

ANNEX I
SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Agenerase 50 mg soft capsules

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains 50 mg of amprenavir.

For excipients, see 6.1.

3. PHARMACEUTICAL FORM

Soft capsule.

The soft capsules are oblong, opaque, off-white to cream coloured, printed with 'GX CC1'.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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

In protease inhibitor naive patients, Agenerase is less effective than indinavir.

In heavily pretreated protease inhibitor experienced patients, the use of Agenerase has not been sufficiently studied.

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 5.2 Pharmacokinetic properties).

Adults and adolescents of 12 years of age and older (greater than 50 kg body weight): the recommended dose of Agenerase capsules is 1200 mg twice daily in combination with other antiretroviral agents.

If Agenerase capsules are used in combination with ritonavir in adults, reduced doses of amprenavir (600 mg twice daily) and ritonavir (100-200 mg twice daily) are recommended. When efavirenz is included in the treatment regimen, due consideration should be given to pharmacokinetic interactions

and the doses adjusted accordingly (see 4.5 Interaction with other medicinal products and other forms of interaction).

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.

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

Children less than 4 years of age: Agenerase is not recommended in children less than 4 years of age (see 5.3 Preclinical safety data).

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

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

Hepatic impairment: the principal route of metabolism of amprenavir is via the liver. Agenerase should be used with caution in patients with hepatic impairment. Clinical efficacy and safety have not been determined in this patient group. Based on pharmacokinetic data, the dose of Agenerase 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 5.2 Pharmacokinetic properties).

4.3 Contraindications

Known hypersensitivity to amprenavir or any ingredient of Agenerase capsules.

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. terfenadine, astemizole, cisapride, pimozide), prolonged sedation or respiratory depression (e.g. triazolam, diazepam, flurazepam, midazolam), or other events (e.g. ergot derivatives).

Agenerase must not be given with rifampicin because rifampicin reduces trough plasma concentrations of amprenavir by approximately 92 % (see 4.5 Interaction with other medicinal products and other forms of interaction).

Patients on amprenavir should not use products containing St John's wort (*Hypericum perforatum*) because co-administration may be expected to reduce plasma concentrations of amprenavir. This may result in loss of therapeutic effect and development of resistance (see 4.5 Interaction with other medicinal products and other forms of interaction).

4.4 Special warnings and special 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 5.1 Pharmacodynamic properties).

The principal route of metabolism of amprenavir is via the liver. Agenerase should be used with caution in patients with hepatic impairment. The dose of Agenerase should be reduced in adult patients with moderate or severe hepatic impairment (see 4.2 Posology and method of administration).

Amprenavir, like other HIV protease inhibitors, is an inhibitor of the cytochrome CYP3A4 enzyme. Agenerase should not be administered concurrently with medications with narrow therapeutic windows which are substrates of CYP3A4 (see 4.3 Contraindications). Combination with other agents may result in serious and/or life-threatening interactions, therefore caution is advised whenever Agenerase is co-administered with medicinal products that are inducers, inhibitors or substrates of CYP3A4 (see 4.5 Interaction with other medicinal products and other forms of interaction).

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

Because of the potential for metabolic interactions with amprenavir, the efficacy of hormonal contraceptives may be reduced. Therefore, additional reliable barrier methods of contraception are recommended for women of childbearing potential (see 4.5 Interaction with other medicinal products and other forms of interaction).

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

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.

Rashes/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 4.8 Undesirable effects).

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.

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

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.

4.5 Interaction with other medicinal products and other forms of interaction

Amprenavir 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 amprenavir. Similarly, amprenavir might also modify the pharmacokinetics of other medicinal products that share this metabolic pathway.

Terfenadine, cisapride, pimozide, triazolam, diazepam, midazolam, flurazepam, ergotamine, dihydroergotamine and astemizole are contraindicated in patients receiving Agenerase. Concurrent administration can lead to competitive inhibition of the metabolism of these products and thus result in serious, life-threatening events (see 4.3 Contraindications).

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.

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, C_{\min} and C_{\max} of amprenavir were increased by 131 %, 484 % and 33 %, respectively, when ritonavir (200 mg twice daily) was given in combination with amprenavir (1200 mg twice daily) in adults. When given in combination in adults, reduced doses of both medicinal products should be used (see 4.2 Posology and method of administration) (see also efavirenz below). In clinical practice, doses of amprenavir 600 mg twice daily and ritonavir 100 mg twice daily are being used; the evaluation of the safety and efficacy of these regimens is ongoing.

No dose recommendation can be given for the use of amprenavir in combination with other protease inhibitors in children and patients with renal impairment. Such combinations should be avoided in patients with hepatic impairment.

- ***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. If efavirenz is given to adults in combination with amprenavir and

ritonavir, reduced doses of both ritonavir and amprenavir should be used (see ritonavir above). 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 and patients with renal impairment. Such combinations should be avoided in patients with hepatic impairment.

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

Delavirdine: delavirdine may increase the serum concentrations of amprenavir.

Antibiotics/antifungals

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

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: 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. No dose adjustment for either medicinal product is necessary when ketoconazole is administered in combination with amprenavir.

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.

Benzodiazepines: the serum concentrations of alprazolam, triazolam, midazolam, clorazepam, diazepam and flurazepam may be increased by amprenavir resulting in enhanced sedation (see 4.3 Contraindications).

Calcium-channel blockers: amprenavir may lead to increased serum concentrations of diltiazem, nifedipine, nifedipine or nimodipine, 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 sildenafil to patients receiving Agenerase. Co-administration of Agenerase with sildenafil may substantially increase sildenafil plasma concentrations and may result in sildenafil-associated adverse events.

Lipid-lowering drugs: amprenavir may increase the serum concentrations of atorvastatin, cerivastatin, fluvastatin, lovastatin, pravastatin and simvastatin, potentially increasing their toxicity.

Methadone and opiate derivatives: until results from an interaction study with methadone are available, subjects undergoing detoxification treatments should be monitored carefully as the concurrent administration of amprenavir and opiate derivatives may result in a significant interaction.

Steroids: oestrogens, progestogens and some glucocorticoids can show interactions with amprenavir. However, the information currently available is not sufficient for determining the nature of the interaction. The effect of hormonal contraceptives can be reduced as a result of the potential for interactions with amprenavir. Since the effects of hormonal contraceptives can be reduced, women of childbearing age are advised to use other, or additional, reliable contraceptive methods.

St John's wort: patients on amprenavir should not use concomitantly products containing St John's wort (*Hypericum perforatum*) since it may be expected to result in reduced plasma concentrations of amprenavir. This effect may be due to an induction of CYP3A4 and may result in the loss of therapeutic effect and development of resistance (see 4.3 Contraindications).

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

4.6 Pregnancy and lactation

Pregnancy: the safe use of amprenavir in human pregnancy has not been established. Placental transfer of amprenavir and/or its related metabolites has been shown to occur in animals (see 5.3 Preclinical safety data).

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.

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.

The most frequent clinical adverse events related to study drugs, of at least moderate intensity (Grade 2 or more), reported in two large clinical studies in adults are summarised below. All events reported in at least 1 % of subjects treated with amprenavir are included.

Adverse Events by body system	PROAB3001		PROAB3006	
	Antiretroviral Naïve Patients		NRTI-Experienced Patients	
	Agenerase / Lamivudine / Zidovudine (n = 113)	Lamivudine / Zidovudine (n = 109)	Agenerase/ NRTIs (n = 245)	Indinavir / NRTIs (n = 241)
Digestive				
Nausea	31%	17%	10%	5%
Vomiting	11%	4%	3%	4%
Gaseous symptoms	10%	14%	3%	2%
Diarrhoea	9%	6%	19%	5%
Abdominal discomfort	4%	< 1%	< 1%	1%
Abdominal pain	4%	< 1%	4%	5%
Dyspeptic symptoms	3%	< 1%	< 1%	1%
Loose stools	< 1%	< 1%	1%	< 1%
Skin				
Rash	19%	< 1%	9%	< 1%
Neurological				
Headache	11%	12%	4%	2%
Sleep disorders	2%	2%	< 1%	< 1%
Tremors	2%	0%	-	-
Oral/perioral paraesthesia	< 1%	< 1%	2%	0%
Psychiatry				
Mood disorders	4%	0%	-	-
Depressive disorders	3%	0%	< 1%	0%
Non site specific				
Fatigue	11%	8%	2%	2%
Anorexia	2%	3%	< 1%	0%

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, including Stevens-Johnson syndrome, have rarely (< 1 %) occurred in patients treated with amprenavir (see 4.4. Special warnings and special precautions for use).

Symptoms of abnormal fat redistribution were infrequent 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 ($p < 0.001$).

Laboratory abnormalities occurred infrequently with amprenavir, and primarily in patients with abnormal values at baseline. In phase III trials, in combination with various NRTIs, the most frequent treatment-emergent laboratory abnormalities (Grade 2 or more) were elevated transaminases (5 %), hypertriglyceridaemia (4 %), elevated amylase (2.5 %),

hyperbilirubinemia (< 1 %) and hyperglycaemia (< 1 %); almost all subjects with abnormal liver function tests were co-infected with Hepatitis B or C virus.

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

4.9 Overdose

There are limited reports of overdose with Agenerase. If overdose occurs, the patient should be monitored for evidence of toxicity (see 4.8 Undesirable effects) 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: JO5A E05

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

Serial passage experiments have demonstrated the protease mutation I50V to be key to the development of amprenavir resistance *in vitro*, with the triple variant, I50V+M46I/L+I47V, resulting in a greater than 10-fold increase in IC₅₀ to amprenavir. This triple mutation resistance profile has not been observed with other protease inhibitors either from *in vitro* studies or in clinical settings. *In vitro* variants resistant to amprenavir remained sensitive to saquinavir, indinavir and nelfinavir, but showed three to five-fold reduced susceptibility to ritonavir. The triple mutant, I50V+M46I/L+I47V, was unstable during *in vitro* passage in the presence of saquinavir, with loss of the I47V mutation, and the development of resistance to saquinavir resulted in resensitisation to amprenavir. Passage of the triple mutant in either indinavir, nelfinavir or ritonavir resulted in additional protease mutations being selected, leading to dual resistance. Mutation I84V, observed transiently *in vitro* has rarely been selected during amprenavir therapy.

The resistance profile seen with amprenavir in clinical practice is different from that observed with other protease inhibitors. Consistent with *in vitro* experiments, the development of amprenavir resistance during therapy, is in the majority cases, associated with the mutation I50V. However, three alternative mechanisms have also been observed to result in the development of amprenavir resistance in the clinic, and involve either mutations I54L/M or V32I+I47V or, rarely, I84V. Each of the four genetic patterns produces viruses with reduced susceptibility to amprenavir, some cross-resistance to ritonavir, but susceptibility to indinavir, nelfinavir and saquinavir is retained.

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

Protease mutations acquired on amprenavir-containing therapy which have been demonstrated to result in reduced phenotypic susceptibility to amprenavir:

I50V or I54L/M or I84V or V32I with I47V
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The pre-existence of resistance to other components of a first-line PI-containing regimen is significantly associated with subsequent development of protease mutations, highlighting the importance of considering all components of a treatment regimen when change is indicated.

Many *in vitro* PI-resistant variants, and 322 of 433 (74 %) clinical PI-resistant variants with multiple protease inhibitor resistance mutations were susceptible to amprenavir. The principal protease mutation associated with cross-resistance to amprenavir following treatment failure with other protease inhibitors was I84V, particularly when mutations L10I/V/F were also present.

In multiple protease inhibitor-experienced subjects, the likelihood of a successful virological response is increased with an increasing number of active drugs (i.e. agents to which the virus is susceptible) in the rescue regimen. The presence at the time of therapy change in PI-experienced subjects of multiple key mutations associated with PI-resistance, or the development of such mutations during PI therapy, is significantly associated with treatment outcome. The total number of all types of protease mutations present at the time of therapy change was also correlated with outcome in PI-experienced populations. The presence of 3 or more mutations from M46I/L, I54L/M/V, V82A/F/I/T, I84V and L90M in a population of multiple PI-experienced subjects was significantly related to amprenavir treatment failure.

The following table summarises the mutations, identified in clinical isolates from highly PI-experienced patients, associated with an increased risk of treatment failure of amprenavir-containing regimens.

Protease mutations in virus from PI-experienced patients associated with reduced virological response to subsequent amprenavir containing regimens:

COMBINATION OF AT LEAST THREE OF:

M46I/L or I54L/M/V or V82A/F/I/T or I84V or L90M.

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.

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

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

Clinical experience:

Agenerase in combination with other antiretroviral agents including nucleoside analogues, non-nucleoside analogues and protease inhibitors, has been shown to be effective in the treatment of HIV infection in adults and children aged 4 years or more.

In a double-blind study in antiretroviral naive HIV-infected adults (n = 232), amprenavir in combination with zidovudine and lamivudine was significantly superior to zidovudine and lamivudine. In an intent-to-treat analysis (any missing value or premature discontinuation considered as failure i.e. ≥ 400 copies/ml), the proportion of subjects with plasma HIV-1 RNA < 400 copies/ml through week 48 was 41 % in the amprenavir/lamivudine/zidovudine group and 3 % in the lamivudine/zidovudine group ($p < 0.001$).

In an open-label randomised study in NRTI-experienced PI-naive adults (n = 504), in combination with various NRTIs amprenavir was found to be less effective than indinavir: the proportion of subjects with plasma HIV-1 RNA < 400 copies/ml at week 48 was 30 % in the amprenavir arm and

46 % in the indinavir arm in the intent-to-treat analysis (any missing value or premature discontinuation considered as failure, i.e. ≥ 400 copies/ml).

Preliminary results from two paediatric studies with amprenavir oral solution and/or capsules in 268 heavily pre-treated children aged 2 to 18 years indicate that amprenavir is an effective antiretroviral agent in children. Decreases in median HIV-1 RNA greater than $1 \log_{10}$ copies/ml were observed in protease inhibitor naive subjects and improvements in immune category (CD4 %) were reported.

Data from several clinical studies indicate that amprenavir-containing regimen may be useful for the treatment of other PI-experienced subjects. Correlation analyses of viral resistance profiles with treatment outcome support the concept of utilising resistance testing to select appropriate treatment regimen. Important pharmacokinetic drug / drug interactions should also be taken into account when selecting agents for use in combination with amprenavir (see 4.5 Interaction with other medicinal products and other forms of interaction). Non-controlled data suggest that amprenavir-experienced subjects might be successfully treated with other PIs (e.g. indinavir).

The use of Agenerase has not been sufficiently studied in heavily pretreated protease inhibitor experienced patients.

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, but is estimated to be approximately 90 %. 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 4.2 Posology and method of administration).

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 4.3 Contraindications, 4.4 Special warnings and special precautions for use and 4.5 Interaction with other medicinal products and other forms of interaction).

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. The dosage should therefore be reduced in these patients (see 4.2 Posology and method of administration).

5.3 Preclinical safety data

Long-term carcinogenicity studies of amprenavir in rats and mice are in progress. Amprenavir was not mutagenic or genotoxic in a battery of *in vitro* and *in vivo* assays including bacterial reverse mutation (Ames), mouse lymphoma, rat micronucleus and chromosome aberrations in human 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 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 both species 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 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

2 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 Instructions for use/handling and disposal

No special requirements.

7. MARKETING AUTHORISATION HOLDER

Glaxo Group Ltd
Greenford Road
Greenford
Middlesex UB6 0NN
United Kingdom

8. NUMBER IN THE COMMUNITY REGISTER OF MEDICINAL PRODUCTS

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

10. DATE OF THE REVISION OF THE TEXT

1. NAME OF THE MEDICINAL PRODUCT

Agenerase 150 mg soft capsules

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains 150 mg amprenavir.

For excipients, see 6.1.

3. PHARMACEUTICAL FORM

Soft capsule.

The soft capsules are oblong, opaque, off-white to cream coloured, printed with 'GX CC2'.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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

In protease inhibitor naive patients, Agenerase is less effective than indinavir.

In heavily pretreated protease inhibitor experienced patients, the use of Agenerase has not been sufficiently studied.

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 5.2 Pharmacokinetic properties).

Adults and adolescents of 12 years of age and older (greater than 50 kg body weight): the recommended dose of Agenerase capsules is 1200 mg twice daily in combination with other antiretroviral agents.

If Agenerase capsules are used in combination with ritonavir in adults, reduced doses of amprenavir (600 mg twice daily) and ritonavir (100-200 mg twice daily) are recommended. When efavirenz is included in the treatment regimen, due consideration should be given to pharmacokinetic interactions and the doses adjusted accordingly (see 4.5 Interaction with other medicinal products and other forms of interaction).

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.

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

Children less than 4 years of age: Agenerase is not recommended in children less than 4 years of age (see 5.3 Preclinical safety data).

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

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

Hepatic impairment: the principal route of metabolism of amprenavir is via the liver. Agenerase should be used with caution in patients with hepatic impairment. Clinical efficacy and safety have not been determined in this patient group. Based on pharmacokinetic data, the dose of Agenerase 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 5.2 Pharmacokinetic properties).

4.3 Contraindications

Known hypersensitivity to amprenavir or any ingredient of Agenerase capsules.

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. terfenadine, astemizole, cisapride, pimozone), prolonged sedation or respiratory depression (e.g. triazolam, diazepam, flurazepam, midazolam), or other events (e.g. ergot derivatives).

Agenerase must not be given with rifampicin because rifampicin reduces trough plasma concentrations of amprenavir by approximately 92 % (see 4.5 Interaction with other medicinal products and other forms of interaction).

Patients on amprenavir should not use products containing St John's wort (*Hypericum perforatum*) because co-administration may be expected to reduce plasma concentrations of amprenavir. This may result in loss of therapeutic effect and development of resistance (see 4.5 Interaction with other medicinal products and other forms of interaction).

4.4 Special warnings and special 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 5.1 Pharmacodynamic properties). The principal route of metabolism of amprenavir is via the liver. Agenerase should be used with caution in patients with hepatic impairment. The dose of Agenerase should be reduced in adult patients with moderate or severe hepatic impairment (see 4.2 Posology and method of administration).

Amprenavir, like other HIV protease inhibitors, is an inhibitor of the cytochrome CYP3A4 enzyme. Agenerase should not be administered concurrently with medications with narrow therapeutic windows which are substrates of CYP3A4 (see 4.3 Contraindications). Combination with other agents may result in serious and/or life-threatening interactions, therefore caution is advised whenever Agenerase is co-administered with medicinal products that are inducers, inhibitors or substrates of CYP3A4 (see 4.5 Interaction with other medicinal products and other forms of interaction).

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

Because of the potential for metabolic interactions with amprenavir, the efficacy of hormonal contraceptives may be reduced. Therefore, additional reliable barrier methods of contraception are recommended for women of childbearing potential (see 4.5 Interaction with other medicinal products and other forms of interaction).

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

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.

Rashes/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 4.8 Undesirable effects).

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.

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

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.

4.5 Interaction with other medicinal products and other forms of interaction

Amprenavir 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 amprenavir. Similarly, amprenavir might also modify the pharmacokinetics of other medicinal products that share this metabolic pathway.

Terfenadine, cisapride, pimozide, triazolam, diazepam, midazolam, flurazepam, ergotamine, dihydroergotamine and astemizole are contraindicated in patients receiving Agenerase. Concurrent administration can lead to competitive inhibition of the metabolism of these products and thus result in serious, life-threatening events (see 4.3 Contraindications).

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 18 %, respectively.

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, C_{\min} and C_{\max} of amprenavir were increased by 131 %, 484 % and 33 %, respectively, when ritonavir (200 mg twice daily) was given in combination with amprenavir (1200 mg twice daily) in adults. When given in combination in adults, reduced doses of both medicinal products should be used (see 4.2 Posology and method of administration) (see also efavirenz below). In clinical practice, doses of amprenavir 600 mg twice daily and ritonavir 100 mg twice daily are being used; the evaluation of the safety and efficacy of these regimens is ongoing.

No dose recommendation can be given for the use of amprenavir in combination with other protease inhibitors in children and patients with renal impairment. Such combinations should be avoided in patients with hepatic impairment.

- ***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. If efavirenz is given to adults in combination with amprenavir and ritonavir, reduced doses of both ritonavir and amprenavir should be used (see ritonavir above). 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 and patients with renal impairment. Such combinations should be avoided in patients with hepatic impairment.

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

Delavirdine: delavirdine may increase the serum concentrations of amprenavir.

Antibiotics/antifungals

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

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: 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. No dose adjustment for either medicinal product is necessary when ketoconazole is administered in combination with amprenavir.

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.

Benzodiazepines: the serum concentrations of alprazolam, triazolam, midazolam, clorazepam, diazepam and flurazepam may be increased by amprenavir resulting in enhanced sedation (see 4.3 Contraindications).

Calcium-channel blockers: amprenavir may lead to increased serum concentrations of diltiazem, nifedipine, nifedipine or nimodipine, 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 sildenafil to patients receiving Agenerase. Co-administration of Agenerase with sildenafil may substantially increase sildenafil plasma concentrations and may result in sildenafil-associated adverse events.

Lipid-lowering drugs: amprenavir may increase the serum concentrations of atorvastatin, cerivastatin, fluvastatin, lovastatin, pravastatin and simvastatin, potentially increasing their toxicity.

Methadone and opiate derivatives: until results from an interaction study with methadone are available, subjects undergoing detoxification treatments should be monitored carefully as the concurrent administration of amprenavir and opiate derivatives may result in a significant interaction.

Steroids: oestrogens, progestogens and some glucocorticoids can show interactions with amprenavir. However, the information currently available is not sufficient for determining the nature of the interaction. The effect of hormonal contraceptives can be reduced as a result of the potential for interactions with amprenavir. Since the effects of hormonal contraceptives can be reduced, women of childbearing age are advised to use other, or additional, reliable contraceptive methods.

St John's wort: patients on amprenavir should not use concomitantly products containing St John's wort (*Hypericum perforatum*) since it may be expected to result in reduced plasma concentrations of amprenavir. This effect may be due to an induction of CYP3A4 and may result in the loss of therapeutic effect and development of resistance (see 4.3 Contraindications).

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

4.6 Pregnancy and lactation

Pregnancy: the safe use of amprenavir in human pregnancy has not been established. Placental transfer of amprenavir and/or its related metabolites has been shown to occur in animals (see 5.3 Preclinical safety data).

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.

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.

The most frequent clinical adverse events related to study drugs, of at least moderate intensity (Grade 2 or more), reported in two large clinical studies in adults are summarised below. All events reported in at least 1 % of subjects treated with amprenavir are included.

Adverse Events by body system	PROAB3001 Antiretroviral Naïve Patients		PROAB3006 NRTI-Experienced Patients	
	Agenerase / Lamivudine / Zidovudine (n = 113)	Lamivudine / Zidovudine (n = 109)	Agenerase/ NRTIs (n = 245)	Indinavir / NRTIs (n = 241)
Digestive				
Nausea	31%	17%	10%	5%
Vomiting	11%	4%	3%	4%
Gaseous symptoms	10%	14%	3%	2%
Diarrhoea	9%	6%	19%	5%
Abdominal discomfort	4%	< 1%	< 1%	1%
Abdominal pain	4%	< 1%	4%	5%
Dyspeptic symptoms	3%	< 1%	< 1%	1%
Loose stools	< 1%	< 1%	1%	< 1%
Skin				
Rash	19%	< 1%	9%	< 1%
Neurological				
Headache	11%	12%	4%	2%
Sleep disorders	2%	2%	< 1%	< 1%
Tremors	2%	0%	-	-
Oral/perioral paraesthesia	< 1%	< 1%	2%	0%
Psychiatry				
Mood disorders	4%	0%	-	-
Depressive disorders	3%	0%	< 1%	0%
Non site specific				
Fatigue	11%	8%	2%	2%
Anorexia	2%	3%	< 1%	0%

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 subjects treated with amprenavir in combination with efavirenz. Severe or life-threatening skin reactions, including Stevens-Johnson syndrome, have rarely (< 1 %) occurred in patients treated with amprenavir (see 4.4. Special warnings and special precautions for use).

Symptoms of abnormal fat redistribution were infrequent 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 ($p < 0.001$).

Laboratory abnormalities occurred infrequently with amprenavir, and primarily in patients with abnormal values at baseline. In phase III trials, in combination with various NRTIs, the most frequent treatment-emergent laboratory abnormalities (Grade 2 or more) were elevated transaminases (5 %), hypertriglyceridaemia (4 %), elevated amylase (2.5 %),

hyperbilirubinemia (< 1 %) and hyperglycaemia (< 1 %); almost all subjects with abnormal liver function tests were co-infected with hepatitis B or C virus.

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

4.9 Overdose

There are limited reports of overdose with Agenerase. If overdose occurs, the patient should be monitored for evidence of toxicity (see 4.8 Undesirable effects), 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: JO5A E05

Amprenavir is a competitive inhibitor of the HIV protease. It blocks the ability of the viral protease to cleave the precursor polyproteins necessary for viral replication.

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

Serial passage experiments have demonstrated the protease mutation I50V to be key to the development of amprenavir resistance *in vitro*, with the triple variant, I50V+M46I/L+I47V, resulting in a greater than 10-fold increase in IC₅₀ to amprenavir. This triple mutation resistance profile has not been observed with other protease inhibitors either from *in vitro* studies or in clinical settings. *In vitro* variants resistant to amprenavir remained sensitive to saquinavir, indinavir and nelfinavir, but showed three to five-fold reduced susceptibility to ritonavir. The triple mutant, I50V+M46I/L+I47V, was unstable during *in vitro* passage in the presence of saquinavir, with loss of the I47V mutation, and the development of resistance to saquinavir resulted in resensitisation to amprenavir. Passage of the triple mutant in either indinavir, nelfinavir or ritonavir resulted in additional protease mutations being selected, leading to dual resistance. Mutation I84V, observed transiently *in vitro* has rarely been selected during amprenavir therapy.

The resistance profile seen with amprenavir in clinical practice is different from that observed with other protease inhibitors. Consistent with *in vitro* experiments, the development of amprenavir resistance during therapy, is in the majority cases, associated with the mutation I50V. However, three alternative mechanisms have also been observed to result in the development of amprenavir resistance in the clinic, and involve either mutations I54L/M or V32I+I47V or, rarely, I84V. Each of the four genetic patterns produces viruses with reduced susceptibility to amprenavir, some cross-resistance to ritonavir, but susceptibility to indinavir, nelfinavir and saquinavir is retained.

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

Protease mutations acquired on amprenavir-containing therapy which have been demonstrated to result in reduced phenotypic susceptibility to amprenavir:

I50V or I54L/M or I84V or V32I with I47V

The pre-existence of resistance to other components of a first-line PI-containing regimen is significantly associated with subsequent development of protease mutations, highlighting the importance of considering all components of a treatment regimen when change is indicated.

Many *in vitro* PI-resistant variants, and 322 of 433 (74 %) clinical PI-resistant variants with multiple protease inhibitor resistance mutations were susceptible to amprenavir. The principal protease mutation associated with cross-resistance to amprenavir following treatment failure with other protease inhibitors was I84V, particularly when mutations L10I/V/F were also present.

In multiple PI-experienced subjects, the likelihood of a successful virological response is increased with an increasing number of active drugs (ie. agents to which the virus is susceptible) in the rescue regimen. The presence at the time of therapy change in PI-experienced subjects of multiple key mutations associated with PI-resistance, or the development of such mutations during PI therapy, is significantly associated with treatment outcome. The total number of all types of protease mutations present at the time of therapy change was also correlated with outcome in PI-experienced populations. The presence of 3 or more mutations from M46I/L, I54L/M/V, V82A/F/I/T, I84V and L90M in a population of multiple PI-experienced subjects was significantly related to amprenavir treatment failure.

The following table summarises the mutations, identified in clinical isolates from highly PI-experienced patients, associated with an increased risk of treatment failure of amprenavir-containing regimens.

Protease mutations in virus from PI-experienced patients associated with reduced virological response to subsequent amprenavir containing regimens:

COMBINATION OF AT LEAST THREE OF:

M46I/L or I54L/M/V or V82A/F/I/T or I84V or L90M.

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.

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

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

Clinical experience:

Agenerase in combination with other antiretroviral agents including nucleoside analogues, non-nucleoside analogues and protease inhibitors, has been shown to be effective in the treatment of HIV infection in adults and children aged 4 years or more.

In a double-blind study in antiretroviral naive HIV-infected adults (n = 232), amprenavir in combination with zidovudine and lamivudine was significantly superior to zidovudine and lamivudine. In an intent-to-treat analysis (any missing value or premature discontinuation considered as failure i.e. ≥ 400 copies/ml), the proportion of subjects with plasma HIV-1 RNA < 400 copies/ml through week 48 was 41 % in the amprenavir/lamivudine/zidovudine group and 3 % in the lamivudine/zidovudine group (p < 0.001).

In an open-label randomised study in NRTI experienced PI naive adults (n = 504), in combination with various NRTIs amprenavir was found to be less effective than indinavir: the proportion of subjects with plasma HIV-1 RNA < 400 copies/ml at week 48 was 30 % in the amprenavir arm and 46 % in the indinavir arm in the intent-to-treat analysis (any missing value or premature discontinuation considered as failure, i.e. ≥ 400 copies/ml).

Preliminary results from two paediatric studies with amprenavir oral solution and/or capsules in 268 heavily pre-treated children aged 2 to 18 years indicate that amprenavir is an effective antiretroviral agent in children. Decreases in median HIV-1 RNA greater than 1 log₁₀ copies/ml were observed in protease inhibitor naive subjects and improvements in immune category (CD4 %) were reported.

Data from several clinical studies indicate that amprenavir-containing regimen may be useful for the treatment of other PI-experienced subjects. Correlation analyses of viral resistance profiles with treatment outcome support the concept of utilising resistance testing to select appropriate treatment regimen. Important pharmacokinetic drug/drug interactions should also be taken into account when selecting agents for use in combination with amprenavir (see 4.5 Interactions with other medicinal products and other forms of interaction). Non-controlled data suggest that amprenavir-experienced subjects might be successfully treated with other PIs (e.g. indinavir).

The use of Agenerase has not been sufficiently studied in heavily pretreated protease inhibitor experienced patients,

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, but it is estimated to be approximately 90 %. 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 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 4.2 Posology and method of administration).

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 4.3 Contraindications, 4.4 Special warnings and special precautions for use and 4.5 Interaction with other medicinal products and other forms of interaction).

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. The dosage should therefore be reduced in these patients (see 4.2 Posology and method of administration).

5.3 Preclinical safety data

Long-term carcinogenicity studies of amprenavir in rats and mice are in progress. Amprenavir was not mutagenic or genotoxic in a battery of *in vitro* and *in vivo* assays including bacterial reverse mutation (Ames), mouse lymphoma, rat micronucleus and chromosome aberrations in human 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 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 both species 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 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

2 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 Instructions for use/handling and disposal

No special requirements.

7. MARKETING AUTHORISATION HOLDER

Glaxo Group Ltd
Greenford Road
Greenford
Middlesex UB6 0NN
United Kingdom

8. NUMBER IN THE COMMUNITY REGISTER OF MEDICINAL PRODUCTS

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

10. DATE OF THE REVISION OF THE TEXT

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.

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

In protease inhibitor naive patients, Agenerase is less effective than indinavir.

In heavily pretreated protease inhibitor experienced patients, the use of Agenerase has not been sufficiently studied.

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 5.2 Pharmacokinetic properties).

Patients should discontinue Agenerase oral solution as soon as they are able to swallow the capsule formulation (see 4.4 Special warnings and special precautions for use).

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.

The pharmacokinetic interactions between Agenerase and low doses of ritonavir or other protease inhibitors have not yet been evaluated in children. Such combinations should be avoided in children (see also section 4.5 Interactions with other medicinal products and other forms of interaction).

Children less than 4 years of age: Agenerase is not recommended for use in children less than 4 years of age. (see 4.3 Contraindications, 5.3 Preclinical safety data).

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

Renal impairment: no dose adjustment is considered necessary, however Agenerase oral solution should be used with caution in patients with renal impairment (see 4.4 Special warnings and special precautions for use, 5.2 Pharmacokinetic properties).

Hepatic impairment: Agenerase oral solution should not be used in patients with hepatic impairment (see 4.3 Contraindications) (see Summary of Product Characteristics of Agenerase Capsules for prescribing information)

4.3 Contraindications

Known hypersensitivity to amprenavir or any ingredient of Agenerase oral solution.

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 or renal failure and patients treated with disulfiram or metronidazole (see 4.4 Special warnings and special precautions for use, 5.1 Pharmacodynamic properties).

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. terfenadine, astemizole, cisapride, pimozide), prolonged sedation or respiratory depression (e.g. triazolam, diazepam, flurazepam, midazolam), or other events (e.g. ergot derivatives).

Agenerase must not be given with rifampicin because rifampicin reduces trough plasma concentrations of amprenavir by approximately 92 % (see 4.5 Interaction with other medicinal products and other forms of interaction).

Patients on amprenavir should not use products containing St John's wort (*Hypericum perforatum*) because co-administration may be expected to reduce plasma concentrations of amprenavir. This may result in loss of therapeutic effect and development of resistance (see 4.5 Interaction with other medicinal products and other forms of interaction).

4.4 Special warnings and special 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 5.1 Pharmacodynamic properties).

As the principal route of metabolism of amprenavir and the propylene glycol excipient is via the liver, Agenerase oral solution should not be used in patients with hepatic impairment (see 4.2 Posology and method of administration).

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 or hepatic failure, children and pregnant women, see section 4.3 Contraindications. 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 should be avoided (see 4.5 Interactions with other medicinal products and other forms of interactions).

Amprenavir, like other HIV protease inhibitors, is an inhibitor of the cytochrome CYP3A4 enzyme. Agenerase should not be administered concurrently with medications with narrow therapeutic windows which are substrates of CYP3A4 (see 4.3 Contraindications). Combination with other agents may result in serious and/or life-threatening interactions, therefore caution is advised whenever Agenerase is co-administered with medicinal products that are inducers, inhibitors or substrates of CYP3A4 (see 4.5 Interaction with other medicinal products and other forms of interaction).

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

Because of the potential for metabolic interactions with amprenavir, the efficacy of hormonal contraceptives may be reduced. Therefore, additional reliable barrier methods of contraception are recommended for women of childbearing potential (see 4.5 Interaction with other medicinal products and other forms of interaction).

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

Rashes/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 4.8 Undesirable effects).

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.

Combination antiretroviral therapy, including regimens containing a protease inhibitor, is associated with redistribution of body fat in some patients. Protease inhibitors are also associated with metabolic abnormalities such as hypertriglyceridaemia, hypercholesterolaemia, insulin resistance and hyperglycaemia.

Clinical examination should include evaluation for physical signs of fat redistribution. Consideration should be given to measurements of serum lipids and blood glucose. The mechanisms of these events and long term consequences, such as increased risk of cardiovascular disease, are currently unknown.

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.

4.5 Interaction with other medicinal products and other forms of interaction

Amprenavir 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 amprenavir. Similarly, amprenavir might also modify the pharmacokinetics of other medicinal products that share this metabolic pathway.

Terfenadine, cisapride, pimozone, triazolam, diazepam, midazolam, flurazepam, ergotamine, dihydroergotamine and astemizole are contraindicated in patients receiving Agenerase. Concurrent administration can lead to competitive inhibition of the metabolism of these products and thus result in serious, life-threatening events (see 4.3 Contraindications).

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, C_{\min} and C_{\max} of amprenavir were increased by 131 %, 484 % and 33 %, respectively, when ritonavir (200 mg twice daily) was given in combination with amprenavir (1200 mg twice daily) in adults. When given in combination in adults, reduced doses of both medicinal products should be used (see 4.2 Posology and method of administration) (see also efavirenz below). In clinical practice, doses of amprenavir 600 mg twice daily and ritonavir 100 mg twice daily are being used; the evaluation of the safety and efficacy of these regimens is still ongoing (see also efavirenz below). No dose recommendation can be given for the use of Agenerase oral solution in combination with other protease inhibitors. Agenerase oral solution and ritonavir oral solution should not be co-administered (see 4.4 Special warnings and special precautions for use).

- **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. If efavirenz is given to adults in combination with amprenavir and ritonavir, reduced doses of both ritonavir and amprenavir should be used (see ritonavir above). 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 and patients with renal impairment.

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

Delavirdine: delavirdine may increase the serum concentrations of amprenavir.

Antibiotics/antifungals

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

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: 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. No dose adjustment for either medicinal product is necessary when ketoconazole is administered in combination with amprenavir.

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

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 should not be co-administered (see 4.3 Contraindications and 4.4 Special warnings and special precautions for use).

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.

Benzodiazepines: the serum concentrations of alprazolam, triazolam, midazolam, clorazepam, diazepam and flurazepam may be increased by amprenavir resulting in enhanced sedation (see 4.3 Contraindications).

Calcium-channel blockers: amprenavir may lead to increased serum concentrations of diltiazem, nifedipine, nifedipine or nimodipine, 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 sildenafil to patients receiving Agenerase. Co-administration of Agenerase with sildenafil may substantially increase sildenafil plasma concentrations and may result in sildenafil-associated adverse events.

Lipid-lowering drugs: amprenavir may increase the serum concentrations of atorvastatin, cerivastatin, fluvastatin, lovastatin, pravastatin and simvastatin, potentially increasing their toxicity.

Methadone and opiate derivatives: until results from an interaction study with methadone are available, subjects undergoing detoxification treatments should be monitored carefully as the concurrent administration of amprenavir and opiate derivatives may result in a significant interaction.

Steroids: oestrogens, progestogens and some glucocorticoids can show interactions with amprenavir. However, the information currently available is not sufficient for determining the nature of the interaction. The effect of hormonal contraceptives can be reduced as a result of the potential for interactions with amprenavir. Since the effects of hormonal contraceptives can be reduced, women of childbearing age are advised to use other, or additional, reliable contraceptive methods.

St John's wort: patients on amprenavir should not use concomitantly products containing St John's wort (*Hypericum perforatum*) since it may be expected to result in reduced plasma concentrations of amprenavir. This effect may be due to an induction of CYP3A4 and may result in the loss of therapeutic effect and development of resistance (see 4.3 Contraindications).

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

4.6 Pregnancy and lactation

Pregnancy: the safe use of amprenavir in human pregnancy has not been established. 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 4.3 Contraindications).

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.

4.8 Undesirable effects

The safety of Agenerase has been studied in adults and children of at least 4years 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.

The most frequent clinical adverse events related to study drugs, of at least moderate intensity (Grade 2 or more), reported in two large clinical studies in adults are summarised below. All events reported in at least 1 % of subjects treated with amprenavir are included.

Adverse Events by body system	PROAB3001 Antiretroviral Naïve Patients		PROAB3006 NRTI-Experienced Patients	
	Agenerase / Lamivudine / Zidovudine (n = 113)	Lamivudine / Zidovudine (n = 109)	Agenerase/ NRTIs (n = 245)	Indinavir / NRTIs (n = 241)
Digestive				
Nausea	31%	17%	10%	5%
Vomiting	11%	4%	3%	4%
Gaseous symptoms	10%	14%	3%	2%
Diarrhoea	9%	6%	19%	5%
Abdominal discomfort	4%	< 1%	< 1%	1%
Abdominal pain	4%	< 1%	4%	5%
Dyspeptic symptoms	3%	< 1%	< 1%	1%
Loose stools	< 1%	< 1%	1%	< 1%
Skin				
Rash	19%	< 1%	9%	< 1%
Neurological				
Headache	11%	12%	4%	2%
Sleep disorders	2%	2%	< 1%	< 1%
Tremors	2%	0%	-	-
Oral/perioral paraesthesia	< 1%	< 1%	2%	0%
Psychiatry				
Mood disorders	4%	0%	-	-
Depressive disorders	3%	0%	< 1%	0%
Non site specific				
Fatigue	11%	8%	2%	2%
Anorexia	2%	3%	< 1%	0%

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 subjects treated with amprenavir in combination with efavirenz. Severe or life-threatening skin reactions, including Stevens-Johnson syndrome, have rarely (< 1 %) occurred in patients treated with amprenavir (see 4.4. Special warnings and special precautions for use).

Symptoms of abnormal fat redistribution were infrequent 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).

Laboratory abnormalities occurred infrequently, and primarily in patients with abnormal values at baseline. In phase III trials, in combination with various NRTIs, the most frequent treatment-emergent laboratory abnormalities (Grade 2 or more) were elevated transaminases (5 %), hypertriglyceridaemia (4 %), elevated amylase (2.5 %), hyperbilirubinemia (< 1 %)

and hyperglycaemia (<1 %); almost all subjects with abnormal liver function tests were co-infected with hepatitis B or C virus.

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

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

4.9 Overdose

There are limited reports of overdose with Agenerase. If overdose occurs, the patient should be monitored for evidence of toxicity (see 4.8 Undesirable effects), and standard supportive treatment provided as necessary. Agenerase oral solution contains a large amount of propylene glycol (see 4.4 Special warnings and special precautions for use). 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, hemodialysis is unlikely to be helpful in reducing blood levels of amprenavir.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: protease inhibitor; ATC Code: JO5A E05

Amprenavir is a competitive inhibitor of the HIV protease. It blocks the ability of the viral protease to cleave the precursor polyproteins necessary for viral replication.

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

Serial passage experiments have demonstrated the protease mutation I50V to be key to the development of amprenavir resistance *in vitro*, with the triple variant, I50V+M46I/L+I47V, resulting in a greater than 10-fold increase in IC₅₀ to amprenavir. This triple mutation resistance profile has not been observed with other protease inhibitors either from *in vitro* studies or in clinical settings. *In vitro* variants resistant to amprenavir remained sensitive to saquinavir, indinavir and nelfinavir, but showed three to five-fold reduced susceptibility to ritonavir. The triple mutant, I50V+M46I/L+I47V, was unstable during *in vitro* passage in the presence of saquinavir, with loss of the I47V mutation, and the development of resistance to saquinavir resulted in resensitisation to amprenavir. Passage of the triple mutant in either indinavir, nelfinavir or ritonavir resulted in additional protease mutations being selected, leading to dual resistance. Mutation I84V, observed transiently *in vitro* has rarely been selected during amprenavir therapy.

The resistance profile seen with amprenavir in clinical practice is different from that observed with other protease inhibitors. Consistent with *in vitro* experiments, the development of

amprenavir resistance during therapy, is in the majority cases, associated with the mutation I50V. However, three alternative mechanisms have also been observed to result in the development of amprenavir resistance in the clinic, and involve either mutations I54L/M or V32I+I47V or, rarely, I84V. Each of the four genetic patterns produces viruses with reduced susceptibility to amprenavir, some cross-resistance to ritonavir, but susceptibility to indinavir, nelfinavir and saquinavir is retained.

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

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

The pre-existence of resistance to other components of a first-line PI-containing regimen is significantly associated with subsequent development of protease mutations, highlighting the importance of considering all components of a treatment regimen when change is indicated.

Many *in vitro* PI-resistant variants, and 322 of 433 (74%) clinical PI-resistant variants with multiple protease inhibitor resistance mutations were susceptible to amprenavir. The principal protease mutation associated with cross-resistance to amprenavir following treatment failure with other protease inhibitors was I84V, particularly when mutations L10I/V/F were also present.

In multiple protease inhibitor-experienced subjects, the likelihood of a successful virological response is increased with an increasing number of active drugs (ie. agents to which the virus is susceptible) in the rescue regimen. The presence at the time of therapy change in PI-experienced subjects of multiple key mutations associated with PI-resistance, or the development of such mutations during PI therapy, is significantly associated with treatment outcome. The total number of all types of protease mutations present at the time of therapy change was also correlated with outcome in PI-experienced populations. The presence of 3 or more mutations from M46I/L, I54L/M/V, V82A/F/I/T, I84V and L90M in a population of multiple PI-experienced subjects was significantly related to amprenavir treatment failure.

The following table summarises the mutations, identified in clinical isolates from highly PI-experienced patients, associated with an increased risk of treatment failure of amprenavir-containing regimens.

Protease mutations in virus from PI-experienced patients associated with reduced virological response to subsequent amprenavir containing regimens:								
COMBINATION OF AT LEAST THREE OF:								
M46I/L	or	I54L/M/V	or	V82A/F/I/T	or	I84V	or	L90M.

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.

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

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

Clinical experience:

Agenerase in combination with other antiretroviral agents including nucleoside analogues, non-nucleoside analogues and protease inhibitors, has been shown to be effective in the treatment of HIV infection in adults and children aged 4 years or more.

In a double-blind study in antiretroviral naive HIV-infected adults (n = 232), amprenavir in combination with zidovudine and lamivudine was significantly superior to zidovudine and lamivudine. In an intent-to-treat analysis (any missing value or premature discontinuation considered as failure i.e. ≥ 400 copies/ml), the proportion of subjects with plasma HIV-1 RNA < 400 copies/ml through week 48 was 41 % in the amprenavir/lamivudine/zidovudine group and 3 % in the lamivudine/zidovudine group (p < 0.001).

In an open-label randomised study in NRTI-experienced PI-naive adults (n = 504), in combination with various NRTIs amprenavir was found to be less effective than indinavir: the proportion of subjects with plasma HIV-1 RNA < 400 copies/ml at week 48 was 30 % in the amprenavir arm and 46 % in the indinavir arm in the intent-to-treat analysis (any missing value or premature discontinuation considered as failure, i.e. ≥ 400 copies/ml).

Preliminary results from two paediatric studies with amprenavir oral solution and/or capsules in 268 heavily pre-treated children aged 2 to 18 years indicate that amprenavir is an effective antiretroviral agent in children. Decreases in median HIV-1 RNA greater than 1 log₁₀ copies/ml were observed in protease inhibitor naive subjects and improvements in immune category (CD4 %) were reported.

Data from several clinical studies indicate that amprenavir-containing regimen may be useful for the treatment of other PI-experienced subjects. Correlation analyses of viral resistance profiles with treatment outcome support the concept of utilising resistance testing to select appropriate treatment regimen. Important pharmacokinetic drug / drug interactions should also be taken into account when selecting agents for use in combination with amprenavir (see 4.5 Interaction with other medicinal products and other forms of interaction).

Non-controlled data suggest that amprenavir-experienced subjects might be successfully treated with other PIs (e.g. indinavir).

The use of Agenerase has not been sufficiently studied in heavily pretreated protease inhibitor experienced patients

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, but is estimated to be approximately 90 %. 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 4.2 Posology and method of administration).

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 4.3 Contraindications, 4.4 Special warnings and special precautions for use and 4.5 Interaction with other medicinal products and other forms of interaction).

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 failure (see 4.3 Contraindications).

5.3 Preclinical safety data

Long-term carcinogenicity studies of amprenavir in rats and mice are in progress. Amprenavir was not mutagenic or genotoxic in a battery of *in vitro* and *in vivo* assays including bacterial reverse mutation (Ames), mouse lymphoma, rat micronucleus and chromosome aberrations in human 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 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 both species 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

2 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 Instructions for use/handling and disposal

No special requirements.

7. MARKETING AUTHORISATION HOLDER

Glaxo Group Ltd
Greenford Road
Greenford

Middlesex UB6 0NN
United Kingdom

- 8. NUMBER IN THE COMMUNITY REGISTER OF MEDICINAL PRODUCTS**
- 9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**
- 10. DATE OF THE REVISION OF THE TEXT**

ANNEX II

- A. MANUFACTURING AUTHORISATION HOLDERS RESPONSIBLE FOR BATCH RELEASE**
- B. CONDITIONS OF THE MARKETING AUTHORISATION**
- C. SPECIFIC OBLIGATIONS TO BE FULFILLED BY THE MARKETING AUTHORISATION HOLDER**

A. MANUFACTURING AUTHORISATION HOLDERS RESPONSIBLE FOR BATCH RELEASE

Soft capsules

- Glaxo Wellcome UK Limited, trading as Glaxo Wellcome Operations
Priory Street, Ware, Hertfordshire SG12 ODJ, 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 UK Limited, trading as Glaxo Wellcome Operations
Speke Boulevard, Speke, Liverpool, L24 9JD, United Kingdom

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).

- **OTHER CONDITIONS**

None

C. SPECIFIC OBLIGATIONS TO BE FULFILLED BY THE MARKETING AUTHORISATION HOLDER

The Marketing Authorisation Holder shall complete the following programme of studies within the specified time frame, the results of which shall form the basis of the annual reassessment of the benefit/risk profile.

The Company commits to conduct a phase III study comprising two separate randomised components described below as Study A and Study B.

Study A: A randomised, multicentre, open-label study to compare the efficacy, safety and tolerance of amprenavir/ritonavir versus other protease inhibitors in PI-experienced HIV-infected adults experiencing virological failure.

This study will compare Agenerase, combined with low dose ritonavir, with other protease inhibitors in a standard of care regimen. The results of viral resistance tests at screening will

be used to identify eligible patients and to optimise the number of active drugs in both treatment arms. This study will be based on a non-inferiority design. The anticipated sample size will be 156 and the study will begin to recruit patients in October 2000 with a report available Q4 2001. Quarterly progress updates will be provided to the CPMP starting from Q4 2000.

Study B: A randomised, multicentre, open-label study to assess the efficacy, safety and tolerance of amprenavir/ritonavir in adults infected with HIV resistant to all approved protease inhibitors.

This study will assess Agenerase, combined with low dose ritonavir, in the treatment of heavily treated PI-experienced subjects with virus resistant to all other approved PIs. This study will be based on a superiority design. The anticipated sample size will be 80 and the study will begin to recruit patients in October 2000. Week 4 results are expected to be available June 2001. Quarterly updates will be provided to the CPMP starting from Q4200.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

Agenerase 50 mg soft capsules

Amprenavir

480 soft capsules

Each capsule contains 50 mg amprenavir. This product contains glycerol and propylene glycol.

Oral use

EU/0/00/000/000

Glaxo Group Ltd
Greenford
Middlesex UB6 0NN
United Kingdom

Read the package leaflet before use

Keep out of the reach and sight of children.

Do not store above 30°C.

Keep the container tightly closed.

Medicinal product subject to medical prescription.

LOT
EXP

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

Agenerase 150 mg soft capsules

Amprenavir

240 soft capsules

Each capsule contains 150 mg amprenavir. This product contains glycerol and propylene glycol.

Oral use

EU/0/00/000/000

Glaxo Group Ltd
Greenford
Middlesex UB6 0NN
United Kingdom

Read the package leaflet before use

Keep out of the reach and sight of children.

Do not store above 30°C.

Keep the container tightly closed.

Medicinal product subject to medical prescription.

LOT
EXP

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

Agenerase 150 mg soft capsules

Amprenavir

Pack contents:

Two bottles each containing 240 soft capsules.

Each capsule contains 150 mg amprenavir. This product contains glycerol and propylene glycol.

Oral use

EU/0/00/000/000

Glaxo Group Ltd
Greenford
Middlesex UB6 0NN
United Kingdom

Read the package leaflet before use

Keep out of the reach and sight of children.

Do not store above 30°C.

Keep the container tightly closed.

Medicinal product subject to medical prescription.

LOT
EXP

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

Agenerase 15 mg/ml oral solution

Amprenavir

Bottle contents:

240 ml oral solution containing 15 mg/ml amprenavir.

A 20 ml measuring cup is provided in the pack.

This product contains propylene glycol.

Oral use

EU/0/00/000/000

Glaxo Group Ltd
Greenford
Middlesex UB6 0NN
United Kingdom

Read the package leaflet before use

Keep out of the reach and sight of children.

Do not store above 25°C.

Discard the oral solution 15 days after first opening the bottle.
Medicinal product subject to medical prescription.

LOT

EXP

PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING

Agenerase 15 mg/ml oral solution

Amprenavir

Bottle contents:

240 ml oral solution containing 15 mg/ml amprenavir.

A 20 ml measuring cup is provided in the pack.

This product contains propylene glycol.

Oral use

EU/0/00/000/000

Glaxo Group Ltd

Greenford

Middlesex UB6 0NN

United Kingdom

Read the package leaflet before use

Keep out of the reach and sight of children.

Do not store above 25°C.

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

Medicinal product subject to medical prescription.

LOT

EXP

B. PACKAGE LEAFLET

PACKAGE LEAFLET
Agenerase 50 mg soft capsules

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, please ask your doctor or pharmacist.
- This medicine has been prescribed for you personally and you should not pass it on to others. It may harm them even if their symptoms are the same as yours.

In this leaflet:

- 1) What Agenerase is and what it is used for
- 2) Important information before you take Agenerase
- 3) How to take Agenerase
- 4) Possible side effects
- 5) Storing Agenerase

Name of the medicinal product

Agenerase 50 mg soft capsules
(amprenavir)

Composition

Active substance: 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.

Manufacturer	Marketing Authorisation Holder
Glaxo Wellcome Operations Priory Street Ware Hertfordshire SG12 ODJ United Kingdom	Glaxo Group Ltd Greenford Road Greenford Middlesex UB6 ONN United Kingdom

1. WHAT AGENERASE IS AND WHAT IT IS USED FOR

- **Pharmaceutical form and contents**

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.

- **Pharmacotherapeutic group**

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

- **Therapeutic indication**

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

In protease inhibitor naive patients, Agenerase is less effective than indinavir.

In heavily pretreated protease inhibitor experienced patients, the use of Agenerase has not been sufficiently studied.

2. IMPORTANT INFORMATION BEFORE YOU TAKE AGENERASE

- **Contraindications**

You must not take Agenerase if you are hypersensitive (allergic) to amprenavir or to any of the other ingredients in Agenerase.

There are some medicines such as terfenadine, cisapride, pimozone, astemizole, triazolam, diazepam, flurazepam, midazolam, ergot derivatives and rifampicin that must not be taken with Agenerase.

Patients on Agenerase must not take products containing St John's wort (*Hypericum perforatum*), as this may result in the loss of therapeutic effect and development of resistance. Talk to your doctor if you are taking or are planning on taking St John's wort.

- **Precautions for use and special warnings**

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.

At present, there is insufficient information to recommend the use of Agenerase in children less than four years of age.

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.

- If you suffer from liver disease the dose of Agenerase may need to be reduced.
- 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.
- In some patients taking protease inhibitors, there have been reports of increased sugar in the blood and worsening or development of diabetes mellitus.
- If you have any other health concerns, discuss these with your doctor.

In some individuals, treatment with a combination of antiretroviral medicines that includes a protease inhibitor has caused a change in body shape due to changes in fat distribution. These may include decreased fat under the skin, increased fat in the abdomen (belly), breast enlargement and fatty lumps on the back of the neck.

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 tell your doctor about all the medicines you are taking, including those not prescribed by your doctor. 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.

Some of the medicines that can interact with amprenavir include terfenadine, astemizole, cisapride, pimozone, triazolam, diazepam, flurazepam, midazolam, ergot derivatives and rifampicin. While taking Agenerase, you **must not** take any of these medicines. If you are currently taking any of these medicines, ask your doctor about switching to a different medicine while you are taking Agenerase.

Agenerase may interact with certain other medications. The use of the following medicines, together with Agenerase, should only take place on the basis of medical advice: antibiotics (i.e. rifabutin, clarithromycin, dapsone and erythromycin), antifungals (i.e. ketoconazole, itraconazole), benzodiazepines (i.e. alprazolam and clorazepam), calcium channel blockers (i.e. diltiazem, nifedipine, nifedipine and nimodipine), cholesterol lowering agents (i.e. atorvastatin, cerivastatin, fluvastatin, lovastatin, pravastatin and simvastatin), erectile dysfunction agents (sildenafil), non-nucleoside reverse transcriptase inhibitors (i.e. efavirenz, nevirapine and delavirdine), opioids (i.e. methadone), steroids (i.e. oestrogens, progestogens and some glucocorticoids) and other substances (i.e. clozapine, carbamazepine, cimetidine and loratadine).

If you are taking certain medicines that can cause serious side effects, such as amiodarone, phenobarbital, phenytoin, lidocaine, tricyclic antidepressants, quinidine 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 additional reliable barrier method (e.g. a condom) to prevent pregnancy while you are taking Agenerase. This is because Agenerase may interact with the hormones in the pill and reduce its effect.

- **Pregnancy and breast feeding**

Inform your doctor if you are pregnant or planning to become pregnant soon or if you are breast feeding. The safe use of Agenerase in pregnancy has not been established. This medicine should be taken during pregnancy only on the advice of your doctor.

Breast feeding your baby is not recommended while you are taking Agenerase. Health experts recommend that, where possible, 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.

- **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.

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

3. HOW TO TAKE AGENERASE

- **Dosage and instructions for proper use**

Always take Agenerase exactly as your doctor has instructed you. You should check with your doctor or pharmacist if you are unsure.

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 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.

4. POSSIBLE SIDE EFFECTS

Like all medicines, Agenerase can have side effects. 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.

The most frequent side effects that may occur while taking Agenerase are associated with the digestive system, such as nausea, vomiting, flatulence and diarrhoea. Tingling of your lips and mouth, skin rash, abdominal pain, mood/sleep and depressive disorders, indigestion, loss of appetite, headache and fatigue are also side effects that were reported by patients treated with Agenerase. These usually get better without stopping treatment with Agenerase. Occasionally, the skin rash may be severe and you may have to stop taking this medicine. If your doctor considers that this reaction means that you are allergic to Agenerase, you must not take it again.

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).

Increases in liver enzymes and blood fat have been reported in patients taking Agenerase. Your doctor will test your blood regularly for any abnormalities. Your blood will also be checked for increases in blood sugar levels, as occasionally protease inhibitors have been shown to cause this.

Always tell your doctor or pharmacist about any side effects that occur while taking Agenerase, even those not mentioned in this leaflet.

5. STORING AGENERASE

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

Do not take the medicine after the expiry date on the container.

As with all medicines, keep Agenerase out of the sight and reach of children.

This leaflet was last approved on 00-00.

Further information

For any information about this medicinal product please contact the local representative of the Marketing Authorisation Holder.

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PACKAGE LEAFLET
Agenerase 150 mg soft capsules

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, please ask your doctor or pharmacist.
- This medicine has been prescribed for you personally and you should not pass it on to others. It may harm them even if their symptoms are the same as yours.

In this leaflet:

- 1) What Agenerase is and what it is used for.
- 2) Important information before you take Agenerase
- 3) How to take Agenerase
- 4) Possible side effects
- 5) Storing Agenerase

Name of the medicinal product

Agenerase 150 mg soft capsules
(amprenavir)

Composition

Active substance: 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.

Manufacturer

Glaxo Wellcome Operations
Priory Street
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Hertfordshire SG12 ODJ
United Kingdom

**Marketing Authorisation
Holder**

Glaxo Group Ltd
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Middlesex UB6 ONN
United Kingdom

1. WHAT AGENERASE IS AND WHAT IT IS USED FOR

- **Pharmaceutical form and contents**

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.

- **Pharmacotherapeutic group**

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

- **Therapeutic indication**

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

In protease inhibitor naive patients, Agenerase is less effective than indinavir.

In heavily pretreated protease inhibitor experienced patients, the use of Agenerase has not been sufficiently studied.

2. IMPORTANT INFORMATION BEFORE YOU TAKE AGENERASE

- **Contraindications**

You must not take Agenerase if you are hypersensitive (allergic) to amprenavir or to any of the other ingredients in Agenerase.

There are some medicines such as terfenadine, cisapride, pimozide, astemizole, triazolam, diazepam, flurazepam, midazolam, ergot derivatives and rifampicin that must not be taken with Agenerase.

Patients on Agenerase must not take products containing St John's wort (*Hypericum perforatum*), as this may result in the loss of therapeutic effect and development of resistance. Talk to your doctor if you are taking or are planning on taking St John's wort.

- **Precautions for use and special warnings**

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.

At present, there is insufficient information to recommend the use of Agenerase in children less than four years of age.

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.

- If you suffer from liver disease the dose of Agenerase may need to be reduced.
- 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.
- In some patients taking protease inhibitors, there have been reports of increased sugar in the blood and worsening or development of diabetes mellitus.
- If you have any other health concerns, discuss these with your doctor.

In some individuals, treatment with a combination of antiretroviral medicines that includes a protease inhibitor has caused a change in body shape due to changes in fat distribution. These may include decreased fat under the skin, increased fat in the abdomen (belly), breast enlargement and fatty lumps on the back of the neck.

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 tell your doctor about all the medicines you are taking, including those not prescribed by your doctor. 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.

Some of the medicines that can interact with amprenavir include terfenadine, astemizole, cisapride, pimozone, triazolam, diazepam, flurazepam, midazolam, ergot derivatives and rifampicin. While taking Agenerase, you **must not** take any of these medicines. If you are currently taking any of these medicines, ask your doctor about switching to a different medicine while you are taking Agenerase.

Agenerase may interact with certain other medications. The use of the following medicines, together with Agenerase, should only take place on the basis of medical advice: antibiotics (i.e. rifabutin, clarithromycin, dapson and erythromycin), antifungals (i.e. ketoconazole, itraconazole), benzodiazepines (i.e. alprazolam and clorazepam), calcium channel blockers (i.e. diltiazem, nifedipine, nifedipine and nimodipine), cholesterol lowering agents (i.e. atorvastatin, cerivastatin, fluvastatin, lovastatin, pravastatin and simvastatin), erectile dysfunction agents (sildenafil), non-nucleoside reverse transcriptase inhibitors (i.e. efavirenz, nevirapine and delavirdine), opioids (i.e. methadone), steroids (i.e. oestrogens, progestogens and some glucocorticoids) and other substances (i.e. clozapine, carbamazepine, cimetidine and loratadine).

If you are taking certain medicines that can cause serious side effects, such as amiodarone, phenobarbital, phenytoin, lidocaine, tricyclic antidepressants, quinidine 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 additional reliable barrier method (e.g. a condom) to prevent pregnancy while you are taking Agenerase. This is because Agenerase may interact with the hormones in the pill and reduce its effect.

- **Pregnancy and breast feeding**

Inform your doctor if you are pregnant or planning to become pregnant soon or if you are breast feeding. The safe use of Agenerase in pregnancy has not been established. This medicine should be taken during pregnancy only on the advice of your doctor.

Breast feeding your baby is not recommended while you are taking Agenerase. Health experts recommend that, where possible, 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.

- **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.

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

3. HOW TO TAKE AGENERASE

- **Dosage and instructions for proper use**

Always take Agenerase exactly as your doctor has instructed you. You should check with your doctor or pharmacist if you are unsure.

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 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.

4. POSSIBLE SIDE EFFECTS

Like all medicines, Agenerase can have side effects. 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.

The most frequent side effects that may occur while taking Agenerase are associated with the digestive system, such as nausea, vomiting, flatulence and diarrhoea. Tingling of your lips and mouth, skin rash, abdominal pain, mood/sleep and depressive disorders, indigestion, loss of appetite, headache and fatigue are also side effects that were reported by patients treated with Agenerase. These usually get better without stopping treatment with Agenerase. Occasionally, the skin rash may be severe and you may have to stop taking this medicine. If your doctor considers that this reaction means that you are allergic to Agenerase, you must not take it again.

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).

Increases in liver enzymes and blood fat have been reported in patients taking Agenerase. Your doctor will test your blood regularly for any abnormalities. Your blood will also be checked for increases in blood sugar levels, as occasionally protease inhibitors have been shown to cause this.

Always tell your doctor or pharmacist about any side effects that occur while taking Agenerase, even those not mentioned in this leaflet.

5. STORING AGENERASE

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

Do not take the medicine after the expiry date on the container.

As with all medicines, keep Agenerase out of the sight and reach of children.

This leaflet was last approved on 00-00.

Further information

For any information about this medicinal product please contact the local representative of the Marketing Authorisation Holder.

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PACKAGE LEAFLET
Agenerase 150 mg soft capsules

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, please ask your doctor or pharmacist.
- This medicine has been prescribed for you personally and you should not pass it on to others. It may harm them even if their symptoms are the same as yours.

In this leaflet:

- 1) What Agenerase is and what it is used for
- 2) Important information before you take Agenerase
- 3) How to take Agenerase
- 4) Possible side effects
- 5) Storing Agenerase

Name of the medicinal product

Agenerase 150 mg soft capsules
(amprenavir)

Composition

Active substance: 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.

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1. WHAT AGENERASE IS AND WHAT IT IS USED FOR

- **Pharmaceutical form and contents**

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.

- **Pharmacotherapeutic group**

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

- **Therapeutic indication**

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

In protease inhibitor naive patients, Agenerase is less effective than indinavir.

In heavily pretreated protease inhibitor experienced patients, the use of Agenerase has not been sufficiently studied.

2. IMPORTANT INFORMATION BEFORE YOU TAKE AGENERASE

- **Contraindications**

You must not take Agenerase if you are hypersensitive (allergic) to amprenavir or to any of the other ingredients in Agenerase.

There are some medicines such as terfenadine, cisapride, pimozide, astemizole, triazolam, diazepam, flurazepam, midazolam, ergot derivatives and rifampicin that must not be taken with Agenerase.

Patients on Agenerase must not take products containing St John's wort (*Hypericum perforatum*), as this may result in the loss of therapeutic effect and development of resistance. Talk to your doctor if you are taking or are planning on taking St John's wort.

- **Precautions for use and special warnings**

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.

At present, there is insufficient information to recommend the use of Agenerase in children less than four years of age.

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.

- If you suffer from liver disease the dose of Agenerase may need to be reduced.
- 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.
- In some patients taking protease inhibitors, there have been reports of increased sugar in the blood and worsening or development of diabetes mellitus.
- If you have any other health concerns, discuss these with your doctor.

In some individuals, treatment with a combination of antiretroviral medicines that includes a protease inhibitor has caused a change in body shape due to changes in fat distribution. These

may include decreased fat under the skin, increased fat in the abdomen (belly), breast enlargement and fatty lumps on the back of the neck.

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 tell your doctor about all the medicines you are taking, including those not prescribed by your doctor. 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.

Some of the medicines that can interact with amprenavir include terfenadine, astemizole, cisapride, pimozone, triazolam, diazepam, flurazepam, midazolam, ergot derivatives and rifampicin. While taking Agenerase, you **must not** take any of these medicines. If you are currently taking any of these medicines, ask your doctor about switching to a different medicine while you are taking Agenerase.

Agenerase may interact with certain other medications. The use of the following medicines, together with Agenerase, should only take place on the basis of medical advice: antibiotics (i.e. rifabutin, clarithromycin, dapson and erythromycin), antifungals (i.e. ketoconazole, itraconazole), benzodiazepines (i.e. alprazolam and clorazepam), calcium channel blockers (i.e. diltiazem, nifedipine, nifedipine and nimodipine), cholesterol lowering agents (i.e. atorvastatin, cerivastatin, fluvastatin, lovastatin, pravastatin and simvastatin), erectile dysfunction agents (sildenafil), non-nucleoside reverse transcriptase inhibitors (i.e. efavirenz, nevirapine and delavirdine), opioids (i.e. methadone), steroids (i.e. oestrogens, progestogens and some glucocorticoids) and other substances (i.e. .clozapine, carbamazepine, cimetidine and loratadine).

If you are taking certain medicines that can cause serious side effects, such as amiodarone, phenobarbital, phenytoin, lidocaine, tricyclic antidepressants, quinidine 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 additional reliable barrier method (e.g. a condom) to prevent pregnancy, while you are taking Agenerase. This is because Agenerase may interact with the hormones in the pill and reduce its effect.

- **Pregnancy and breast feeding**

Inform your doctor if you are pregnant or planning to become pregnant soon or if you are breast feeding. The safe use of Agenerase in pregnancy has not been established. This medicine should be taken during pregnancy only on the advice of your doctor.

Breast feeding your baby is not recommended while you are taking Agenerase. Health experts recommend that, where possible, 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.

- **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.

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

3. HOW TO TAKE AGENERASE

- **Dosage and instructions for proper use**

Always take Agenerase exactly as your doctor has instructed you. You should check with your doctor or pharmacist if you are unsure.

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 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.

4. POSSIBLE SIDE EFFECTS

Like all medicines, Agenerase can have side effects. 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.

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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).

Increases in liver enzymes and blood fat have been reported in patients taking Agenerase. Your doctor will test your blood regularly for any abnormalities. Your blood will also be checked for increases in blood sugar levels, as occasionally protease inhibitors have been shown to cause this.

Always tell your doctor or pharmacist about any side effects that occur while taking Agenerase, even those not mentioned in this leaflet.

5. STORING AGENERASE

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

Do not take the medicine after the expiry date on the container.

As with all medicines, keep Agenerase out of the sight and reach of children.

This leaflet was last approved on 00-00.

Further information

For any information about this medicinal product please contact the local representative of the Marketing Authorisation Holder.

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PACKAGE LEAFLET
Agenerase 15 mg/ml oral solution

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, please ask your doctor or pharmacist.
- This medicine has been prescribed for you personally and you should not pass it on to others. It may harm them even if their symptoms are the same as yours.

In this leaflet:

- 1) What Agenerase is and what it is used for
- 2) Important information before you take Agenerase
- 3) How to take Agenerase
- 4) Possible side effects
- 5) Storing Agenerase

Name of the medicinal product

Agenerase 15 mg/ml oral solution
(amprenavir)

Composition

Active substance: amprenavir
The 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.

Manufacturer	Marketing Authorisation Holder
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1. WHAT AGENERASE IS AND WHAT IT IS USED FOR

- **Pharmaceutical form and contents**

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.

- **Pharmacotherapeutic group**

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

- **Therapeutic indication**

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

In protease inhibitor naive patients, Agenerase is less effective than indinavir.

In heavily pretreated protease inhibitor experienced patients, the use of Agenerase has not been sufficiently studied.

Patients should take Agenerase capsules as soon as they are able to swallow them.

2. IMPORTANT INFORMATION BEFORE YOU TAKE AGENERASE

- **Contraindications**

You must not take Agenerase if you are hypersensitive (allergic) to amprenavir or to any of the other ingredients in Agenerase.

There are some medicines such as terfenadine, cisapride, pimozide, astemizole, triazolam, diazepam, flurazepam, midazolam, ergot derivatives and rifampicin that must not be taken with Agenerase oral solution.

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 or renal failure, and patients treated with disulfiram or metronidazole (see also Precautions for use and special warnings).

Patients on Agenerase must not take products containing St John's wort (*Hypericum perforatum*), as this may result in the loss of therapeutic effect and development of resistance. Talk to your doctor if you are taking or are planning on taking St John's wort.

- **Precautions for use and special warnings**

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.

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 Contraindications).

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.
- 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.
- In some patients taking protease inhibitors, there have been reports of increased sugar in the blood and worsening or development of diabetes mellitus.
- If you have any other health concerns, discuss these with your doctor.

In some individuals, treatment with a combination of antiretroviral medicines that includes a protease inhibitor has caused a change in body shape due to changes in fat distribution. These may include decreased fat under the skin, increased fat in the abdomen (belly), breast enlargement and fatty lumps on the back of the neck.

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 tell your doctor about all the medicines you are taking, including those not prescribed by your doctor. 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.

Some of the medicines that can interact with amprenavir include terfenadine, astemizole, cisapride, pimozide, triazolam, diazepam, flurazepam, midazolam, ergot derivatives and rifampicin. While taking Agenerase, you **must not** take any of these medicines. If you are currently taking any of these medicines, ask your doctor about switching to a different medicine while you are taking Agenerase.

Agenerase may interact with certain other medications. The use of the following medicines, together with Agenerase, should only take place on the basis of medical advice: antibiotics (i.e. rifabutin, clarithromycin, dapsone and erythromycin), antifungals (i.e. ketoconazole, itraconazole), benzodiazepines (i.e. alprazolam and clorazepam, calcium channel blockers (i.e. diltiazem, nifedipine, nifedipine and nimodipine), cholesterol lowering agents (i.e. atorvastatin, cerivastatin, fluvastatin, lovastatin, pravastatin and simvastatin), erectile dysfunction agents (sildenafil), non-nucleoside reverse transcriptase inhibitors (i.e. efavirenz, nevirapine and delavirdine), opioids (i.e. methadone), steroids (i.e. oestrogens, progestogens and some glucocorticoids) and other substances (i.e. clozapine, carbamazepine, cimetidine and loratadine).

If you are taking certain medicines that can cause serious side effects, such as amiodarone, phenobarbital, phenytoin, lidocaine, tricyclic antidepressants, quinidine 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) and avoid taking preparations that contain alcohol or additional propylene glycol while you are taking Agenerase oral solution.

If you are taking the contraceptive pill, it is recommended that you use an additional reliable barrier method (e.g. a condom) to prevent pregnancy, while you are taking Agenerase. This is because Agenerase may interact with the hormones in the pill and reduce its effect.

- **Pregnancy and breast feeding**

Inform your doctor if you are pregnant or planning to become pregnant soon or are breast feeding. The safe use of Agenerase in pregnancy has not been established. Agenerase oral solution must not be used during pregnancy (see Contraindications).

Breast feeding your baby is not recommended while you are taking Agenerase. Health experts recommend that where possible, 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.

- **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 Contraindications, Precautions for use and special warnings).

Because Agenerase oral solution contains vitamin E, you should not take additional vitamin E supplements.

3. HOW TO TAKE AGENERASE

- **Dosage and instructions for proper use**

Always take Agenerase exactly as your doctor has instructed you. You should check with your doctor or pharmacist if you are unsure. 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.

4. POSSIBLE SIDE EFFECTS

Like all medicines, Agenerase can have side effects. 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.

The most frequent side effects that may occur while taking Agenerase are associated with the digestive system, such as nausea, vomiting, flatulence and diarrhoea. Tingling of your lips and mouth, skin rash, abdominal pain, mood /sleep and depressive disorders, indigestion, loss of appetite, headache and fatigue are also side effects that were reported by patients treated with Agenerase. These usually get better without stopping treatment with Agenerase. Occasionally, the skin rash may be severe and you may have to stop taking this medicine. If your doctor considers that this reaction means that you are allergic to Agenerase, you must not take it again.

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).

Increases in liver enzymes and blood fat have been reported in patients taking Agenerase. Your doctor will test your blood regularly for any abnormalities. Your blood will also be checked for increases in blood sugar levels, as occasionally protease inhibitors have been shown to cause this.

Always tell your doctor or pharmacist about any side effects that occur while taking Agenerase, even those not mentioned in this leaflet.

5. STORING AGENERASE

Do not store above 25°C.

Do not take the medicine after the expiry date on the container. Discard Agenerase oral solution 15 days after first opening the bottle.

As with all medicines, keep Agenerase out of the sight and reach of children.

This leaflet was last approved on 00-00.

Further information

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