No recommendations can currently be made regarding adjustment of amprenavir dose when amprenavir is co-administered with methadone due to the inherent low reliability of non-matched historical controls.

**Oral anticoagulants:** a reinforced monitoring of the International Normalised Ratio is recommended in case of administration of Agenerase with warfarin or other oral anticoagulants, due to a possible decrease or increase of their antithrombotic effect (see section 4.4).

**Steroids:** oestrogens and progestogens may interact with amprenavir. However, the information currently available is not sufficient for determining the nature of the interaction. Co-administration of 0.035 mg ethinyl estradiol plus 1.0 mg norethindrone resulted in a decrease of the amprenavir AUC and  $C_{min}$  of 22% and 20% respectively,  $C_{max}$  being unchanged. The  $C_{min}$  of ethinyl estradiol was increased by 32%, whilst the AUC and  $C_{min}$  of norethindrone were increased by 18% and 45% respectively. Alternative methods of contraception are recommended for women of childbearing potential.

**Tricyclic antidepressants:** careful monitoring of the therapeutic and adverse reactions of tricyclic antidepressants is recommended when they (for example desipramine and nortriptyline) are concomitantly administered with Agenerase (see section 4.4).

**Paroxetine:** plasma concentrations of paroxetine may be significantly decreased when co-administered with amprenavir and ritonavir. The mechanism of this interaction remains unknown. Based on historical comparison, amprenavir pharmacokinetic parameters were not altered by paroxetine. Therefore, if paroxetine is co-administered with Agenerase and ritonavir, the recommended approach is a dose titration of paroxetine based on a clinical assessment of antidepressant response. In addition, patients on stable dose of paroxetine who start treatment with Agenerase and ritonavir should be monitored for antidepressant response.

**Other substances:** plasma concentrations of other substances may be increased by amprenavir. These include substances such as: clozapine, cimetidine, dapsone and loratadine. Some substances (e.g. lidocaine (by systemic route) and halofantrine) given with Agenerase may cause serious adverse reactions. Concomitant use is not recommended (see section 4.4).

## 4.6 Pregnancy and lactation

**Pregnancy:** there are no adequate data from the use of amprenavir in pregnant women. Studies in animals have shown reproductive toxicity (see section 5.3). The potential risk to humans is unknown. Agenerase oral solution should not be used during pregnancy due to the potential risk of toxicity to the foetus from the propylene glycol content (see section 4.3).

**Lactation:** 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 weight gains in the offspring during the nursing period. The systemic exposure to the dams associated with this finding was similar to exposure in humans, following administration of the recommended dose. The subsequent development of the offspring, including fertility and reproductive performance, was 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 that HIV infected women do not breast-feed their infants in order to avoid transmission of HIV.

## 4.7 Effects on ability to drive and use machines

No studies on the effects on ability to drive and use machines have been performed (see section 4.8).

## 4.8 Undesirable effects

The safety of Agenerase has been studied in adults and children of at least 4 years of age in controlled clinical trials, in combination with various other antiretroviral agents. Adverse events considered associated with the use of Agenerase are gastro-intestinal symptoms, rash and oral/peri-oral paraesthesia. Most undesirable effects associated with Agenerase therapy were mild to moderate in severity, early in onset, and rarely treatment limiting. For many of these events it is unclear whether they are related to Agenerase, to concomitant treatment used in the management of HIV disease or to the disease process.

In children, the nature of the safety profile is similar 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 1200mg twice daily. Events (grade 2-4) reported by study investigators as attributable to study medication and occurring in >1% of patients, 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, elevated amylase, abnormal fat redistribution, anorexia
Uncommon:	Hyperglycaemia, hypercholesterolaemia

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

Elevations in cholesterol were of grade 3-4 intensity.

Combination antiretroviral therapy has been associated with redistribution of body fat (lipodystrophy) in HIV patients including the loss of peripheral and facial subcutaneous fat, increased intra-abdominal and visceral fat, breast hypertrophy and dorsocervical fat accumulation (buffalo hump).

Symptoms of abnormal fat redistribution were infrequent in PROAB3001 with amprenavir. Only one case (a buffalo hump) was reported in 113 (< 1 %) antiretroviral naive subjects treated with amprenavir in combination with lamivudine/zidovudine for a median duration of 36 weeks. In study PROAB3006, seven cases (3 %) were reported in 245 NRTI-experienced subjects treated with amprenavir and in 27 (11 %) of 241 subjects treated with indinavir, in combination with various NRTIs for a median duration of 56 weeks ( $p < 0.001$ ).

Combination antiretroviral therapy has been associated with metabolic abnormalities such as hypertriglyceridaemia, hypercholesterolaemia, insulin resistance, hyperglycaemia and hyperlactataemia (see section 4.4).

#### Psychiatric disorders

Common: Mood disorders, depressive disorders

#### Nervous system disorders

Very Common: Headache

Common: Oral/perioral paraesthesia, tremors, sleep disorders

#### Gastrointestinal disorders

Very Common: Diarrhoea, nausea, flatulence, vomiting

Common: Abdominal pain, abdominal discomfort, dyspeptic symptoms, loose stools

#### Hepatobiliary disorders

Common: Elevated transaminases

Uncommon: Hyperbilirubinaemia

Elevated transaminases and hyperbilirubinaemia (grade 3-4) were reported primarily in patients with abnormal values at baseline. Almost all subjects with abnormal liver function tests were co-infected with Hepatitis B or C virus.

#### Skin and subcutaneous tissue disorders

Very Common: Rash

Uncommon: Angioedema

Rare: Stevens Johnson syndrome

Rashes were usually mild to moderate, erythematous or maculopapular cutaneous eruptions, with or without pruritus, occurring during the second week of therapy and resolving spontaneously within two weeks, without discontinuation of treatment with amprenavir. A higher incidence of rash was reported in patients treated with amprenavir in combination with efavirenz. Severe or life-threatening skin reactions have also occurred in patients treated with amprenavir (see section 4.4).

#### Musculoskeletal and connective tissue disorders

Increased CPK, myalgia, myositis, and rarely rhabdomyolysis have been reported with protease inhibitors, particularly in combination with nucleoside analogues.

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

#### General disorders and administration site conditions

Very Common:            Fatigue

In HIV-infected patients with severe immune deficiency at the time of initiation of combination antiretroviral therapy (CART), an inflammatory reaction to asymptomatic or residual opportunistic infections may arise (see section 4.4).

Limited experience with Agenerase oral solution indicate a similar safety profile as for the capsules.

In PI experienced patients receiving Agenerase capsules 600 mg twice daily and low dose ritonavir, 100 mg twice daily, the nature and frequency of adverse events (grade 2-4) and Grade 3/4 laboratory abnormalities were similar to those observed with Agenerase alone, with the exception of elevated triglyceride levels, and elevated CPK levels which were very common in patients receiving Agenerase and low dose ritonavir.

#### **4.9 Overdose**

There are limited reports of overdose with Agenerase. If overdose occurs, the patient should be monitored for evidence of toxicity (see section 4.8), and standard supportive treatment provided as necessary. Agenerase oral solution contains a large amount of propylene glycol (see section 4.4). In the event of overdosage, monitoring and management of acid-base abnormalities are recommended. Propylene glycol can be removed by hemodialysis. However, since amprenavir is highly protein bound, dialysis is unlikely to be helpful in reducing blood levels of amprenavir.

### **5. PHARMACOLOGICAL PROPERTIES**

#### **5.1 Pharmacodynamic properties**

Pharmacotherapeutic group: protease inhibitor; ATC Code: J05A E05

#### Mechanism of Action

Amprenavir is a competitive inhibitor of HIV-1 protease. Amprenavir binds to the active site of HIV-1 protease and thereby prevents the processing of viral gag and gag-pol polyprotein precursors, resulting in the formation of immature non-infectious viral particles. The *in vitro* antiviral activity observed with fosamprenavir is due to the presence of trace amounts of amprenavir.

#### Antiviral activity *in vitro*

The *in vitro* antiviral activity of amprenavir was evaluated against HIV-1 IIIB in both acutely and chronically infected lymphoblastic cell lines (MT-4, CEM-CCRF, H9) and in peripheral blood lymphocytes. The 50% inhibitory concentration (IC<sub>50</sub>) of amprenavir ranged from 0.012 to 0.08 µM in acutely infected cells and was 0.41 µM in chronically infected cells (1 µM = 0.50 µg/ml). The relationship between *in vitro* anti-HIV-1 activity of amprenavir and the inhibition of HIV-1 replication in humans has not been defined.

#### Resistance

### In vitro

HIV-1 isolates with decreased susceptibility to amprenavir have been selected during *in vitro* serial passage experiments. Reduced susceptibility to amprenavir was associated with virus that had developed I50V or I84V or V32I+I47V or I54M mutations.

### In vivo

#### a) ART-naïve or PI-naïve patients

(Note: Agenerase is not approved in ART-naïve or PI-naïve patients).

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

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

Genotypic analysis of isolates from 13 of 14 paediatric patients exhibiting virological failure among the 59 PI-naïve patients enrolled, demonstrated resistance patterns similar to those observed in adults.

#### b) PI-experienced patients

### Amprenavir

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

### Fosamprenavir

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

In the paediatric studies APV20003 and APV29005, 67 PI-experienced patients were treated with fosamprenavir / ritonavir and of 22 virological failure isolates genotyped, nine patients were found with treatment-emergent protease mutations. The mutational profiles were similar to those described for PI-experienced adults treated with fosamprenavir / ritonavir.

### **Analyses based on genotypic resistance testing.**

Genotypic interpretation systems may be used to estimate the activity of amprenavir / ritonavir or fosamprenavir / ritonavir in subjects with PI-resistant isolates. The current (July 2006) ANRS AC-11

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

#### **Analyses based on phenotypic resistance testing.**

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

#### **Cross-Resistance**

HIV-1 isolates with a decreased susceptibility to amprenavir have been selected during in vitro serial passage experiments. Reduced susceptibility to amprenavir was associated with virus that had developed I50V or I84V or V32I+I47V or I54M mutations. Each of these four genetic patterns associated with reduced susceptibility to amprenavir produces some cross-resistance to ritonavir but susceptibility to indinavir, nelfinavir and saquinavir is generally retained. There are currently data on cross-resistance between amprenavir and other protease inhibitors for all 4 fosamprenavir resistance pathways, either alone or in combination with other mutations. Based on data from twenty-five antiretroviral naïve patients failing a fosamprenavir containing regimen (one of whom showed Baseline resistance to lopinavir and saquinavir and another to tipranavir) the resistance pathways associated with amprenavir produce limited cross-resistance to atazanavir/ritonavir (three of 25 isolates), darunavir/ritonavir (four of 25 isolates), indinavir/ritonavir (one of 25 isolates), lopinavir/ritonavir (three of 24 isolates), saquinavir (three of 24 isolates) and tipranavir/ritonavir (four of 24 isolates).. Conversely amprenavir retains activity against some isolates with resistance to other PIs and this retained activity would depend on the number and type of protease resistance mutations present in the isolates.

The number of key PI-resistance mutations increases markedly the longer a failing PI-containing regimen is continued. Early discontinuation of failing therapies is recommended in order to limit the accumulation of multiple mutations, which may be detrimental to a subsequent rescue regimen.

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

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

#### ***Clinical experience:***

##### **PI-experienced adults, boosted Agenerase capsules**

The evidence of efficacy of Agenerase in combination with ritonavir 100 mg twice daily is based on study PRO30017, a randomized, open-label study, in which PI-experienced adults experiencing virological failure (viral load  $\geq 1000$  copies/ml) received either Agenerase (600 mg twice daily) in combination with ritonavir (100 mg twice daily) and nucleoside analogues (NRTI) or a standard of care (SOC) PI, predominantly boosted with low-dose RTV.

One hundred and sixty-three (163) patients with virus sensitive to Agenerase, at least one other PI, and at least one NRTI were included in PRO30017 substudy A. The primary analysis assessed the non-inferiority of APV/r to the SOC PI group with respect to time-weighted average change from baseline (AAUCMB) in plasma viral load (HIV-1 RNA) at week 16 using a non-inferiority margin of 0.4 log10 copies/ml.

Results at week 16

	<b>Amprenavir / ritonavir (n = 80)</b>	<b>SOC PI (n = 83): Indinavir / RTV (29%) Lopinavir / RTV (36%) Saquinavir / RTV(20%)</b>	<b>Treatment difference</b>
<i>Baseline characteristics</i>			
Median HIV-1 RNA (log <sub>10</sub> copies/ml) (range)	4.11 (2.51–5.97)	4.10 (2.34–6.07)	
Median CD4 (cells/ml) (range)	265 (8–837)	322 (36–955)	
Prior number of PIs taken [n (%)]			
1	27 (34)	25 (30)	
2	18 (23)	29 (35)	
≥ 3	35 (44)	29 (35)	
Median number of PI primary mutations <sup>1</sup>	1.0 (range 0-2)	1.0 (range 0-2)	
Prior number of NRTIs taken [n (%)]			
≥ 4	49 (61)	40 (48)	
<i>Outcomes<sup>a</sup></i>			
Mean plasma HIV-1 RNA AAUCMB (log <sub>10</sub> copies/ml)	-1.315	-1.343	0.043 <sup>b</sup> (-0.250, 0.335) <sup>c</sup>
Plasma HIV-1 RNA below 400 copies/ml (%)	66	70	6 (-21, 9) <sup>c</sup>

<sup>a</sup> Intent To Treat (Exposed) Population: Observed analysis

<sup>b</sup> Mean stratified difference

<sup>c</sup> 95% confidence interval

<sup>1</sup> Primary mutations were as defined by the IAS USA at the time of the original analysis, 2002 D30N, M46I/L, G48V, I50V, V82A/F/T/S, I84V, L90M.

Heavily pre-treated children, unboosted Agenerase

The evidence of efficacy of unboosted Agenerase was based on two uncontrolled clinical studies involving 288 HIV infected children aged between 2 and 18 years, 152 of whom were PI experienced. The studies evaluated Agenerase oral solution and capsules at doses of 15 mg/kg three times daily, 20 mg/kg three times daily, 20 mg/kg twice daily and 22.5 mg/kg twice daily although the majority received 20 mg/kg twice daily. Those of at least 13 years of age and weighing at least 50 kg received 1200 mg Agenerase twice daily. Concomitant low dose ritonavir was not administered and the majority of the PI experienced subjects had prior exposure to at least one (78 %) or two (42 %) of the NRTIs co-administered with Agenerase. At Week 48, approximately 25 % of those enrolled had

plasma HIV-1 RNA < 10,000 copies/ml and 9 % < 400 copies/ml with a median change from baseline in CD4+ cells of 26 cells/mm<sup>3</sup> (n=74).

Based on these data, careful consideration should be given to the expected benefit of unboosted Agenerase when optimising therapy for PI experienced children.

There is no data on the efficacy of boosted Agenerase in children.

## 5.2 Pharmacokinetic properties

**Absorption:** after oral administration, amprenavir is rapidly and well absorbed. The absolute bioavailability is unknown due to the lack of an acceptable intravenous formulation for use in man. Approximately 90 % of an orally administered radiolabelled amprenavir dose was recovered in the urine and the faeces, primarily as amprenavir metabolites. Following oral administration, the mean time ( $t_{max}$ ) to maximal serum concentrations of amprenavir is between 1-2 hours for the capsule and 0.5 to 1 hour for the oral solution. A second peak is observed after 10 to 12 hours and may represent either delayed absorption or enterohepatic recirculation.

At therapeutic dosages (1200 mg twice daily), the mean maximum steady state concentration ( $C_{max,ss}$ ) of amprenavir capsules is 5.36 µg/ml (0.92-9.81) and the minimum steady state concentration ( $C_{min,ss}$ ) is 0.28 µg/ml (0.12-0.51). The mean AUC over a dosing interval of 12 hours is 18.46 µg.h/ml (3.02-32.95). The 50 mg and 150 mg capsules have been shown to be bioequivalent. The bioavailability of the oral solution at equivalent doses is lower than that of the capsules, with an AUC and  $C_{max}$  approximately 14 % and 19 % lower, respectively (see section 4.2).

While administration of amprenavir with food results in a 25 % reduction in AUC, it had no effect on the concentration of amprenavir 12 hours after dosing ( $C_{12}$ ). Therefore, although food affects the extent and rate of absorption, the steady-state trough concentration ( $C_{min,ss}$ ) was not affected by food intake.

**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.

In *in vitro* studies, the protein binding of amprenavir is approximately 90 %. Amprenavir is primarily bound to the alpha-1-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 active substance concentration in the plasma, however the amount of unbound amprenavir, which is the active moiety, is likely to be unchanged. While absolute free active substance concentrations remain constant, the percent of free active substance will fluctuate directly with total active substance concentrations at steady-state go from  $C_{max,ss}$  to  $C_{min,ss}$  over the course of the dosing interval. This will result in a fluctuation in the apparent volume of distribution of total active substance, but the volume of distribution of free active substance does not change.

Clinically significant binding displacement interactions involving medicinal products primarily bound to AAG are generally not observed. Therefore, interactions with amprenavir 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 medicinal products that are inducers, inhibitors or substrates of CYP3A4 must be used with caution when administered concurrently with Agenerase (see sections 4.3, 4.4 and 4.5).

**Elimination:** the plasma elimination half-life of amprenavir ranges from 7.1 to 10.6 hours. Following multiple oral doses of amprenavir (1200 mg twice a day), there is no significant active substance

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 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 with Agenerase capsules provided similar daily amprenavir exposure to 1200 mg twice a day in adults. 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 milligram per milligram basis.

**Elderly:** the pharmacokinetics of amprenavir have not been studied in patients over 65 years of age.

**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. Agenerase oral solution should not be used in patients with hepatic impairment or failure (see section 4.3).

### **5.3 Preclinical safety data**

In long-term carcinogenicity studies with amprenavir in mice and rats, there were benign hepatocellular adenomas in males at exposure levels equivalent to 2.0-fold (mice) or 3.8-fold (rats) those in humans given 1200 mg twice daily of amprenavir alone. In male mice altered hepatocellular foci were seen at doses that were at least 2.0 times human therapeutic exposure.

A higher incidence of hepatocellular carcinoma was seen in all amprenavir male mouse treatment groups. However, this increase was not statistically significantly different from male control mice by appropriate tests. The mechanism for the hepatocellular adenomas and carcinomas found in these studies has not been elucidated and the significance of the observed effects for humans is uncertain. However, there is little evidence from the exposure data in humans, both in clinical trials and from 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.

In toxicological studies with mature animals, the clinically relevant findings were mostly confined to the liver and gastrointestinal disturbances. 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 measurements 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 Agenerase or after discontinuation.

Amprenavir did not affect fertility. Local toxicity and sensitising potential was absent in animal studies, but slight irritating properties to the rabbit eye were identified.

Toxicity studies in young animals, treated from four days of age, resulted in high mortality in both the control animals and those receiving amprenavir. These results imply that young animals lack fully developed metabolic pathways enabling them to excrete amprenavir or some critical components of the formulation (e.g. propylene glycol, PEG 400). However, the possibility of anaphylactic reaction

related to PEG 400 cannot be excluded. In clinical studies, the safety and efficacy of amprenavir have not yet been established in children below four years of age.

In pregnant mice, rabbits and rats there were no major effects on embryo-foetal development. However, at systemic plasma exposures significantly below (rabbits) or not significantly higher (rat) than the expected human exposures during therapeutic dosing, a number of minor changes, including thymic elongation and minor skeletal variations were seen, indicating developmental delay. A dose-dependent increase in placental weight was found in the rabbit and rat which may indicate effects on placental function. It is therefore recommended that women of child-bearing potential taking Agenerase should practice effective contraception (e.g. barrier methods).

## **6. PHARMACEUTICAL PARTICULARS**

### **6.1 List of excipients**

Propylene glycol,  
macrogol 400 (PEG 400),  
d-alpha tocopheryl polyethylene glycol 1000 succinate,  
acesulfame potassium,  
saccharin sodium,  
sodium chloride,  
artificial grape bubblegum flavour,  
natural peppermint flavour,  
menthol,  
citric acid,  
anhydrous,  
sodium citrate dihydrate,  
purified water.

### **6.2 Incompatibilities**

Not applicable.

### **6.3 Shelf life**

3 years.

### **6.4 Special precautions for storage**

Do not store above 25°C.

Discard the oral solution 15 days after first opening the bottle.

### **6.5 Nature and contents of container**

White High Density Polyethylene (HDPE) bottles containing 240 ml of oral solution. A 20 ml measuring cup is provided in the pack.

### **6.6 Special precautions for disposal**

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

## **7. MARKETING AUTHORISATION HOLDER**

Glaxo Group Ltd

Glaxo Wellcome House  
Berkeley Avenue  
Greenford  
Middlesex UB6 0NN  
United Kingdom

**8.     MARKETING AUTHORISATION NUMBERS**

EU/1/00/148/004

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

Date of first authorisation: 20 October 2000

Date of last renewal: 17 November 2005

**10.    DATE OF THE REVISION OF THE TEXT**

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

Medicinal product no longer authorised

**ANNEX II**

- A. MANUFACTURING AUTHORISATION HOLDERS  
RESPONSIBLE FOR BATCH RELEASE**
- B. CONDITIONS OF THE MARKETING AUTHORISATION**

Medicinal product no longer authorised

**A. MANUFACTURING AUTHORISATION HOLDERS RESPONSIBLE FOR BATCH RELEASE**

Soft capsules

- Glaxo Operations UK Limited, trading as Glaxo Wellcome Operations  
Priory Street, Ware, Hertfordshire SG12 0DJ, United Kingdom  
Manufacturing authorisation issued on 30 June 1995 by the Medicine Control Agency, Market Towers, 1 Nine Elms Lane, Vauxhall, London SW8 5NQ, United Kingdom.

Oral solution

- Glaxo Wellcome GmbH & Co. KG  
Industrie straÙe 32-36, 23843 Bad Oldesloe, Germany

The printed package leaflet of the medicinal product must state the name and address of the manufacturer responsible for the release of the concerned batch

**B. CONDITIONS OF THE MARKETING AUTHORISATION**

- **CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE IMPOSED ON THE MARKETING AUTHORISATION HOLDER**

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

- **CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT**

Not applicable

**ANNEX III**

**LABELLING AND PACKAGE LEAFLET**

Medicinal product no longer authorised

**A. LABELLING**

Medicinal product no longer authorised

**PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING**

**BOTTLE LABEL LEAFLET**

**1. NAME OF THE MEDICINAL PRODUCT**

Agenerase 50 mg soft capsules  
Amprenavir

**2. STATEMENT OF ACTIVE SUBSTANCE(S)**

Each capsule contains 50 mg amprenavir

**3. LIST OF EXCIPIENTS**

This product contains glycerol, sorbitol E420 and propylene glycol  
See leaflet for further information

**4. PHARMACEUTICAL FORM AND CONTENTS**

480 soft capsules

**5. METHOD AND ROUTE(S) OF ADMINISTRATION**

Oral use

**Read the package leaflet before use**

**6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN**

Keep out of the reach and sight of children.

**7. OTHER SPECIAL WARNING(S), IF NECESSARY**

**8. EXPIRY DATE**

EXP {MM/YYYY}

**9. SPECIAL STORAGE CONDITIONS**

Do not store above 30°C.

Keep the container tightly closed.

**10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE**

Any unused product or waste material should be disposed of in accordance with local requirements.

**11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER**

Glaxo Group Ltd  
Glaxo Wellcome House  
Berkeley Avenue  
Greenford  
Middlesex UB6 0NN  
United Kingdom

**12. MARKETING AUTHORISATION NUMBER(S)**

EU/1/00/148/001

**13. BATCH NUMBER**

LOT

**14. GENERAL CLASSIFICATION FOR SUPPLY**

Medicinal product subject to medical prescription.

**15. INSTRUCTIONS ON USE**

**16. INFORMATION IN BRAILLE**

**PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING**

**BOTTLE LABEL LEAFLET**

**1. NAME OF THE MEDICINAL PRODUCT**

Agenerase 150 mg soft capsules  
Amprenavir

**2. STATEMENT OF ACTIVE SUBSTANCE(S)**

Each capsule contains 150 mg amprenavir

**3. LIST OF EXCIPIENTS**

This product contains glycerol, sorbitol E420 and propylene glycol  
See leaflet for further information

**4. PHARMACEUTICAL FORM AND CONTENTS**

240 soft capsules

**5. METHOD AND ROUTE OF ADMINISTRATION**

Oral use

**Read the package leaflet before use**

**6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN**

Keep out of the reach and sight of children.

**7. OTHER SPECIAL WARNING(S), IF NECESSARY**

**8. EXPIRY DATE**

EXP {MM/YYYY}

**9. SPECIAL STORAGE CONDITIONS**

Do not store above 30°C.

Keep the container tightly closed.

**10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE**

Any unused product or waste material should be disposed of in accordance with local requirements.

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Glaxo Wellcome House  
Berkeley Avenue  
Greenford  
Middlesex UB6 0NN  
United Kingdom

**12. MARKETING AUTHORISATION NUMBER**

EU/1/00/148/002

**13. BATCH NUMBER**

LOT

**14. GENERAL CLASSIFICATION FOR SUPPLY**

Medicinal product subject to medical prescription.

**15. INSTRUCTIONS ON USE**

**16. INFORMATION IN BRAILLE**

**PARTICULARS TO APPEAR ON THE OUTER PACKAGING**

**CARTON**

**1. NAME OF THE MEDICINAL PRODUCT**

Agenerase 150 mg soft capsules  
Amprenavir

**2. STATEMENT OF ACTIVE SUBSTANCE(S)**

Each capsule contains 150 mg amprenavir

**3. LIST OF EXCIPIENTS**

This product contains glycerol, sorbitol E420 and propylene glycol  
See leaflet for further information

**4. PHARMACEUTICAL FORM AND CONTENTS**

Pack contents : Two bottles each containing 240 soft capsules

**5. METHOD AND ROUTE(S) OF ADMINISTRATION**

Oral use

**Read the package leaflet before use**

**6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN**

Keep out of the reach and sight of children.

**7. OTHER SPECIAL WARNING(S), IF NECESSARY**

**8. EXPIRY DATE**

EXP {MM/YYYY}

**9. SPECIAL STORAGE CONDITIONS**

Do not store above 30°C.

Keep the container tightly closed.

**10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE**

Any unused product or waste material should be disposed of in accordance with local requirements.

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Berkeley Avenue  
Greenford  
Middlesex UB6 0NN  
United Kingdom

**12. MARKETING AUTHORISATION NUMBER**

EU/1/00/148/003

**13. BATCH NUMBER**

LOT

**14. GENERAL CLASSIFICATION FOR SUPPLY**

Medicinal product subject to medical prescription.

**15. INSTRUCTIONS ON USE**

**16. INFORMATION IN BRAILLE**

**PARTICULARS TO APPEAR ON THE OUTER PACKAGING**

**CARTON**

**1. NAME OF THE MEDICINAL PRODUCT**

Agenerase 15 mg/ml oral solution  
Amprenavir

**2. STATEMENT OF ACTIVE SUBSTANCE(S)**

15 mg/ml amprenavir

**3. LIST OF EXCIPIENTS**

This product contains propylene glycol, potassium and sodium  
See leaflet for further information

**4. PHARMACEUTICAL FORM AND CONTENTS**

Bottle contents : 240 ml oral solution containing 15 mg/ml amprenavir  
A 20 ml measuring cup is provided in the pack.

**5. METHOD AND ROUTE(S) OF ADMINISTRATION**

Oral use

**Read the package leaflet before use**

**6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN**

Keep out of the reach and sight of children.

**7. OTHER SPECIAL WARNING(S), IF NECESSARY**

**8. EXPIRY DATE**

EXP {MM/YYYY}

**9. SPECIAL STORAGE CONDITIONS**

Do not store above 25°C.

Discard the oral solution 15 days after first opening the bottle.

**10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE**

Any unused product or waste material should be disposed of in accordance with local requirements.

**11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER**

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Glaxo Wellcome House  
Berkeley Avenue  
Greenford  
Middlesex UB6 0NN  
United Kingdom

**12. MARKETING AUTHORISATION NUMBER**

EU/1/00/148/004

**13. BATCH NUMBER**

LOT

**14. GENERAL CLASSIFICATION FOR SUPPLY**

Medicinal product subject to medical prescription.

**15. INSTRUCTIONS ON USE**

**16. INFORMATION IN BRAILLE**

**PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING**

**LEAFLET**

**1. NAME OF THE MEDICINAL PRODUCT**

Agenerase 15 mg/ml oral solution  
Amprenavir

**2. STATEMENT OF ACTIVE SUBSTANCE(S)**

15 mg/ml amprenavir

**3. LIST OF EXCIPIENTS**

This product contains propylene glycol, potassium and sodium  
See leaflet for further information

**4. PHARMACEUTICAL FORM AND CONTENTS**

Bottle contents : 240 ml oral solution containing 15 mg/ml amprenavir.  
A 20 ml measuring cup is provided in the pack.

**5. METHOD AND ROUTE(S) OF ADMINISTRATION**

Oral use

**Read the package leaflet before use**

**6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN**

Keep out of the reach and sight of children.

**7. OTHER SPECIAL WARNING(S), IF NECESSARY**

**8. EXPIRY DATE**

EXP {MM/YYYY}

**9. SPECIAL STORAGE CONDITIONS**

Do not store above 25°C.

Discard the oral solution 15 days after first opening the bottle.

**10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE**

Any unused product or waste material should be disposed of in accordance with local requirements.

**11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER**

Glaxo Group Ltd  
Glaxo Wellcome House  
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United Kingdom

**12. MARKETING AUTHORISATION NUMBER**

EU/1/00/148/004

**13. BATCH NUMBER**

LOT

**14. GENERAL CLASSIFICATION FOR SUPPLY**

Medicinal product subject to medical prescription.

**15. INSTRUCTIONS ON USE**

Medicinal product no longer authorised

**B. PACKAGE LEAFLET**

## PACKAGE LEAFLET : INFORMATION FOR THE USER

### Agenerase 50 mg soft capsules

Amprenavir

**Read all of this leaflet carefully before you start taking this medicine.**

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them even if their symptoms are the same as yours.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

#### **In this leaflet:**

- 1) What Agenerase is and what it is used for
- 2) Before you take Agenerase
- 3) How to take Agenerase
- 4) Possible side effects
- 5) How to store Agenerase
- 6) Further information

### **1. WHAT AGENERASE IS AND WHAT IT IS USED FOR**

Agenerase belongs to a group of antiviral medicines called protease inhibitors. These medicines are used for treating human immunodeficiency virus (HIV) infection.

Agenerase is used in protease inhibitor experienced HIV-1 infected adults and children above the age of 4 years. Agenerase is prescribed for use in combination with other antiretroviral medicinal products. Your doctor will normally direct that Agenerase capsules should be taken with low doses of ritonavir to boost its efficacy. The choice of Agenerase will be based on any resistance testing your doctor may have carried out and your treatment history.

The benefit of amprenavir boosted with ritonavir has not been demonstrated in PI naïve patients.

### **2. BEFORE YOU TAKE AGENERASE**

#### **Do not take Agenerase**

- if you are allergic (hypersensitive) to amprenavir or to any of the other ingredients in Agenerase.
- if you have severe liver disease (see 'Take special care with Agenerase').
- you are currently taking any of the following medicines:
  - astemizole or terfenadine (commonly used to treat allergy symptoms – these medicines may be available without prescription)
  - pimozide (used to treat schizophrenia)
  - cisapride (used to relieve certain stomach problems)
  - ergot derivatives (used to treat headaches)
  - rifampicin (used to treat tuberculosis)
  - amiodarone, quinidine (used to treat abnormal heart beat)
  - flecainide and propafenone (heart medicines)
  - triazolam and oral (taken by mouth) midazolam (used to help you sleep and / or relieve anxiety)
  - bepridil (used to treat hypertension).

- if you are currently taking any products containing St John's wort (*Hypericum perforatum*) as this may stop Agenerase from working properly (see Taking/using other medicines).

*Tell your doctor if you have any of these listed conditions, or are taking any of the medicines listed above.*

### **Take special care with Agenerase**

You will need to take Agenerase every day. This medicine helps to control your condition, but it is not a cure for HIV infection. You can still continue to develop other infections and other illnesses associated with HIV disease. You should keep in regular contact with your doctor. Do not stop taking your medicine without first talking to your doctor.

If your doctor has recommended that you take Agenerase capsules together with low doses of ritonavir, used to boost its activity, then please make sure that you carefully read the ritonavir Package Leaflet before starting therapy.

At present, there is insufficient information to recommend the use of Agenerase in children less than four years of age. There is also insufficient information to recommend the use of Agenerase capsules boosted with ritonavir in children of 4 to 12 years of age or any patients weighing less than fifty kilograms.

Agenerase may interact with other medicines that you are taking, so it is important that you read the next section "Taking/using other medicines" before taking this medicine.

You should tell your doctor about any medical conditions that you have or have had.

- Please speak with your doctor if you have a history of liver disease. Patients with chronic hepatitis B or C and treated with antiretroviral agents are at increased risk for severe and potentially fatal liver adverse events and may require blood tests for control of liver function.
- The use of Agenerase together with ritonavir has not been studied in patients with liver disease. If your liver disease is severe you must not use this combination.
- Agenerase capsules (without the boosting effect of ritonavir) have been studied in patients with liver impairment. If you suffer from liver disease and your doctor decides to use unboosted Agenerase capsules (that is without ritonavir), the dose of Agenerase may need to be adjusted.
- There have been reports of increased bleeding in patients with haemophilia taking protease inhibitors. The reason for this is not known. You may need additional factor VIII to control bleeding.
- Redistribution, accumulation or loss of body fat may occur in patients receiving combination antiretroviral therapy. Contact your doctor if you notice changes in body fat.
- In some patients with advanced HIV infection (AIDS) and a history of opportunistic infection, signs and symptoms of inflammation from previous infections may occur soon after anti-HIV treatment is started. It is believed that these symptoms are due to an improvement in the body's immune response, enabling the body to fight infections that may have been present with no obvious symptoms. If you notice any symptoms of infection, please inform your doctor immediately.
- If you have any other health concerns, discuss these with your doctor.

### **Bone problems**

Some patients taking combination antiretroviral therapy may develop a bone disease called osteonecrosis (death of bone tissue caused by loss of blood supply to the bone). The length of combination antiretroviral therapy, corticosteroid use, alcohol consumption, severe immunosuppression, higher body mass index, among others, may be some of the many risk factors for developing this disease. Signs of osteonecrosis are joint stiffness, aches and pains (especially of the hip, knee and shoulder) and difficulty in movement. If you notice any of these symptoms please inform your doctor.

Treatment with Agenerase has not been shown to reduce the risk of passing HIV infection on to others by sexual contact or by blood transfer. You should continue to use appropriate precautions to prevent this.

### **Taking/using other medicines**

Before starting treatment with Agenerase, please tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription. This is **very important**, as taking some types of medicines at the same time as Agenerase can strengthen or weaken the effect of the medicines. This can sometimes lead to serious medical conditions.

There are some medicines that you **must not take** with Agenerase (please see 'Do not take Agenerase' for further information).

Agenerase may interact with certain other medicines. The use of the following medicines, together with Agenerase, should only take place on the basis of medical advice: anaesthetics (e.g. lidocaine), antibiotics (e.g. rifabutin, clarithromycin, dapsone and erythromycin), antifungals (e.g. ketoconazole, itraconazole), antimalarials (e.g. halofantrine), anticonvulsant medicines (e.g. carbamazepine, phenytoin and phenobarbital), calcium channel blockers (e.g. amlodipine, diltiazem, felodipine, isradipine, nifedipine, nifedipine, nimodipine, nisoldipine and verapamil), cholesterol lowering medicines (e.g. atorvastatin, lovastatin and simvastatin), erectile dysfunction medicines (e.g. sildenafil and vardenafil), non-nucleoside reverse transcriptase inhibitors (e.g. delavirdine, efavirenz and nevirapine), opioids (e.g. methadone), hormones like oestrogens and progestogens (e.g. hormonal contraceptives such as the 'pill'), some glucocorticoids (e.g. fluticasone propionate and budesonide), tricyclic antidepressants (e.g. desipramine and nortriptyline), sedative agents (e.g. midazolam administered by injection), paroxetine, and others (e.g. clozapine and loratadine).

If you are taking certain medicines that can cause serious side effects, such as carbamazepine, phenobarbital, phenytoin, lidocaine, cyclosporine, tacrolimus, rapamycin, tricyclic antidepressants and warfarin, at the same time as you are taking Agenerase, your doctor may carry out additional blood tests to minimise any potential safety problems.

If you are taking the contraceptive pill, it is recommended that you use an alternative method (e.g. a condom) to prevent pregnancy while you are taking Agenerase. The concomitant use of Agenerase and contraceptive pill may result in a decrease of the therapeutic effect of Agenerase.

### **Taking Agenerase with food and drink**

Agenerase capsules should be swallowed whole with water or another drink. They can be taken with or without food.

### **Pregnancy and breast-feeding**

Inform your doctor if you are pregnant or planning to become pregnant soon. The safe use of Agenerase in pregnancy has not been established. Ask your doctor or pharmacist before taking any medicine.

Breast feeding your baby is not recommended while you are taking Agenerase. It is recommended that HIV positive women do not breast feed their infants in order to avoid transmission of HIV.

### **Driving and using machines**

No studies on the effects of Agenerase on the ability to drive and use machines have been done. If Agenerase makes you dizzy, do not operate any tools or machines.

### **Important information about ingredients of Agenerase capsules**

These capsules contain glycerol, which can cause adverse effects in high doses. Glycerol can cause headache, stomach upset and diarrhoea.

These capsules also contain sorbitol. If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicinal product

Because Agenerase capsules contain vitamin E, you should not take additional vitamin E supplements.

### 3. HOW TO TAKE AGENERASE

Always take Agenerase exactly as your doctor has told you. You should check with your doctor or pharmacist if you are not sure.

If you need to take an antacid for indigestion, or if you are taking a drug containing an antacid (e.g. didanosine), you are advised to take it more than an hour before or after Agenerase, otherwise the effects of Agenerase may be reduced.

- Swallow Agenerase capsules whole with water or another drink. They can be taken with or without food.
- *Adults and adolescents (of 12 years of age and older) (greater than 50 kg body weight):* the usual dose of Agenerase capsules is 600 mg twice daily with ritonavir 100 mg twice daily, in combination with other antiretroviral medicinal products. If your doctor decides it is inappropriate for you to take ritonavir, you will need to take increased doses of Agenerase (1200 mg twice a day).
- *Children (4 to 12 years) and patients less than 50 kg body weight:* the dose will be calculated according to your weight by your doctor. The usual dose for Agenerase capsules is 20 mg for each kg of body weight, twice a day. You should not take more than 2400 mg per day. In some cases, your doctor may adapt the dose of Agenerase when other drugs are administered concomitantly with Agenerase.

To derive the full benefit of Agenerase, it is very important that you take the **full** daily dose prescribed by your doctor.

An oral solution of Agenerase is available for children or adults unable to swallow capsules.

#### **If you take more Agenerase than you should**

If you have taken more than the prescribed dose of Agenerase, you should contact your doctor or pharmacist immediately for advice.

#### **If you forget to take Agenerase**

If you forget to take a dose of Agenerase, take it as soon as you remember and then continue as before. Do not take a double dose to make up for a forgotten dose.

#### **If you stop taking Agenerase**

You **must not** stop taking Agenerase without consulting your doctor.

If you have any further questions on the use of this product, ask your doctor or pharmacist.

### 4. POSSIBLE SIDE EFFECTS

Like all medicines, Agenerase can cause side effects, although not everybody gets them. When treating HIV infection, it is not always possible to tell whether some of the undesirable effects that occur are caused by Agenerase, by other medicines taken at the same time or by the HIV disease. For this reason, it is very important that you inform your doctor about any changes in your health.

**Very common side effects** (these can affect more than 10 in 100 patients treated)

- Headache, feeling tired

- Diarrhoea, feeling sick, vomiting, flatulence
- Skin Rashes (red, raised or itchy) – Occasionally, the skin rash may be severe and you may have to stop taking this medicine.

**Common side effects** (these can affect 1 to 10 in 100 patients treated)

- Increases in triglycerides (a type of blood fat), changes in body shape because of fat redistribution,
- Moodiness, depression, difficulty sleeping, loss of appetite
- Tingling or numbness around the lips and mouth, uncontrolled movements
- Pain, discomfort or excess acid in the stomach, loose stools,
- Increases in enzymes produced by the liver called transaminases, increases of an enzyme produced by the pancreas called amylase

**Uncommon side effects** (these can affect less than 1 in 100 patients treated)

- Increases in blood sugar or cholesterol (a type of blood fat)
- Increases in the blood of a substance called bilirubin
- Swelling of the face, lips and tongue (angioedema)

**Rare side effects** (these can affect 1 in 1,000 patients treated)

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

**Other possible effects**

In patients with haemophilia Type A and B, there have been reports of increased bleeding while taking protease inhibitors. Should this happen to you, seek immediate advice from your doctor.

There have been reports of muscle pain, tenderness or weakness, particularly with antiretroviral therapy including protease inhibitors and nucleoside analogues. On rare occasions, these muscle disorders have been serious (rhabdomyolysis).

Combination antiretroviral therapy may cause changes in body shape due to changes in fat distribution. These may include loss of fat from legs, arms and face, increased fat in the abdomen (belly) and other internal organs, breast enlargement and fatty lumps on the back of the neck ('buffalo hump'). The cause and long-term health effects of these conditions are not known at this time. Combination antiretroviral therapy may also cause raised lactic acid and sugar in the blood, hyperlipaemia (increased fats in the blood) and resistance to insulin.

If any of the side effects gets serious, or you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

**5. HOW TO STORE AGENERASE**

Keep out of the reach and sight of children.

Do not store above 30° C. Keep the container tightly closed, in order to protect from moisture.

Do not use Agenerase after the expiry date which is stated on the carton.

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

## 6. FURTHER INFORMATION

### What Agenerase contains

The active substance is amprenavir  
Each Agenerase capsule contains 50 mg of amprenavir.

The other ingredients within the capsule are d-alpha tocopheryl polyethylene glycol 1000 succinate (TPGS), macrogol 400 (polyethylene glycol 400) and propylene glycol. The capsule shell contains gelatin, glycerol, d-sorbitol and sorbitans solution, titanium dioxide and red printing ink.

### What Agenerase looks like and contents of the pack

Agenerase 50 mg soft capsules are supplied in plastic bottles containing 480 soft capsules. These soft capsules are oblong, opaque, off white to cream in colour and marked with the code GX CC1.

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**This leaflet was last approved on**

## PACKAGE LEAFLET : INFORMATION FOR THE USER

### Agenerase 150 mg soft capsules

Amprenavir

**Read all of this leaflet carefully before you start taking this medicine.**

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them even if their symptoms are the same as yours.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

#### **In this leaflet:**

- 1) What Agenerase is and what it is used for.
- 2) Before you take Agenerase
- 3) How to take Agenerase
- 4) Possible side effects
- 5) How to store Agenerase
- 6) Further information

### **1. WHAT AGENERASE IS AND WHAT IT IS USED FOR**

Agenerase belongs to a group of antiviral medicines called protease inhibitors. These medicines are used for treating human immunodeficiency virus (HIV) infection.

Agenerase is used in protease inhibitor experienced HIV-1 infected adults and children above the age of 4 years. Agenerase is prescribed for use in combination with other antiretroviral medicinal products. Your doctor will normally direct that Agenerase capsules should be taken with low doses of ritonavir to boost its efficacy. The choice of Agenerase will be based on any resistance testing your doctor may have carried out and your treatment history.

The benefit of amprenavir boosted with ritonavir has not been demonstrated in PI naïve patients.

### **2. BEFORE YOU TAKE AGENERASE**

#### **Do not take Agenerase**

- if you are allergic (hypersensitive) to amprenavir or to any of the other ingredients in Agenerase.
- if you have severe liver disease (see 'Take special care with Agenerase').
- you are currently taking any of the following medicines:
  - astemizole or terfenadine (commonly used to treat allergy symptoms – these medicines may be available without prescription)
  - pimozide (used to treat schizophrenia)
  - cisapride (used to relieve certain stomach problems)
  - ergot derivatives (used to treat headaches)
  - rifampicin (used to treat tuberculosis)
  - amiodarone, quinidine (used to treat abnormal heart beat)
  - flecainide and propafenone (heart medicines)
  - triazolam and oral (taken by mouth) midazolam (used to help you sleep and / or relieve anxiety)

- bepridil (used to treat hypertension).
- if you are currently taking any products containing St John's wort (*Hypericum perforatum*) as this may stop Agenerase from working properly (see Taking/using other medicines).

*Tell your doctor if you have any of these listed conditions, or are taking any of the medicines listed above.*

### **Take special care with Agenerase**

You will need to take Agenerase every day. This medicine helps to control your condition, but it is not a cure for HIV infection. You can still continue to develop other infections and other illnesses associated with HIV disease. You should keep in regular contact with your doctor. Do not stop taking your medicine without first talking to your doctor.

If your doctor has recommended that you take Agenerase capsules together with low doses of ritonavir, used to boost its activity, then please make sure that you carefully read the ritonavir Package Leaflet before starting therapy.

At present, there is insufficient information to recommend the use of Agenerase in children less than four years of age. There is also insufficient information to recommend the use of Agenerase capsules boosted with ritonavir in children of 4 to 12 years of age or any patients weighing less than fifty kilograms.

Agenerase may interact with other medicines that you are taking, so it is important that you read the next section "Taking/using other medicines" before taking this medicine.

You should tell your doctor about any medical conditions that you have or have had.

- Please speak with your doctor if you have a history of liver disease. Patients with chronic hepatitis B or C and treated with antiretroviral agents are at increased risk for severe and potentially fatal liver adverse events and may require blood tests for control of liver function.
- The use of Agenerase together with ritonavir has not been studied in patients with liver disease. If your liver disease is severe you must not use this combination.
- Agenerase capsules (without the boosting effect of ritonavir) have been studied in patients with liver impairment. If you suffer from liver disease and your doctor decides to use unboosted Agenerase capsules (that is without ritonavir), the dose of Agenerase may need to be adjusted.
- There have been reports of increased bleeding in patients with haemophilia taking protease inhibitors. The reason for this is not known. You may need additional factor VIII to control bleeding.
- Redistribution, accumulation or loss of body fat may occur in patients receiving combination antiretroviral therapy. Contact your doctor if you notice changes in body fat.
- In some patients with advanced HIV infection (AIDS) and a history of opportunistic infection, signs and symptoms of inflammation from previous infections may occur soon after anti-HIV treatment is started. It is believed that these symptoms are due to an improvement in the body's immune response, enabling the body to fight infections that may have been present with no obvious symptoms. If you notice any symptoms of infection, please inform your doctor immediately.
- If you have any other health concerns, discuss these with your doctor.

### Bone problems

Some patients taking combination antiretroviral therapy may develop a bone disease called osteonecrosis (death of bone tissue caused by loss of blood supply to the bone). The length of combination antiretroviral therapy, corticosteroid use, alcohol consumption, severe immunosuppression, higher body mass index, among others, may be some of the many risk factors for developing this disease. Signs of osteonecrosis are joint stiffness, aches and pains (especially of the hip, knee and shoulder) and difficulty in movement. If you notice any of these symptoms please inform your doctor.

Treatment with Agenerase has not been shown to reduce the risk of passing HIV infection on to others by sexual contact or by blood transfer. You should continue to use appropriate precautions to prevent this.

### **Taking/using other medicines**

Before starting treatment with Agenerase, please tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription. This is **very important**, as taking some types of medicines at the same time as Agenerase can strengthen or weaken the effect of the medicines. This can sometimes lead to serious medical conditions.

There are some medicines that you **must not take** with Agenerase (please see 'Do not take Agenerase' for further information).

Agenerase may interact with certain other medicines. The use of the following medicines, together with Agenerase, should only take place on the basis of medical advice: anaesthetics (e.g. lidocaine), antibiotics (e.g. rifabutin, clarithromycin, dapsone and erythromycin), antifungals (e.g. ketoconazole, itraconazole), antimalarials (e.g. halofantrine), anticonvulsant medicines (e.g. carbamazepine, phenytoin and phenobarbital), calcium channel blockers (e.g. amlodipine, diltiazem, felodipine, isradipine, nifedipine, nifedipine, nimodipine, nisoldipine and verapamil), cholesterol lowering medicines (e.g. atorvastatin, lovastatin and simvastatin), erectile dysfunction medicines (e.g. sildenafil and vardenafil), non-nucleoside reverse transcriptase inhibitors (e.g. delavirdine, efavirenz and nevirapine), opioids (e.g. methadone), hormones like oestrogens and progestogens (e.g. hormonal contraceptives such as the 'pill'), some glucocorticoids (e.g. fluticasone propionate and budesonide), tricyclic antidepressants (i.e. desipramine and nortriptyline), sedative agents (e.g. midazolam administered by injection), paroxetine, and others (e.g. clozapine and loratadine).

If you are taking certain medicines that can cause serious side effects, such as carbamazepine, phenobarbital, phenytoin, lidocaine, cyclosporine, tacrolimus, rapamycin, tricyclic antidepressants and warfarin, at the same time as you are taking Agenerase, your doctor may carry out additional blood tests to minimise any potential safety problems.

If you are taking the contraceptive pill, it is recommended that you use an alternative method (e.g. a condom) to prevent pregnancy while you are taking Agenerase. The concomitant use of Agenerase and contraceptive pill may result in a decrease of the therapeutic effect of Agenerase.

### **Taking Agenerase with food and drink**

Agenerase capsules should be swallowed whole with water or another drink. They can be taken with or without food.

### **Pregnancy and breast-feeding**

Inform your doctor if you are pregnant or planning to become pregnant soon. The safe use of Agenerase in pregnancy has not been established. Ask your doctor or pharmacist before taking any medicine.

Breast feeding your baby is not recommended while you are taking Agenerase. It is recommended that HIV positive women do not breast feed their infants in order to avoid transmission of HIV.

### **Driving and using machines**

No studies on the effects of Agenerase on the ability to drive and use machines have been done. If Agenerase makes you dizzy, do not operate any tools or machines.

### **Important information about ingredients of Agenerase capsules**

These capsules contain glycerol, which can cause adverse effects in high doses. Glycerol can cause headache, stomach upset and diarrhoea.

These capsules also contain sorbitol. If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicinal product

Because Agenerase capsules contain vitamin E, you should not take additional vitamin E supplements.

### 3. HOW TO TAKE AGENERASE

Always take Agenerase exactly as your doctor has told you. You should check with your doctor or pharmacist if you are not sure.

If you need to take an antacid for indigestion, or if you are taking a drug containing an antacid (e.g. didanosine), you are advised to take it more than an hour before or after Agenerase, otherwise the effects of Agenerase may be reduced.

- Swallow Agenerase capsules whole with water or another drink. They can be taken with or without food.
- *Adults and adolescents (of 12 years of age and older) (greater than 50 kg body weight):* the usual dose of Agenerase capsules is 600 mg twice daily with ritonavir 100 mg twice daily, in combination with other antiretroviral medicinal products. If your doctor decides it is inappropriate for you to take ritonavir, you will need to take increased doses of Agenerase (1200 mg twice a day).
- *Children (4 to 12 years) and patients less than 50 kg body weight:* the dose will be calculated according to your weight by your doctor. The usual dose for Agenerase capsules is 20 mg for each kg of body weight, twice a day. You should not take more than 2400 mg per day.

In some cases, your doctor may adapt the dose of Agenerase when other drugs are administered concomitantly with Agenerase.

To derive the full benefit of Agenerase, it is very important that you take the **full** daily dose prescribed by your doctor.

An oral solution of Agenerase is available for children or adults unable to swallow capsules.

#### **If you take more Agenerase than you should**

If you have taken more than the prescribed dose of Agenerase, you should contact your doctor or pharmacist immediately for advice.

#### **If you forget to take Agenerase**

If you forget to take a dose of Agenerase, take it as soon as you remember and then continue as before. Do not take a double dose to make up for forgotten individual doses.

#### **If you stop taking Agenerase**

You **must not** stop taking Agenerase without consulting your doctor.

If you have any further questions on the use of this product, ask your doctor or pharmacist.

### 4. POSSIBLE SIDE EFFECTS

Like all medicines, Agenerase can cause side effects, although not everybody gets them. When treating HIV infection, it is not always possible to tell whether some of the undesirable effects that occur are caused by Agenerase, by other medicines taken at the same time or by the HIV disease. For this reason, it is very important that you inform your doctor about any changes in your health.

**Very common side effects** (these can affect more than 10 in 100 patients treated)

- Headache, feeling tired
- Diarrhoea, feeling sick, vomiting, flatulence
- Skin Rashes (red, raised or itchy) – Occasionally, the skin rash may be severe and you may have to stop taking this medicine.

**Common side effects** (these can affect 1 to 10 in 100 patients treated)

- Increases in triglycerides (a type of blood fat), changes in body shape because of fat redistribution,
- Moodiness, depression, difficulty sleeping, loss of appetite
- Tingling or numbness around the lips and mouth, uncontrolled movements
- Pain, discomfort or excess acid in the stomach, loose stools,
- Increases in enzymes produced by the liver called transaminases, increases of an enzyme produced by the pancreas called amylase

**Uncommon side effects** (these can affect less than 1 in 100 patients treated)

- Increases in blood sugar or cholesterol (a type of blood fat)
- Increases in the blood of a substance called bilirubin
- Swelling of the face, lips and tongue (angioedema)

**Rare side effects** (these can affect 1 in 1,000 patients treated)

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

### **Other possible effects**

In patients with haemophilia Type A and B, there have been reports of increased bleeding while taking protease inhibitors. Should this happen to you, seek immediate advice from your doctor.

There have been reports of muscle pain, tenderness or weakness, particularly with antiretroviral therapy including protease inhibitors and nucleoside analogues. On rare occasions, these muscle disorders have been serious (rhabdomyolysis).

Combination antiretroviral therapy may cause changes in body shape due to changes in fat distribution. These may include loss of fat from legs, arms and face, increased fat in the abdomen (belly) and other internal organs, breast enlargement and fatty lumps on the back of the neck ('buffalo hump'). The cause and long-term health effects of these conditions are not known at this time. Combination antiretroviral therapy may also cause raised lactic acid and sugar in the blood, hyperlipaemia (increased fats in the blood) and resistance to insulin.

If any of the side effects gets serious, or you notice any effects not listed in this leaflet, please tell your doctor or pharmacist.

## **5. HOW TO STORE AGENERASE**

Keep out of the reach and sight of children.

Do not store above 30° C. Keep the container tightly closed, in order to protect from moisture.

Do not use Agenerase after the expiry date which is stated on the carton

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

## 6. FURTHER INFORMATION

### What Agenerase contains

The active substance is amprenavir  
Each Agenerase capsule contains 150 mg of amprenavir.

The other ingredients within the capsule are d-alpha tocopheryl polyethylene glycol 1000 succinate (TPGS), macrogol 400 (polyethylene glycol 400) and propylene glycol. The capsule shell contains gelatin, glycerol, d-sorbitol and sorbitans solution, titanium dioxide and red printing ink.

### What Agenerase looks like and the contents of the pack

Agenerase 150 mg soft capsules are supplied in plastic bottles containing 240 soft capsules. These soft capsules are oblong, opaque, off white to cream in colour and marked with the code GX CC2.

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## PACKAGE LEAFLET : INFORMATION FOR THE USER

### Agenerase 150 mg soft capsules

Amprenavir

**Read all of this leaflet carefully before you start taking this medicine.**

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them even if their symptoms are the same as yours.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

#### **In this leaflet:**

- 1) What Agenerase is and what it is used for
- 2) Before you take Agenerase
- 3) How to take Agenerase
- 4) Possible side effects
- 5) How to store Agenerase
- 6) Further information

### **1. WHAT AGENERASE IS AND WHAT IT IS USED FOR**

Agenerase belongs to a group of antiviral medicines called protease inhibitors. These medicines are used for treating human immunodeficiency virus (HIV) infection.

Agenerase is used in protease inhibitor experienced HIV-1 infected adults and children above the age of 4 years. Agenerase is prescribed for use in combination with other antiretroviral medicinal products. Your doctor will normally direct that Agenerase capsules should be taken with low doses of ritonavir to boost its efficacy. The choice of Agenerase will be based on any resistance testing your doctor may have carried out and your treatment history.

The benefit of amprenavir boosted with ritonavir has not been demonstrated in PI naïve patients.

### **2. BEFORE YOU TAKE AGENERASE**

#### **Do not take Agenerase**

- if you are allergic (hypersensitive) to amprenavir or to any of the other ingredients in Agenerase.
- if you have severe liver disease (see 'Take special care with Agenerase').
- you are currently taking any of the following medicines:
  - astemizole or terfenadine (commonly used to treat allergy symptoms – these medicines may be available without prescription)
  - pimozide (used to treat schizophrenia)
  - cisapride (used to relieve certain stomach problems)
  - ergot derivatives (used to treat headaches)
  - rifampicin (used to treat tuberculosis)
  - amiodarone, quinidine (used to treat abnormal heart beat)
  - flecainide and propafenone (heart medicines)
  - triazolam, oral (taken by mouth) midazolam (used to help you sleep and / or relieve anxiety)

- bepridil (used to treat hypertension).
- if you are currently taking any products containing St John's wort (*Hypericum perforatum*) as this may stop Agenerase from working properly (see Taking/using other medicines).

*Tell your doctor if you have any of these listed conditions, or are taking any of the medicines listed above.*

### **Take special care with Agenerase**

You will need to take Agenerase every day. This medicine helps to control your condition, but it is not a cure for HIV infection. You can still continue to develop other infections and other illnesses associated with HIV disease. You should keep in regular contact with your doctor. Do not stop taking your medicine without first talking to your doctor.

If your doctor has recommended that you take Agenerase capsules together with low doses of ritonavir, used to boost its activity, then please make sure that you carefully read the ritonavir Package Leaflet before starting therapy.

At present, there is insufficient information to recommend the use of Agenerase in children less than four years of age. There is also insufficient information to recommend the use of Agenerase capsules boosted with ritonavir in children of 4 to 12 years of age or any patients weighing less than fifty kilograms.

Agenerase may interact with other medicines that you are taking, so it is important that you read the next section "Taking/using other medicines" before taking this medicine.

You should tell your doctor about any medical conditions that you have or have had.

- Please speak with your doctor if you have a history of liver disease. Patients with chronic hepatitis B or C and treated with antiretroviral agents are at increased risk for severe and potentially fatal liver adverse events and may require blood tests for control of liver function.
- The use of Agenerase together with ritonavir has not been studied in patients with liver disease. If your liver disease is severe you must not use this combination.
- Agenerase capsules (without the boosting effect of ritonavir) have been studied in patients with liver impairment. If you suffer from liver disease and your doctor decides to use unboosted Agenerase capsules (that is without ritonavir), the dose of Agenerase may need to be adjusted.
- There have been reports of increased bleeding in patients with haemophilia taking protease inhibitors. The reason for this is not known. You may need additional factor VIII to control bleeding.
- Redistribution, accumulation or loss of body fat may occur in patients receiving combination antiretroviral therapy. Contact your doctor if you notice changes in body fat.
- In some patients with advanced HIV infection (AIDS) and a history of opportunistic infection, signs and symptoms of inflammation from previous infections may occur soon after anti-HIV treatment is started. It is believed that these symptoms are due to an improvement in the body's immune response, enabling the body to fight infections that may have been present with no obvious symptoms. If you notice any symptoms of infection, please inform your doctor immediately.
- If you have any other health concerns, discuss these with your doctor.

### Bone problems

Some patients taking combination antiretroviral therapy may develop a bone disease called osteonecrosis (death of bone tissue caused by loss of blood supply to the bone). The length of combination antiretroviral therapy, corticosteroid use, alcohol consumption, severe immunosuppression, higher body mass index, among others, may be some of the many risk factors for developing this disease. Signs of osteonecrosis are joint stiffness, aches and pains (especially of the hip, knee and shoulder) and difficulty in movement. If you notice any of these symptoms please inform your doctor.

Treatment with Agenerase has not been shown to reduce the risk of passing HIV infection on to others by sexual contact or by blood transfer. You should continue to use appropriate precautions to prevent this.

### **Taking/using other medicines**

Before starting treatment with Agenerase, please tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription. This is **very important**, as taking some types of medicines at the same time as Agenerase can strengthen or weaken the effect of the medicines. This can sometimes lead to serious medical conditions.

There are some medicines that you **must not take** with Agenerase (please see 'Do not take Agenerase' for further information).

Agenerase may interact with certain other medicines. The use of the following medicines, together with Agenerase, should only take place on the basis of medical advice: anaesthetics (e.g. lidocaine), antibiotics (e.g. rifabutin, clarithromycin, dapson and erythromycin), antifungals (e.g. ketoconazole, itraconazole), antimalarials (e.g. halofantrine), anticonvulsant medicines (e.g. carbamazepine, phenytoin and phenobarbital), calcium channel blockers (e.g. amlodipine, diltiazem, felodipine, isradipine, nifedipine, nimodipine, nisoldipine and verapamil), cholesterol lowering medicines (e.g. atorvastatin, lovastatin and simvastatin), erectile dysfunction medicines (e.g. sildenafil and vardenafil), non-nucleoside reverse transcriptase inhibitors (e.g. delavirdine, efavirenz and nevirapine), opioids (e.g. methadone), hormones like oestrogens and progestogens (e.g. hormonal contraceptives such as the 'pill'), some glucocorticoids (e.g. fluticasone propionate and budesonide), tricyclic antidepressants (i.e. desipramine and nortriptyline), sedative agents (e.g. midazolam administered by injection), paroxetine, and others (e.g. clozapine and loratadine).

If you are taking certain medicines that can cause serious side effects, such as carbamazepine, phenobarbital, phenytoin, lidocaine, cyclosporine, tacrolimus, rapamycin, tricyclic antidepressants and warfarin, at the same time as you are taking Agenerase, your doctor may carry out additional blood tests to minimise any potential safety problems.

If you are taking the contraceptive pill, it is recommended that you use an alternative method (e.g. a condom) to prevent pregnancy while you are taking Agenerase. The concomitant use of Agenerase and contraceptive pill may result in a decrease of the therapeutic effect of Agenerase.

### **Taking Agenerase with food and drink**

Agenerase capsules should be swallowed whole with water or another drink. They can be taken with or without food.

### **Pregnancy and breast-feeding**

Inform your doctor if you are pregnant or planning to become pregnant soon. The safe use of Agenerase in pregnancy has not been established. Ask your doctor or pharmacist before taking any medicine.

Breast feeding your baby is not recommended while you are taking Agenerase. It is recommended that HIV positive women do not breast feed their infants in order to avoid transmission of HIV.

### **Driving and using machines**

No studies on the effects of Agenerase on the ability to drive and use machines have been done. If Agenerase makes you dizzy, do not operate any tools or machines.

### **Important information about ingredients of Agenerase capsules**

These capsules contain glycerol, which can cause adverse effects in high doses. Glycerol can cause headache, stomach upset and diarrhoea.

These capsules also contain sorbitol. If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicinal product

Because Agenerase capsules contain vitamin E, you should not take additional vitamin E supplements.

### 3. HOW TO TAKE AGENERASE

Always take Agenerase exactly as your doctor has told you. You should check with your doctor or pharmacist if you are not sure.

If you need to take an antacid for indigestion, or if you are taking a drug containing an antacid (e.g. didanosine), you are advised to take it more than an hour before or after Agenerase, otherwise the effects of Agenerase may be reduced.

- Swallow Agenerase capsules whole with water or another drink. They can be taken with or without food.
- *Adults and adolescents (of 12 years of age and older), (greater than 50 kg body weight):* the usual dose of Agenerase capsules is 600 mg twice daily with ritonavir 100 mg twice daily, in combination with other antiretroviral medicinal products. If your doctor decides it is inappropriate for you to take ritonavir, you will need to take increased doses of Agenerase (1200 mg twice a day).
- *Children (4 to 12 years) and patients less than 50 kg body weight:* the dose will be calculated according to your weight by your doctor. The usual dose for Agenerase capsules is 20 mg for each kg of body weight, twice a day.. You should not take more than 2400 mg per day.

In some cases, your doctor may adapt the dose of Agenerase when other drugs are administered concomitantly with Agenerase.

To derive the full benefit of Agenerase, it is very important that you take the **full** daily dose prescribed by your doctor.

An oral solution of Agenerase is available for children or adults unable to swallow capsules.

#### **If you take more Agenerase than you should**

If you have taken more than the prescribed dose of Agenerase, you should contact your doctor or pharmacist immediately for advice.

#### **If you forget to take Agenerase**

If you forget to take a dose of Agenerase, take it as soon as you remember and then continue as before. Do not take a double dose to make up for forgotten individual doses.

#### **If you stop taking Agenerase**

You **must not** stop taking Agenerase without consulting your doctor.

If you have any further questions on the use of this product, ask your doctor or pharmacist.

### 4. POSSIBLE SIDE EFFECTS

Like all medicines, Agenerase can cause side effects, although not everybody gets them. When treating HIV infection, it is not always possible to tell whether some of the undesirable effects that occur are caused by Agenerase, by other medicines taken at the same time or by the HIV disease. For this reason, it is very important that you inform your doctor about any changes in your health.

**Very common side effects** (these can affect more than 10 in 100 patients treated)

- Headache, feeling tired
- Diarrhoea, feeling sick, vomiting, flatulence
- Skin Rashes (red, raised or itchy) – Occasionally, the skin rash may be severe and you may have to stop taking this medicine.

**Common side effects** (these can affect 1 to 10 in 100 patients treated)

- Increases in triglycerides (a type of blood fat), changes in body shape because of fat redistribution,
- Moodiness, depression, difficulty sleeping, loss of appetite
- Tingling or numbness around the lips and mouth, uncontrolled movements
- Pain, discomfort or excess acid in the stomach, loose stools,
- Increases in enzymes produced by the liver called transaminases, increases of an enzyme produced by the pancreas called amylase

**Uncommon side effects** (these can affect less than 1 in 100 patients treated)

- Increases in blood sugar or cholesterol (a type of blood fat)
- Increases in the blood of a substance called bilirubin
- Swelling of the face, lips and tongue (angioedema)

**Rare side effects** (these can affect 1 in 1,000 patients treated)

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

#### **Other possible effects**

In patients with haemophilia Type A and B, there have been reports of increased bleeding while taking protease inhibitors. Should this happen to you, seek immediate advice from your doctor.

There have been reports of muscle pain, tenderness or weakness, particularly with antiretroviral therapy including protease inhibitors and nucleoside analogues. On rare occasions, these muscle disorders have been serious (rhabdomyolysis).

Combination antiretroviral therapy may cause changes in body shape due to changes in fat distribution. These may include loss of fat from legs, arms and face, increased fat in the abdomen (belly) and other internal organs, breast enlargement and fatty lumps on the back of the neck ('buffalo hump'). The cause and long-term health effects of these conditions are not known at this time. Combination antiretroviral therapy may also cause raised lactic acid and sugar in the blood, hyperlipaemia (increased fats in the blood) and resistance to insulin.

If any of the side effects gets serious, or you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

#### **5. STORING AGENERASE**

Keep out of the reach and sight of children.

Do not store above 30° C. Keep the container tightly closed, in order to protect from moisture.

Do not take Agenerase after the expiry date which is stated on the carton.

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

## 6. FURTHER INFORMATION

### What Agenerase contains

The active substance is amprenavir  
Each Agenerase capsule contains 150 mg of amprenavir.

The other ingredients within the capsule are d-alpha tocopheryl polyethylene glycol 1000 succinate (TPGS), macrogol 400 (polyethylene glycol 400) and propylene glycol. The capsule shell contains gelatin, glycerol, d-sorbitol and sorbitans solution, titanium dioxide and red printing ink.

### What Agenerase looks like and contents of the pack

Agenerase 150 mg soft capsules are supplied in a pack with two plastic bottles each containing 240 soft capsules. These soft capsules are oblong, opaque, off white to cream in colour and marked with the code GX CC2.

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## PACKAGE LEAFLET : INFORMATION FOR THE USER

### Agenerase 15 mg/ml oral solution

Amprenavir

**Read all of this leaflet carefully before you start taking this medicine.**

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them even if their symptoms are the same as yours.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

#### **In this leaflet:**

- 1) What Agenerase is and what it is used for
- 2) Before you take Agenerase
- 3) How to take Agenerase
- 4) Possible side effects
- 5) How to store Agenerase
- 6) Further information

### **1. WHAT AGENERASE IS AND WHAT IT IS USED FOR**

Agenerase belongs to a group of antiviral medicines called protease inhibitors. These medicines are used for treating human immunodeficiency virus (HIV) infection.

Agenerase is used in protease inhibitor experienced HIV-1 infected adults and children above the age of 4 years. Agenerase is prescribed for use in combination with other antiretroviral medicinal products. The choice of Agenerase will be based on any resistance testing your doctor may have carried out and your treatment history.

The benefit of Agenerase oral solution boosted with ritonavir has not been demonstrated either in protease inhibitor naïve patients or protease inhibitor experienced patients.

You should take Agenerase capsules as soon as you are able to swallow them.

### **2. BEFORE YOU TAKE AGENERASE**

#### **Do not take Agenerase**

- if you are allergic (hypersensitive) to amprenavir or to any of the other ingredients in Agenerase.
- you are currently taking any of the following medicines:
  - astemizole or terfenadine (commonly used to treat allergy symptoms – these medicines may be available without prescription)
  - pimozide (used to treat schizophrenia)
  - cisapride (used to relieve certain stomach problems)
  - ergot derivatives (used to treat headaches)
  - rifampicin (used to treat tuberculosis)
  - amiodarone, quinidine (used to treat abnormal heart beat)
  - triazolam and oral (taken by mouth) midazolam (used to help you sleep and / or relieve anxiety)
  - bepridil (used to treat hypertension).

- if you are currently taking any products containing St John's wort (*Hypericum perforatum*) as this may stop Agenerase from working properly (see Taking/using other medicines).

Because of the potential risk of toxicity from the large amount of the excipient propylene glycol, Agenerase oral solution is contraindicated in infants and children below the age of 4 years, pregnant women, patients with hepatic impairment or failure, patients with renal failure, and patients treated with disulfiram or metronidazole or preparations that contain alcohol (e.g. ritonavir oral solution) or additional propylene glycol (see also Take special care with Agenerase).

*Tell your doctor if you have any of these listed conditions, or are taking any of the medicines listed above.*

### **Take special care with Agenerase**

You will need to take Agenerase every day. This medicine helps to control your condition, but it is not a cure for HIV infection. You can still continue to develop other infections and other illnesses associated with HIV disease. You should keep in regular contact with your doctor. Do not stop taking your medicine without first talking to your doctor.

No dosing recommendations can be made regarding the use of low dose ritonavir (normally used as an activity booster with Agenerase capsules) together with Agenerase oral solution. Therefore this combination must be avoided.

Agenerase may interact with other medicines that you are taking, so it is important that you read the next section "Taking/using other medicines" before taking this medicine.

Agenerase oral solution should be used with caution if you have limited liver enzyme activity, kidney impairment or a genetically lower ability to metabolise alcohol (e.g. Asian origin) due to adverse reactions that may be related to the propylene glycol in the solution.

For the same reason you must not take disulfiram or other medicines that reduce alcohol metabolism (e.g. metronidazole) or preparations that contain alcohol (e.g. ritonavir oral solution) or additional propylene glycol while you are taking Agenerase oral solution (see also Do not take Agenerase).

Your doctor may monitor you for adverse reactions potentially related to the propylene glycol content of the Agenerase oral solution, especially when you have renal or hepatic disease. It might also be necessary to reconsider the treatment with Agenerase oral solution.

You should stop taking Agenerase oral solution **as soon** as you are able to swallow the Agenerase capsules.

You should tell your doctor about any medical conditions that you have or have had.

- If you have had liver disease discuss this with your doctor.
- Agenerase oral solution should not be used if you suffer from any liver disease.
- Please speak with your doctor if you have a history of liver disease. Patients with chronic hepatitis B or C and treated with antiretroviral agents are at increased risk for severe and potentially fatal liver adverse events and may require blood tests for control of liver function.
- There have been reports of increased bleeding in patients with haemophilia taking protease inhibitors. The reason for this is not known. You may need additional factor VIII to control bleeding.
- Redistribution, accumulation or loss of body fat may occur in patients receiving combination antiretroviral therapy. Contact your doctor if you notice changes in body fat.

- In some patients with advanced HIV infection (AIDS) and a history of opportunistic infection, signs and symptoms of inflammation from previous infections may occur soon after anti-HIV treatment is started. It is believed that these symptoms are due to an improvement in the body's immune response, enabling the body to fight infections that may have been present with no obvious symptoms. If you notice any symptoms of infection, please inform your doctor immediately.
- If you have any other health concerns, discuss these with your doctor.

### Bone problems

Some patients taking combination antiretroviral therapy may develop a bone disease called osteonecrosis (death of bone tissue caused by loss of blood supply to the bone). The length of combination antiretroviral therapy, corticosteroid use, alcohol consumption, severe immunosuppression, higher body mass index, among others, may be some of the many risk factors for developing this disease. Signs of osteonecrosis are joint stiffness, aches and pains (especially of the hip, knee and shoulder) and difficulty in movement. If you notice any of these symptoms please inform your doctor.

Treatment with Agenerase has not been shown to reduce the risk of passing HIV infection on to others by sexual contact or by blood transfer. You should continue to use appropriate precautions to prevent this.

### **Taking/using other medicines**

Before starting treatment with Agenerase, please inform your doctor or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription. This is **very important**, as taking some types of medicines at the same time as Agenerase can strengthen or weaken the effect of the medicines. This can sometimes lead to serious medical conditions.

There are some medicines that you **must not take** with Agenerase (please see 'Do not take Agenerase' for further information).

Agenerase may interact with certain other medicines. The use of the following medicines, together with Agenerase, should only take place on the basis of medical advice: anaesthetics (e.g. lidocaine), antibiotics (e.g. rifabutin, clarithromycin, dapsone and erythromycin), antifungals (e.g. ketoconazole, itraconazole), antimalarials (e.g. halofantrine), anticonvulsant medicines (e.g. carbamazepine, phenytoin and phenobarbital), calcium channel blockers (e.g. amlodipine, diltiazem, felodipine, isradipine, nifedipine, nimodipine, nisoldipine and verapamil), cholesterol lowering medicines (e.g. atorvastatin, lovastatin and simvastatin), erectile dysfunction medicines (e.g. sildenafil and vardenafil), non-nucleoside reverse transcriptase inhibitors (e.g. delavirdine, efavirenz and nevirapine), opioids (e.g. methadone), hormones like oestrogens and progestogens (e.g. hormonal contraceptives such as the 'pill'), some glucocorticoids (e.g. fluticasone propionate and budesonide), tricyclic antidepressants (i.e. desipramine and nortriptyline), sedative agents (e.g. midazolam administered by injection), paroxetine, and others (e.g. clozapine and loratadine).

If you are taking certain medicines that can cause serious side effects, such as carbamazepine, phenobarbital, phenytoin, lidocaine, cyclosporine, tacrolimus, rapamycin, tricyclic antidepressants and warfarin, at the same time as you are taking Agenerase, your doctor may carry out additional blood tests to minimise any potential safety problems.

Due to the propylene glycol content of the oral solution you should not take disulfiram or other medicines that reduce alcohol metabolism (e.g. metronidazole) or preparations that contain alcohol (e.g. ritonavir oral solution) or additional propylene glycol while you are taking Agenerase oral solution (see Do not take Agenerase ).

If you are taking the contraceptive pill, it is recommended that you use an alternative method (e.g. a condom) to prevent pregnancy, while you are taking Agenerase. The concomitant use of Agenerase and contraceptive pill may result in a decrease of the therapeutic effect of Agenerase.

### **Taking Agenerase with food and drink**

Agenerase oral solution can be taken with or without food.

### **Pregnancy and breast-feeding**

Inform your doctor if you are pregnant or planning to become pregnant soon. The safe use of Agenerase in pregnancy has not been established. Ask your doctor or pharmacist before taking any medicine.

Breast feeding your baby is not recommended while you are taking Agenerase. It is recommended that HIV positive women do not breast feed their infants in order to avoid transmission of HIV.

### **Driving and using machines**

No studies on the effects of Agenerase on the ability to drive and use machines have been done. If Agenerase makes you dizzy, do not operate any tools or machines.

### **Important information about ingredients of Agenerase oral solution**

The oral solution contains propylene glycol, which can cause adverse effects in high doses. Propylene glycol can cause a range of adverse effects including seizures, stupor, rapid heart beat and the breakdown of red blood cells (see also Do not take Agenerase, Take special care with Agenerase).

This medicinal product contains 4 mg sodium per ml. To be taken into consideration by patients on a controlled sodium diet,

This medicinal product also contains 1 mg potassium per ml. To be taken into consideration by patients with reduced kidney function or patients on a controlled potassium diet,

Because Agenerase oral solution contains vitamin E, you should not take additional vitamin E supplements.

## **3. HOW TO TAKE AGENERASE**

Always take Agenerase exactly as your doctor has told you. You should check with your doctor or pharmacist if you are not sure. Agenerase can be taken with or without food.

If you need to take an antacid for indigestion, or if you are taking a drug containing an antacid (e.g. didanosine), you are advised to take it more than an hour before or after Agenerase, otherwise the effects of Agenerase may be reduced.

- *Patients of 4 years of age and older unable to swallow capsules:* The dose will be calculated according to your weight by your doctor. The usual dose of Agenerase oral solution is 17 mg (1.1 ml) for each kg of body weight three times a day. You should not take more than 2800 mg per day.

In some cases, your doctor may adapt the dose of Agenerase when other drugs are administered concomitantly with Agenerase.

To derive the full benefit of Agenerase, it is very important that you take the **full** daily dose prescribed by your doctor.

A 20 ml measuring cup is provided, to help you measure out the correct amount of oral solution for each dose.

### **If you take more Agenerase than you should**

If you have taken more than the prescribed dose of Agenerase, you should contact your doctor or pharmacist immediately for advice.

**If you forget to take Agenerase**

If you forget to take a dose of Agenerase, take it as soon as you remember and then continue as before. Do not take a double dose to make up for forgotten individual doses.

**If you stop taking Agenerase**

You **must not** stop taking Agenerase without consulting your doctor.

If you have any further questions on the use of this product, ask your doctor or pharmacist.

**4. POSSIBLE SIDE EFFECTS**

Like all medicines, Agenerase can cause side effects, although not everybody gets them. When treating HIV infection, it is not always possible to tell whether some of the undesirable effects that occur are caused by Agenerase, by other medicines taken at the same time or by the HIV disease. For this reason, it is very important that you inform your doctor about any changes in your health.

**Very common side effects** (these can affect more than 10 in 100 patients treated)

- Headache, feeling tired
- Diarrhoea, feeling sick, vomiting, flatulence
- Skin Rashes (red, raised or itchy) – Occasionally, the skin rash may be severe and you may have to stop taking this medicine.

**Common side effects** (these can affect 1 to 10 in 100 patients treated)

- Increases in triglycerides (a type of blood fat), changes in body shape because of fat redistribution,
- Moodiness, depression, difficulty sleeping, loss of appetite
- Tingling or numbness around the lips and mouth, uncontrolled movements
- Pain, discomfort or excess acid in the stomach, loose stools,
- Increases in enzymes produced by the liver called transaminases, increases of an enzyme produced by the pancreas called amylase

**Uncommon side effects** (these can affect less than 1 in 100 patients treated)

- Increases in blood sugar or cholesterol (a type of blood fat)
- Increases in the blood of a substance called bilirubin
- Swelling of the face, lips and tongue (angioedema)

**Rare side effects** (these can affect 1 in 1,000 patients treated)

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

**Other possible effects**

In patients with haemophilia Type A and B, there have been reports of increased bleeding while taking protease inhibitors. Should this happen to you, seek immediate advice from your doctor.

There have been reports of muscle pain, tenderness or weakness, particularly with antiretroviral therapy including protease inhibitors and nucleoside analogues. On rare occasions, these muscle disorders have been serious (rhabdomyolysis).

Combination antiretroviral therapy may cause changes in body shape due to changes in fat distribution. These may include loss of fat from legs, arms and face, increased fat in the abdomen (belly) and other internal organs, breast enlargement and fatty lumps on the back of the neck ('buffalo

hump'). The cause and long-term health effects of these conditions are not known at this time. Combination antiretroviral therapy may also cause raised lactic acid and sugar in the blood, hyperlipaemia (increased fats in the blood) and resistance to insulin.

If any of the side effects gets serious, or you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

## 5. HOW TO STORE AGENERASE

Keep out of the reach and sight of children.

Do not store above 25°C.

Do not use Agenerase after the expiry date which is stated on the bottle and carton. Discard Agenerase oral solution 15 days after first opening the bottle.

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

## 6. FURTHER INFORMATION

### What Agenerase contains

The active substance is amprenavir

The Agenerase oral solution contains 15 mg/ml of amprenavir.

The other ingredients are propylene glycol, macrogol 400 (polyethylene glycol 400), d-alpha tocopheryl polyethylene glycol 1000 succinate (TPGS), acesulfame potassium, saccharin sodium, sodium chloride, artificial grape bubblegum flavour, natural peppermint flavour, menthol, citric acid anhydrous, sodium citrate dihydrate, purified water.

### What Agenerase looks like and contents of the pack

Agenerase oral solution is supplied in plastic bottles containing 240 ml of oral solution. It is a clear, pale yellow to yellow solution with grape, bubblegum and peppermint flavouring.

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