PRODUCT MONOGRAPH

Pr AGENERASE™

amprenavir

15 mg/mL oral solution

Antiretroviral Agent

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[Pr]AGENERASE™

amprenavir

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Nonmedicinal Ingredients
Oral	Oral Solution/ 15 mg/mL	acesulfame potassium, artificial grape/bubblegum flavour, citric acid (anhydrous), d-alpha tocopheryl polyethylene glycol 1000 succinate (TPGS), menthol, natural peppermint flavour, polyethylene glycol 400 (PEG400), propylene glycol, saccharin sodium, sodium chloride and sodium citrate (dihydrate).

INDICATIONS AND CLINICAL USE

AGENERASE™ (amprenavir) is indicated for:

- the treatment of protease inhibitor experienced, HIV-1 infected patients, in combination with other antiretroviral agents.

The choice of AGENERASE™ should be based on the treatment history of patients. In protease inhibitor naive patients, AGENERASE™ is less effective than indinavir.

CONTRAINDICATIONS

Because of potential risk of toxicity from the large amount of the excipient propylene glycol AGENERASE™ (amprenavir) 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 WARNINGS AND PRECAUTIONS section).

AGENERASE™ must not be administered concurrently with medicinal products with narrow a therapeutic window that are substrates of cytochrome P450 3A4 (CYP 3A4).

Coadministration may result in competitive inhibition of metabolism of these medicinal products and create the potential for serious and/or life-threatening adverse events such as cardiac arrhythmia (for example terfenadine, astemizole, cisapride, pimozide), prolonged sedation or respiratory depression (for example triazolam, midazolam, diazepam, flurazepam) or peripheral vasospasm or ischaemia (for example ergot derivatives).

Amprenavir oral solution and ritonavir oral solution should not be co-administered (see DRUG INTERACTIONS section).

AGENERASE™ should not be given with rifampin. Rifampin reduces trough plasma concentrations of amprenavir by approximately 92% (see DRUG INTERACTIONS section).

AGENERASE™ is contraindicated in patients with previously demonstrated clinically significant hypersensitivity to any of the components of the products.

WARNINGS AND PRECAUTIONS

General

Because of the possible toxicity associated with the large amount of propylene glycol and the lack of information on chronic exposure to large amounts of propylene glycol, AGENERASE™ (amprenavir) oral solution should be used only when AGENERASE™ capsules or other protease inhibitor formulations are not therapeutic options. Certain ethnic populations (patients of Asian origin, Aboriginals) and women may be at increased risk of propylene glycol-associated adverse events due to diminished ability to metabolize propylene glycol; no data are available on propylene glycol metabolism in these groups (see ACTION AND CLINICAL PHARMACOLOGY: Special Populations and Conditions: Gender sections).

If patients require treatment with AGENERASE™ oral solution, they should be monitored closely for propylene glycol-associated adverse events, including seizures, stupor, tachycardia, hyperosmolality, lactic acidosis, renal toxicity, and hemolysis. Patients should be switched from AGENERASE™ oral solution to AGENERASE™ capsules as soon as they are able to take the capsule formulation.

Use of alcoholic beverages is not recommended in patients treated with AGENERASE™ oral solution.

Serious and/or life-threatening drug interactions could occur between amprenavir and amiodarone, lidocaine (systemic), tricyclic antidepressants, quinidine or warfarin (monitor International Normalized Ratio). Concentration monitoring of these agents is recommended if these agents are used concomitantly with AGENERASE™. Phenobarbital and phenytoin may decrease amprenavir concentrations.

HMG-CoA reductase inhibitors (statins) may interact with protease inhibitors and increase the risk of myopathy including rhabdomyolysis. Concomitant use of protease inhibitors with lovastatin or simvastatin is not recommended. Other HMG-CoA reductase inhibitors (statins) may also interact with protease inhibitors. This warning is based on clinical reports, and on indirect evidence from studies on the cytochrome P-450 CYP3A4 metabolism pathway.

Use the lowest possible dose of atorvastatin with careful monitoring or consider the use of pravastatin or fluvastatin as alternative HMG-CoA reductase inhibitors in combination with AGENERASE™.

Particular caution should be used when prescribing sildenafil in patients receiving protease inhibitors, including amprenavir. Coadministration of protease inhibitors with sildenafil is expected to substantially increase sildenafil concentrations and may result in an increase in sildenafil-associated adverse events, including hypotension, visual changes, and priapism (see DRUG INTERACTIONS section and the complete prescribing information for sildenafil).

Concomitant use of St. John's Wort (*Hypericum perforatum*) or St. John's Wort containing products and amprenavir is not recommended. Coadministration of St. John's Wort with protease inhibitors, including amprenavir, is expected to substantially decrease protease inhibitor concentrations and may result in sub-optimal levels of amprenavir and lead to loss of virologic response and possible resistance to amprenavir or the class of protease inhibitors.

Patients taking the oral solution of AGENERASE™, particularly those with renal impairment or those with decreased ability to metabolize propylene glycol (e.g. patients 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 CONTRAINDICATIONS section. The concomitant administration of AGENERASE™ oral solution with disulfiram or other medicinal products that reduce alcohol metabolism (e.g. or preparations that contain alcohol (e.g. ritonavir oral solution) or additional propylene glycol is contraindicated (see CONTRAINDICATIONS and DRUG INTERACTIONS sections).

Formulations of AGENERASE™ provide high daily doses of vitamin E. The effects of long-term, high-dose vitamin E administration in humans is not well characterized and has not been specifically studied in HIV-infected individuals. High vitamin E doses may exacerbate the blood coagulation defect of vitamin K deficiency caused by anticoagulant therapy or malabsorption. Each mL of AGENERASE™ oral solution contains 46 IU vitamin E. The maximum daily dose of AGENERASE™ oral solution corresponds to vitamin E intake of approximately 8600 IU/day.

AGENERASE™ capsules and AGENERASE™ oral solution are not interchangeable on a milligram-per-milligram basis (see ACTION AND CLINICAL PHARMACOLOGY: Pediatric Patients sections).

Amprenavir is a sulfonamide. The potential for cross-sensitivity between drugs in the sulfonamide class and amprenavir is unknown. Patients with a known sulfonamide allergy should be treated with caution.

Contraceptives
Because of the potential for metabolic interactions with amprenavir, the efficacy of hormonal contraceptives may be modified, but there is insufficient information to predict the nature of the interactions. Therefore, alternative methods of contraception are recommended for women of child-bearing potential.

Information for Patients
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.

AGENERASE™ oral solution should be used only when AGENERASE™ capsules or other protease inhibitor formulations are not therapeutic options.

Patients treated with AGENERASE™ capsules should be cautioned against switching to AGENERASE™ oral solution because of the increased risk of adverse events from the large amount of propylene glycol in AGENERASE™ oral solution.
Women, patients of Asian origin, Aboriginals, as well as patients who have hepatic or renal insufficiency, should be informed that they may be at increased risk of adverse events from the large amount of propylene glycol in AGENERASE™ oral solution.

Patients should inform their doctor if they have a sulfa allergy. The potential for cross-sensitivity between drugs in the sulfonamide class and amprenavir is unknown.

Patients should be advised of the importance of taking AGENERASE™ exactly as prescribed. AGENERASE™ must always be used in combination with other

antiretroviral drugs. AGENERASE™ is not a cure for HIV infection and patients may continue to experience illnesses associated with HIV infection, including opportunistic infections. Patients should be advised that the use of AGENERASE™ has not been shown to reduce the risk of transmission of HIV.

Patients should remain under the care of a physician when using AGENERASE™. The long-term effects of AGENERASE™ are unknown at this time.

AGENERASE™ oral solution is for oral ingestion only.

AGENERASE™ may interact with some drugs, therefore, patients should be advised to report to their doctor the use of any other prescription or nonprescription medication.

Patients taking antacids (or didanosine) should take AGENERASE™ at least 1 hour before or after antacid (or didanosine) use.

Patients should be advised that drinking alcoholic beverages is not recommended while taking AGENERASE™ oral solution.

Patients receiving sildenafil should be advised that they may be at an increased risk of sildenafil-associated adverse events, including hypotension, visual changes, and priapism, and should promptly report any symptoms to their doctor.

Patients receiving hormonal contraceptives should be instructed that alternate contraceptive measures should be used during therapy with AGENERASE™.

High-fat meals may decrease the absorption of AGENERASE™ and should be avoided. AGENERASE™ may be taken with meals of normal fat content.

Patients should be informed that redistribution or accumulation of body fat may occur in patients receiving antiretroviral therapy and that the cause and long-term health effects of these conditions are not known at this time.

AGENERASE™ oral solution contains vitamin E (46 IU/mL), therefore additional vitamin E supplementation is not recommended.

Carcinogenesis and Mutagenesis

Data from long term carcinogenicity studies with amprenavir has revealed histopathological evidence for hepatocellular adenomas in both male mice and rats, and altered hepatocellular foci were seen in male mice only. The clinical relevance of these findings is unknown (see TOXICOLOGY, Carcinogenicity section).

Endocrine and Metabolism

New onset diabetes mellitus, exacerbation of pre-existing diabetes mellitus, and hyperglycemia have been reported during post-marketing surveillance in HIV-infected patients receiving protease inhibitor therapy. Some patients required either initiation or dose adjustments of insulin or oral hypoglycemic agents for treatment of these events. In some cases, diabetic ketoacidosis has occurred. In those patients who discontinued protease inhibitor therapy, hyperglycemia persisted in some cases. Because these events have been reported voluntarily during clinical practice, estimates of frequency cannot be made and causal relationships between protease inhibitor therapy and these events have not been established.

Fat Redistribution

Redistribution/accumulation of body fat, including central obesity, dorsocervical fat enlargement ("buffalo hump"), peripheral wasting, facial wasting, breast enlargement, and "cushingoid appearance", have been observed in patients receiving antiretroviral therapies. The mechanism and long-term consequences of these events are currently unknown. A causal relationship has not been established.

Hematologic

Acute hemolytic anemia has been reported in a patient treated with AGENERASE™.

Patients with Hemophilia

There have been reports of increased bleeding, including spontaneous skin hematomas and hemarthroses, in hemophiliac 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. Hemophiliac patients should therefore be made aware of the possibility of increased bleeding.

Hepatic/Biliary/Pancreatic

Amprenavir is principally metabolized by the liver; therefore caution should be exercised when administering this drug to patients with hepatic impairment (see DOSAGE AND ADMINISTRATION section).

Immune

Immune Reconstitution: During the initial phase of treatment, patients responding to antiretroviral therapy may develop an inflammatory response to indolent or residual opportunistic infections (such as MAC, CMV, PCP, and TB) which may necessitate further evaluation and treatment.

Sensitivity/Resistance

Resistance/Cross-Resistance
Because the potential for HIV cross-resistance among protease inhibitors has not been fully explored, it is unknown what effect amprenavir therapy will have on the activity of subsequently administered protease inhibitors (see MICROBIOLOGY section).

Skin
Severe and life-threatening skin reactions, including Stevens-Johnson syndrome, have occurred in patients treated with AGENERASE™ (see ADVERSE REACTIONS section).

Special Populations

Pregnant Women
AGENERASE™ oral solution is contraindicated during pregnancy due to the potential risk of toxicity to the fetus from the high propylene glycol content. Therefore, if AGENERASE™ is used in pregnant women, the AGENERASE™ capsule formulation should be used (see Product Monograph for AGENERASE™ capsules).

Antiretroviral Pregnancy Registry: To monitor maternal-fetal outcomes of pregnant women exposed to AGENERASE™, an antiretroviral Pregnancy Registry has been established. Physicians are encouraged to register patients by calling GlaxoSmithKline's Drug Surveillance Department (1-800-387-7374).

Nursing Women
Although it is not known if amprenavir is excreted in human milk, amprenavir is secreted into the milk of lactating rats. Because of both the potential for HIV transmission and possible adverse effects of amprenavir, mothers should be instructed not to breastfeed if they are receiving AGENERASE™.

Pediatrics
AGENERASE™ oral solution is contraindicated in infants and children below the age of 4 years due to the potential risk of toxicity from the excipient propylene glycol (see CONTRAINDICATIONS and WARNINGS AND PRECAUTIONS sections). Alcohol dehydrogenase (ADH), which metabolizes propylene glycol, is present in the human fetal liver at 2 months of gestational age, but at only 3% of adult activity. Although the data are limited, it appears that by 12 to 30 months of postnatal age, ADH activity is equal to or greater than that observed in adults.

One hundred and eighteen patients 4 to 17 years of age have received amprenavir as single or multiple doses in Phase I to III studies. An adverse event profile similar to that seen in adults was seen in pediatric patients.

The safety, effectiveness, and pharmacokinetics of amprenavir have not been evaluated in pediatric patients below the age of 4 years.

Geriatrics
Clinical studies of AGENERASE™ did not include sufficient numbers of patients aged 65 and over to determine whether they respond differently from younger adults. In general, dose selection for an elderly patient should be cautious, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

ADVERSE REACTIONS

Clinical Trial Adverse Drug Reactions

> *Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates*.

Rates of discontinuation of randomized therapy due to adverse events were 15% in amprenavir versus 3% in placebo recipients from Study 3001, and 16% in amprenavir versus 8% in indinavir recipients from Study 3006. In these studies, adverse events leading to amprenavir discontinuation included gastrointestinal events (11%), rash (3%), and paresthesias (< 1%).

Most gastrointestinal events (nausea, vomiting, diarrhea, and abdominal pain) that led to amprenavir discontinuation were graded as mild or moderate in severity.
In all multidose studies in HIV-infected patients, skin rash occurred in 28% of patients treated with amprenavir. Rashes were usually maculopapular and of mild or moderate intensity, some with pruritus. Rashes had onsets ranging from 7 to 73 days (median: 10 days) after amprenavir initiation. With mild or moderate rash, amprenavir dosing was often continued without interruption; if interrupted, reintroduction of amprenavir generally did not result in rash recurrence (Phase III studies).

Severe or life-threatening rash, including Stevens-Johnson syndrome, occurred in 1% of recipients of AGENERASE™ (amprenavir) (4% of recipients who developed rash) (see WARNINGS AND PRECAUTIONS section). Amprenavir therapy should be discontinued for severe or life-threatening rashes and for moderate rashes accompanied by systemic symptoms.

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 summarized in Table 1. All events reported in at least 1% of subjects treated with AGENERASE™ are included.

Table 1: Percentage of Patients with Treatment-Emergent Drug-Related Adverse Events of Moderate or Severe Intensity Reported in ≥ 1% of Patients

Adverse Events by body system	Study 3001 Antiretroviral Naïve Patients		Study 3006 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%

* NRTIs = Nucleoside Reverse Transcriptase Inhibitors: lamivudine, zidovudine, didanosine, zalcitabine, stavudine.

In Study 3001 only one case (a buffalo hump) was reported in 113 (< 1%) antiretroviral naive subjects treated with amprenavir in combination with lamivudine/zidovudine for a median duration of 36 weeks. In Study 3006, 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 ($p < 0.001$).

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.

Laboratory data from clinical trials showed that hypercholesterolemia occurred at a higher rate in patients receiving amprenavir (7%) than placebo (3%) in PROAB3001.

None of the patients in the amprenavir- containing regimen developed hypercholesterolemia of grade 3-4 severity. In study PROAB3006, 13% of patients receiving amprenavir and 15% of patients receiving placebo developed hypercholesterolemia. Less than 1% of the patients with in the amprenavir arm developed hypercholesterolemia of grade 3-4 severity.

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

Post-Market Adverse Drug Reactions

In addition to adverse events reported from clinical trials, the following events have been identified during use of AGENERASE™ in clinical practice. Because they were reported voluntarily from a population of unknown size, estimates of frequency cannot be made. These events have been chosen for inclusion due to either their seriousness, frequency of reporting, potential causal connection to AGENERASE™, or a combination of these factors.

Body as a Whole: Redistribution/accumulation of body fat (see WARNINGS AND PRECAUTIONS: Fat Redistribution section).

DRUG INTERACTIONS

Overview

Amprenavir is metabolized in the liver by the cytochrome P450 enzyme system. Amprenavir inhibits CYP3A4. Caution should be used when coadministering medications that are substrates, inhibitors, or inducers of CYP3A4. AGENERASE™ (amprenavir) should not be administered concurrently with medications with a narrow therapeutic window which are substrates of CYP3A4. There are also other agents that may result in serious and/or life-threatening drug interactions (see CONTRAINDICATIONS section).

Interaction studies have been performed with amprenavir as the sole protease inhibitor. When amprenavir and ritonavir are co-administered, the ritonavir metabolic drug interaction profile may predominate because ritonavir is a more potent CYP3A4 inhibitor. The full prescribing information for ritonavir must therefore be consulted prior to initiation of therapy with AGENERASE™ and ritonavir.

Drug interaction studies were performed with AGENERASE™ capsules and other drugs likely to be coadministered or drugs commonly used as probes for pharmacokinetic interactions. The effects of coadministration of amprenavir on the AUC, C_{max}, and C_{min} are summarized in Table 2.

Table 2: Drug Interactions

Pharmacokinetic Parameters for Amprenavir in the Presence of the Coadmininstered Drug			**Coadmininstered Drug**	**Pharmacokinetic Parameters for Coadministered Drug in the Presence of Amprenavir**		
C_{max}	AUC	C_{min}		C_{max}	AUC	C_{min}
↑47%	↑29%	↑27%	Abacavir	↔	↔	↔
↑15%	↑18%	↑39%	Clarithromycin	10%	↔	↔
↑18%	↑33	↑25%	Indinavir	↓22%	↓38	↓27%
↓16%	↑31	NA	Ketoconazole (sd)	↑19%	↑44%	NA
↔	↔	NA	Lamivudine (sd)	↔	↔	NA
↓14%	↔	↑189%	Nelfinavir	↑12%	↑15%	↑14%
↔	↓15%	↓15%	Rifabutin	↑119%	↑193%	↑271%
↓70%	↓82%	↓92%	Rifampin	↔	↔	ND
↓37%	↓32%	↓14%	Saquinavir*	↑21%	↓19%	↓48%
↔	↑13%	NA	Zidovudine (sd)	↑40%	↑31%	NA
NA[(1)]	NA[(1)]	NA[(1)]	R-methadone (active)	↓25%	↓13%	↔
NA[(1)]	NA[(1)]	NA[(1)]	S-methadone (inactive)	↓48%	↓40%	↓23%
↔	↓22%	↓20%	Ethinyl estradiol	↔	↔	↑32%
			norethindrome	↔	↑18%	↑45%

↑ = Increase; ↓ = Decrease; ↔ = no significant change; NA = Not applicable; sd = Single-dose study
ND = Interaction cannot be determined as C_{min} was below lower limit if quantitation.
* = (soft gelatine capsules)
(1) = see Other Possible Interactions, Methadone

Drug-Drug Interactions

The following interaction data was obtained in adults.

Table 3: Established or Potential Drug-Drug Interactions

Proper name	Effect	Clinical comment
Antibiotics/Antifungals		
• Dapsone and Erythromycin	Plasma concentrations may be affected.	Dapsone and erythromycin may have their plasma concentrations increased by amprenavir. Erythromycin may also increase amprenavir serum concentrations.
• Itraconazole	Plasma concentrations may be affected.	Itraconazole may have its plasma concentrations increased by amprenavir. Itraconazole may increase serum concentrations of amprenavir.
• Rifabutin	The pharmacokinetic parameters of both drugs are affected when administered in combination.	Coadministration of amprenavir with rifabutin results in a 15% decrease in amprenavir plasma AUC and a 193% increase in rifabutin plasma AUC. A dosage reduction of rifabutin to at least half the recommended dose is required when amprenavir and rifabutin are coadministered. A complete blood count should be performed weekly and as clinically indicated in order to monitor for neutropenia in patients receiving amprenavir and rifabutin.
• Rifampin	The pharmacokinetic parameters of amprenavir are affected when both drugs are administered in combination.	Rifampin should not be used in combination with amprenavir since it reduces C_{min} of amprenavir by 92% and the AUC by 82% (see CONTRAINDICATIONS section).
Antiretroviral Agents		No dose recommendation can be given for the use of AGENERASE™ oral solution in combination with other protease inhibitors in children and patients with renal impairment. Such combinations should be avoided in patients with hepatic impairment.
• Protease inhibitors (PIs) – Ritonavir	The pharmacokinetic parameters of amprenavir are affected when both drugs are administered in combination.	AGENERASE™ oral solution and ritonavir oral solution should not be co-administered. Coadministration of ritonavir with amprenavir results in a significant increase in the C_{min} and AUC of amprenavir. When amprenavir capsules are given in combination with ritonavir in adults, reduced doses of both medicinal products should be used (see AGENERASE™ Capsules Product Monograph). In clinical trials, doses of amprenavir 600mg twice daily and ritonavir 100mg twice daily have been used; confirming safety and efficacy of this regimen.

Table 3: Established or Potential Drug-Drug Interactions

Proper name	Effect	Clinical comment
Nucleoside analogue reverse transcriptase inhibitors (NRTIs)		
• Didanodsine	Potential interference with absorption.	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 Other Possible Interactions, Antacids).
Non-nucleoside reverse transcriptase inhibitors (NNRTIs)	Serum concentrations may be affected.	NNRTIs have the potential to increase (delavirdine) or decrease (efavirenz, nevirapine) serum concentrations of amprenavir.
• Delavirdine	The pharmacokinetic parameters of both drugs are affected when administered in combination.	Amprenavir and delavirdine should not be given together. A drug interaction resulting in decreased delavirdine levels may lead to loss of virologic response and possible resistance to delavirdine. The AUC, C_{max} and C_{min} of delavirdine were decreased by 61%, 47% and 88% respectively when given with amprenavir. The AUC, C_{max} and C_{min} of amprenavir were increased by 130%, 40% and 125% respectively.
Other Possible Interactions	Potential toxicities may occur when coadministered with either substrates, inhibitors, or inducers of CYP3A4.	Other medications listed below are examples of substrates, inhibitors, or inducers of CYP3A4 that could have potential interactions, when used concomitantly with AGENERASE™. The clinical significance of these potential interactions are unknown and have not been studied. Patients should therefore be monitored for toxicities associated with such drugs when these are used in combination with AGENERASE™.
• Alcohols and inhibitors of alcohol metabolism		AGENERASE™ oral solution contains propylene glycol (550mg/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 with AGENERASE™ oral solution (see CONTRAINDICATIONS and WARNINGS AND PRECAUTIONS sections). Use of alcoholic beverages is not recommended in patients treated with AGENERASE™ oral solution.

Table 3: Established or Potential Drug-Drug Interactions

Proper name	Effect	Clinical comment
• Antacids	Potential interference with absorption.	Antacids (and didanosine secondary to the antacid content) have not been specifically studied. Based upon data with other protease inhibitors, it is advisable that antacids not be taken at the same time as AGENERASE™ because of potential interference with absorption. It is recommended that their administration be separated by at least an hour.
• Benzodiazepines	Possible increased benzodiazepine activity.	Alprazolam, clorazepate, diazepam, flurazepam, midazolam and triazolam may have their serum concentrations increased by AGENERASE™, which could increase their activity (see CONTRAINDICATIONS section).
• Calcium channel blockers	Possible increased calcium channel blocker activity.	Diltiazem, nicardipine, nifedipine, and nimodipine may have their serum concentrations increased by AGENERASE™, which could increase their activity.
• Erectile dysfunction agents	Coadministration may result in substantial increases in sildenafil plasma concentrations.	Based on data for other protease inhibitors caution should be used when prescribing sildenafil to patients receiving AGENERASE™. Coadministration of AGENERASE™ with sildenafil may substantially increase sildenafil plasma concentrations and may result in sildenafil-associated adverse events.
• HMG-CoA reductase inhibitors	May increase the risk of myopathy including rhabdomyolysis.	HMG-CoA reductase inhibitors (statins) may interact with protease inhibitors and increase the risk of myopathy including rhabdomyolysis. Concomitant use of protease inhibitors with lovastatin or simvastatin is not recommended. Other HMG-CoA reductase inhibitors (statins), may also interact with protease inhibitors. Use the lowest possible dose of atorvastatin with careful monitoring or consider the use of pravastatin or fluvastatin as alternative HMG-CoA reductase inhibitors in combination with AGENERASE™. This warning is based on clinical reports, and on indirect evidence from studies on the cytochrome P-450 CYP3A4 metabolism pathway.

Table 3: Established or Potential Drug-Drug Interactions

Proper name	Effect	Clinical comment
• Methadone	The pharmacokinetic parameters of both drugs are affected when administered in combination. Coadministration may result in possible methadone underdosing.	Coadministration of methadone with amprenavir resulted in a decrease in the C_{max} and AUC of the active methadone enantiomer (R-enantiomer) of 25% and 13% respectively, while the C_{max}, AUC and C_{min} of the inactive methadone enantiomer (S-enantiomer) were decreased by 48%, 40% and 23% respectively. When methadone is co-administered with amprenavir, patients should be monitored for methadone underdosing, in particular if low-dose ritonavir is also given. As compared to a non-matched historical control group, co-administration of methadone and amprenavir resulted in a 30%, 27% and 25% decrease in serum amprenavir AUC, C_{max} and C_{min} respectively. No recommendations can be made regarding adjustment of amprenavir dose when amprenavir is co-administered with methadone.
• Steriods	Possible interaction.	Estrogens, progestogens, and some glucocorticoids may have an interaction with AGENERASE™ but there is insufficient information to predict the nature of the interaction. Alternative methods of contraception are recommended for women of childbearing potential.
• St. John's Wort	May result in reduced plasma concentrations of amprenavir.	Patients on AGENERASE™ should not use products containing St. John's Wort (Hypericum perforatum) since it may result in reduced plasma concentrations of amprenavir (see WARNINGS AND PRECAUTIONS section).
Other agents	May affect plasma/serum concentrations of amprenavir.	Caution should be used when amprenavir is coadministered with drugs known to induce CYP 3A4, such as phenobarbital, phenytoin, carbamazepine and dexamethasone. Induction of amprenavir (CYP 3A4) metabolism may result in reduced serum amprenavir concentrations. There are other agents that may have their plasma concentrations increased by AGENERASE™, and include but are not limited to: clozapine, cimetidine and loratadine. Cimetidine may increase amprenavir plasma concentrations.

Legend: C = Case Study; CT = Clinical Trial; T = Theoretical

DOSAGE AND ADMINISTRATION

Dosing Considerations

AGENERASE™ (amprenavir) can be taken with or without food, however, a high-fat meal decreases the absorption of amprenavir and should be avoided.

Each mL of AGENERASE™ oral solution contains 46 IU vitamin E. The maximum daily dose of AGENERASE™ oral solution corresponds to vitamin E intake of approximately 8600 IU/day.

Propylene glycol is included in the oral solution formulation to achieve adequate solubility of amprenavir. The recommended daily dose of AGENERASE™ oral solution of 22.5 mg/kg twice daily corresponds to a propylene glycol intake of 1650 mg/kg per day. Acceptable intake of propylene glycol for pharmaceuticals has not been established.

Recommended Dose and Dosage Adjustment

Patients unable to swallow AGENERASE™ capsules
The recommended dose of AGENERASE™ oral solution is 22.5 mg (1.5 mL)/kg twice a day or 17 mg (1.1 mL)/kg three times a day, in combination with other antiretroviral agents, without exceeding a total daily dose of 2800 mg.

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

Children less than 4 years
AGENERASE™ is not recommended in children less than 4 years of age.

Patients with Hepatic Impairment
AGENERASE™ oral solution is contraindicated in patients with hepatic failure (see CONTRAINDICATIONS section).

Patients with hepatic impairment are at increased risk of propylene glycol-associated adverse events (see WARNINGS AND PRECAUTIONS section). AGENERASE™ oral solution should be used with caution in patients with hepatic impairment. Based on a study with AGENERASE™ capsules, adult patients with a Child-Pugh score ranging from 5 to 8 should receive a reduced dose of AGENERASE™ oral solution of 513 mg (34-mL) twice daily, and adult patients with a Child-Pugh score ranging from 9 to 12 should receive a reduced dose of AGENERASE™ oral solution of 342 mg (23 mL) twice daily (see ACTION AND CLINICAL PHARMACOLOGY: Adults with Impaired Hepatic Function section).

AGENERASE™ oral solution has not been studied in children with hepatic impairment.

Patients with Renal Impairment
AGENERASE™ oral solution is contraindicated in patients with renal failure (see CONTRAINDICATIONS section).

Patients with renal impairment are at increased risk of propylene glycol-associated adverse events. AGENERASE™ oral solution should be used with caution in patients with renal impairment (see WARNINGS AND PRECAUTIONS section).

AGENERASE™ capsules and oral solution are not interchangeable on a milligram-per-milligram basis.

Missed Dose
If you forget to take AGENERASE™, take it as soon as you remember. Then continue as before.

OVERDOSAGE

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

AGENERASE™ oral solution contains large amounts of propylene glycol. In the event of overdosage, monitoring and management of acid-base abnormalities is recommended. Propylene glycol can be removed by hemodialysis.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action
Amprenavir is a non-peptidic competitive inhibitor of HIV-1 protease. It blocks the ability of viral protease to process gag and gag-pol polyproteins necessary for viral replication.

Pharmacokinetics

Absorption and Bioavailability
Amprenavir was rapidly absorbed after oral administration in HIV-1-infected patients with a time to peak concentration (t_{max}) typically between 1 and 2 hours after a single oral dose. The absolute oral bioavailability of amprenavir in humans has not been established.

Increases in the area under the plasma concentration versus time curve (AUC) after single oral doses between 150 and 1200 mg were slightly greater than dose-proportional. Increases in AUC were dose-proportional after 3 weeks of dosing with doses from 300 to 1200 mg twice daily.

The relative bioavailability of AGENERASE™ (amprenavir) capsules and oral solution was assessed in healthy adults. AGENERASE™ oral solution was 14% less bioavailable compared to the capsules.

Effects of Food on Oral Absorption
The relative bioavailability of AGENERASE™ capsules was assessed in the fasting and fed states in healthy volunteers (standardized high-fat meal: 967 kcal, 67 grams fat, 33 grams protein, 58 grams carbohydrate). Administration of a single 1200 mg dose of amprenavir in the fed state compared to the fasted state was associated with changes in C_{max} (fed: 6.18 ± 2.92 µg/mL, fasted: 9.72 ± 2.75 µg/mL), T_{max} (fed: 1.51 ± 0.68 h, fasted 1.05 ± 0.63 h), and AUC (fed: 22.06 ± 11.6 µg •h/mL, fasted: 28.05 ± 10.1 µg•h/mL). AGENERASE™ may be taken with or without food, but should not be taken with a high-fat meal (see DOSAGE AND ADMINISTRATION section).

AGENERASE™ oral solution contains a large amount of propylene glycol, which is hepatically metabolized by the alcohol and aldehyde dehydrogenase enzyme pathway. Alcohol dehydrogenase (ADH) is present in the human fetal liver at 2 months of gestational age, but at only 3% of adult activity. Although the data are limited, it appears that by 12 to 30 months of postnatal age, ADH activity is equal to or greater than that observed in adults. Additionally, certain patient groups (females, patients of Asian origin, Aboriginals) may be at increased risk of propylene glycol-associated adverse events due to diminished ability to metabolize propylene glycol (see ACTION AND CLINICAL PHARMACOLOGY: Special Populations and Conditions: Gender section).

Special Populations and Conditions

Adults with Impaired Renal Function
AGENERASE™ (amprenavir) oral solution is contraindicated in patients with renal failure.

Patients with renal impairment are at increased risk of propylene glycol-associated adverse events. Additionally, because metabolites of the excipient propylene glycol in AGENERASE™ oral solution may alter acid-base balance, patients with renal impairment should be monitored for potential adverse events (see WARNINGS AND PRECAUTIONS section).

AGENERASE™ oral solution should be used with caution in patients with renal impairment. The impact of renal impairment on amprenavir elimination has not been studied. The renal elimination of unchanged amprenavir represents < 3% of the administered dose.

Adults with Impaired Hepatic Function
AGENERASE™ oral solution is contraindicated in patients with hepatic failure.

Patients with hepatic impairment are at increased risk of propylene glycol-associated adverse events (see WARNINGS AND PRECAUTIONS section). AGENERASE™ oral solution should be used with caution in patients with hepatic impairment. AGENERASE™ capsules have been studied in adult patients with impaired hepatic function using a single 600 mg oral dose. The $AUC_{0\infty}$ was significantly greater in patients with moderate cirrhosis (25.76 ± 14.68 µg•h/mL) compared with healthy volunteers (12.00 ± 4.38 µg•h/mL). The $AUC_{0\infty}$ and C_{max} were significantly greater in patients with severe cirrhosis ($AUC_{0\infty}$: 38.66 ± 16.08 µg•h/mL; C_{max}: 9.43 ± 2.61 µg/mL) compared with healthy volunteers ($AUC_{0\infty}$: 12.00 ± 4.38 µg•h/mL; C_{max}: 4.90 ± 1.39 µg/mL). Patients with impaired hepatic function require dosage adjustment (see DOSAGE AND ADMINISTRATION section).

Pediatric Patients
AGENERASE™ oral solution is contraindicated in infants and children below 4 years of age (see CONTRAINDICATIONS and WARNINGS AND PRECAUTIONS sections).

The pharmacokinetics of amprenavir have been studied after either single or repeat doses of AGENERASE™ capsules or oral solution in 84 pediatric patients. Twenty HIV-1-infected children ranging in age from 4 to 12 years received single doses from 5 mg/kg to 20 mg/kg using 25 mg or 150 mg capsules. The C_{max} of amprenavir increased less than proportionally with dose. The $AUC_{0\infty}$ increased proportionally at doses between 5 and 20 mg/kg. Amprenavir is 14% less bioavailable from the liquid formulation than from the capsules; therefore AGENERASE™ capsules and AGENERASE™ oral solution are not interchangeable on a milligram-per-milligram basis.

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

Geriatric Patients
The pharmacokinetics of amprenavir have not been studied in patients over 65 years of age.

Gender
The pharmacokinetics of amprenavir do not differ in males and females. Females may have a lower amount of alcohol dehydrogenase compared with males and may be at increased risk of propylene glycol-associated adverse events; no data are available on propylene glycol metabolism in females.

STORAGE AND STABILITY

AGENERASE™ (amprenavir) oral solution should be stored between 5^{o} and 25^{o}C.

SPECIAL HANDLING INSTRUCTIONS

Not applicable.

DOSAGE FORMS, COMPOSITION AND PACKAGING

AGENERASE™ (amprenavir) oral solution, 15 mg/mL, is a clear, pale yellow to yellow solution with grape/bubblegum flavouring. The oral solution is available in a 240 mL bottle.

Composition

Oral Solution
Each mililitre of AGENERASE™ 15 mg/mL oral solution contains 15 mg of amprenavir and the non-medicinal ingredients acesulfame potassium, artificial grape/bubblegum flavour, citric acid (anhydrous), d-alpha tocopheryl polyethylene glycol 1000 succinate (TPGS), menthol, natural peppermint flavour, polyethylene glycol 400 (PEG400), propylene glycol, saccharin sodium, sodium chloride and sodium citrate (dihydrate).

Each mL of AGENERASE™ oral solution contains 46 IU vitamin E in the form of TPGS. Propylene glycol is in the formulation to achieve adequate solubility of amprenavir. The recommended daily dose of AGENERASE™ oral solution of 22.5 mg/kg twice daily corresponds to a propylene glycol intake of 1650 mg/kg per day. Acceptable intake of propylene glycol for pharmaceuticals has not been established.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

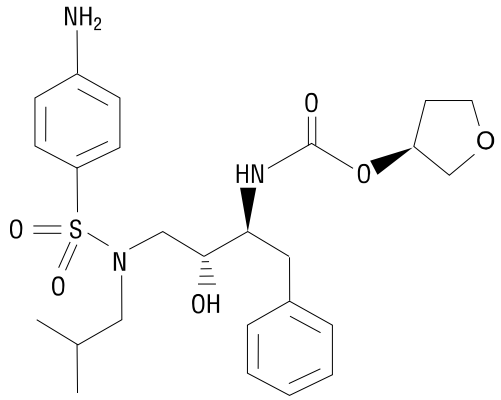
Drug Substance

Proper name: amprenavir

Chemical name: 3*S*-tetrahydro-3-furyl*N*-[(1*S*,2*R*)-3-(4-amino-*N*-isobutylbenzenesulphonamido)-1-benzyl-2-hydroxypropyl]carbamate

Molecular formula and molecular mass: $C_{25}H_{35}N_3O_6S$; 505.64

Structural formula:



Physicochemical properties:

Description: Amprenavir is a white to cream-coloured solid with a solubility of approximately 0.04 mg/mL in water at 25°C. The melting point of amprenavir is around 130°C (maximum rate around 132°C).

pH: The pH of an aqueous solution of amprenavir at 0.041 mg/mL was determined to be 7.5 (± 0.5).

pK_a: The pK_a for amprenavir, as determined by UV spectrophotometry at 25°C and ionic strength 0.1 to 0.43 M, is 1.97.

CLINICAL TRIALS

Not available.

DETAILED PHARMACOLOGY

Pharmacokinetics in Adults

The pharmacokinetic properties of amprenavir have been studied in asymptomatic, HIV-infected adult patients after administration of single oral doses of 150 to 1200 mg and multiple oral doses of 300 to 1200 mg twice daily.

Distribution

The apparent volume of distribution (Vz/F) is approximately 430L in healthy adult subjects. *In vitro* binding is approximately 90% to plasma proteins. The high affinity binding protein for amprenavir is alpha1-acid glycoprotein (AAG). The partitioning of amprenavir into erythrocytes is low, but increases as amprenavir concentrations increase, reflecting the higher amount of unbound drug at higher concentrations.

Metabolism

Amprenavir is primarily metabolized in the liver by the cytochrome P450 CYP3A4 enzyme system. The two major metabolites result from oxidation of the tetrahydrofuran and aniline moieties. Glucuronide conjugates of oxidized metabolites have been identified as minor metabolites in urine and feces.

Elimination

Excretion of unchanged amprenavir in urine and feces is minimal. Approximately 14% and 75% of an administered single dose of ^{14}C-amprenavir can be accounted for as radiocarbon in urine and feces, respectively. Two metabolites accounted for > 90% of the radiocarbon in fecal samples. The plasma elimination half-life of amprenavir ranged from 7.1 to 10.6 hours.

MICROBIOLOGY

Mechanism of Action

Amprenavir is an inhibitor of HIV-1 protease, with a K_i value of 0.6nM. Inhibition of the viral protease prevents cleavage of the gag and gag-pol polyprotein resulting in an inactive, noninfectious virus.

Antiviral Activity *In Vitro*

In vitro, amprenavir is a specific inhibitor of HIV-1 replication in acutely infected human T-cell lymphotropic virus type 1-transformed cells (MT4), peripheral blood lymphocytes, and chronically infected MT4 cells; 50% inhibitory concentration (IC_{50}) values were 0.08, 0.08, and 0.41 μM, respectively. Amprenavir demonstrated synergistic activity against HIV-1 in cell culture when combined with abacavir, zidovudine, didanosine, and saquinavir and an additive effect in combination with indinavir, ritonavir and nelfinavir.

Resistance

Amprenavir-resistant isolates of HIV-1 have been selected *in vitro* and were also obtained from patients treated with amprenavir. *In vitro*, at least three mutations were required at amino acid residues 46 (e.g., Met→Leu or ILE), 47 (ILE→Val), and 50 (ILE→Val) within the HIV protease to produce a strain with a greater than 10-fold increase in IC_{50}. Consistent with *in-vitro* experiments, the development of amprenavir resistance during therapy, is in the majority of 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.

Cross-Resistance

Varying degrees of HIV-1 cross resistance among protease inhibitors have been observed. The potential for protease inhibitor cross-resistance in HIV-1 isolates from amprenavir-treated patients has not been fully evaluated.

No cross-resistance should occur between amprenavir and reverse transcriptase inhibitors because the enzyme targets are different. The resistance profile seen with amprenavir in vitro is different from that observed with other protease inhibitors. *In vitro*, little cross-resistance has been observed between amprenavir-selected resistant variants and other protease inhibitors. Amprenavir-resistant isolates are highly susceptible to indinavir, saquinavir, and nelfinavir, but show reduced susceptibility to ritonavir *in vitro*. 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. 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 associated with reduced virological response to subsequent amprenavir containing regimens.

TOXICOLOGY

Acute Toxicity

Amprenavir has a very low order of acute oral toxicity in mice, rats and monkeys. The median oral lethal doses were greater than 46-fold and greater than 62-fold for male and female mice, respectively, than the proposed therapeutic dose of 1200 mg bid (equivalent to 48 mg/kg/day based on a 50 kg human). For male and female rats, the median lethal dose was greater than 62-fold compared with the proposed human therapeutic dose.

Amprenavir also has a low order of intravenous toxicity. Median lethal intravenous doses were approximately 130 and 99 mg/kg for male and female mice, respectively, and 189 mg/kg for male and female rats.

Long-Term Toxicity

Amprenavir free base has been administered to rats at dose levels of up to 750 mg/kg/day for 6 months and to dogs at dose levels of up to 225 mg/kg/day for 12 months.

Amprenavir caused clinical signs in the study animals, including salivation in rats and dogs, and vomiting and loose (soft to liquid) feces in dogs. Some of the fecal alterations in the dogs were also noted in the vehicle control group. The salivation and vomiting in the dogs occasionally led to dehydration and serum electrolyte losses in some animals, which had to be carefully managed during the study.

Amprenavir caused liver toxicity in both rats and dogs which consisted of increases in serum AST, ALT or alkaline phosphatase activity, increased liver weights and microscopic findings, including hepatocyte necrosis. Some of the liver findings may be the result of induction of drug metabolising enzymes, which in turn, contributed to changes in the thyroid gland that were noted in both species.

The No - (toxicological) Observable Effect Level (NOEL) was generally determined to be lower than the low dose level in the repeat dose studies in rats and dogs because clinical signs (salivation and faecal alterations), some clinical pathology changes and some microscopic organ changes were seen in the low dose animals in longer-term studies. Most of these changes were reversible after cessation of dosing. Systemic exposure to amprenavir at the high dose level at the end of long term rat and dog studies is equivalent to approximately 2.4 to 2.8 and 5.4 to 11.2 times the exposure seen in humans at the proposed therapeutic dose, respectively (AUC human approximately 37 μg•h/mL).

Carcinogenicity

In 104-week carcinogenicity studies with amprenavir, there were benign hepatocellular adenomas in males at the high dose of 500 mg/kg/day in mice or 750 mg/kg/day in rats.

Exposures (AUC) at these dose levels were 62.9 mg.h/mL in mice or 123 mg.h/mL in rats, equivalent to 2.0-fold (mice) or 3.8-fold (rats) those in humans given 1200 mg twice daily of amprenavir alone (AUC 32 mg.h/mL). Altered hepatocellular foci were seen in male mice at doses of 275 (AUC 68.0 mg.h/mL) and 500 mg/kg/day (AUC 62.9 mg.h/mL) with exposure at least 2.0 times human therapeutic exposure. In the mouse study the high dose was reduced from 600 to 500 mg/kg/day on Week 3 of the study due to high mortality. Continued high mortality resulted in discontinuation of dosing in high dose females in Week 89, and early termination of these females in Week 99. High mortaility also lead to the discontinuation of dosing of low dose males in Week 100, however this group continued without further amprenavir administration to finish the study at Week 104.

The significance of the observed effects for humans is uncertain, however there is no evidence from clinical trials or marketed use to suggest that these findings are of clinical significance.

Amprenavir was not mutagenic or genotoxic in a battery of *in vivo* and *in vitro* genetic toxicity assays, including bacterial reverse mutation (Ames Test), mouse lymphoma, rat micronucleus, and chromosome aberration in human peripheral lymphocytes. (See TOXICOLOGY, Mutagenicity section).

Mutagenicity

Amprenavir did not increase the gene mutation frequency in prokaryotic (using Ames and the Yahagi modified Ames tests at concentrations up to 5000 μg/plate) or eukaryotic cells (using the mouse lymphoma L5178Y $tk^{+/-}$ assay at concentrations up to 546 μg/mL) *in vitro*.

There was no evidence that amprenavir had any clastogenic activity either *in vitro* (using the human peripheral lymphocyte assay at concentrations up to 840 μg/mL) or *in vivo* (using an oral rat micronucleus test at doses up to 1000 mg/kg).

Reproduction and Teratology

Amprenavir was without effect on the mating performance and fertility of both male and female rats following oral dosing up to 840 mg/kg/day (males) or 750 mg/kg/day (females).

No major embryo-foetal developmental defects have been observed. Two minor variations in the rat were attributed to amprenavir administration, thymic elongation and incomplete ossification of skull bones. An apparent dose-related increase in pre-implantation loss was noted in rabbits dosed up to 100 mg/kg/day. The toxicological significance of this finding is obscure since dosing commenced after implantation should have been complete. Three minor skeletal variations were seen in rabbits resulting from deficient ossification of the femur, humerus trochlea and humerus.

In a pre- and post-natal study, there was a slight reduction in the body weight gain of weaning rats from dams dosed at 750 mg/kg/day. No other pre- or post-natal developmental changes were noted in F_1 or F_2 pups following oral administration to F_0 dams up to 750 mg/kg/day.

Special Toxicity

In young rats, vehicle-related mortality precluded the determinations of a NOEL in oral pilot studies, and resulted in no definitive studies being carried out. The sensitivity of the very young animal towards the vehicle is thought due to immature metabolic development resulting in vehicle components not being detoxified and excreted. In adult animals the vehicle was well-tolerated.

Coadministration of amprenavir with abacavir (a nucleoside reverse transcriptase inhibitor) to rats caused some clinical pathology changes that were most marked at the highest combination dosage, but these were reversible. Ovarian interstitial cell hypertrophy/hyperplasia occurred only in animals dosed with the combination, but this was reversible and follicular maturation was unaffected. Effects on the liver and adrenal cortex were more severe in the combination groups, but showed evidence of reversal once treatment stopped. Other findings were generally consistent with those observed after administration of either drug alone. Coadministration had no apparent effect on systemic exposure to either compound.

Amprenavir was non-toxic in an acute dermal toxicity study in the rat, and was non-irritant to rabbit skin. Amprenavir was a slight irritant to the rabbit eye, but showed no potential for antigenicity in the rat or guinea pig, and was not a dermal sensitizer in the guinea pig.

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PART III: CONSUMER INFORMATION

[Pr]AGENERASE™
amprenavir

This leaflet is part III of a three-part "Product Monograph" published when AGENERASE™ was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about AGENERASE™. Please read this leaflet carefully before you start to take AGENERASE™. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

What the medication is used for:
The name of your medicine is AGENERASE™ (amprenavir). AGENERASE™ can only be obtained with a prescription from your doctor.

AGENERASE™ is used in combination with other antiretroviral agents to reduce the human immunodeficiency virus (HIV) in your blood.

What it does:
The human immunodeficiency virus (HIV) is a retrovirus. Infection with HIV damages the immune system and can lead to Acquired Immune Deficiency Syndrome (AIDS) and other related illnesses.

AGENERASE™ is an antiretroviral medication. It belongs to a group of medicines called protease inhibitors. AGENERASE™ in combination with other antiretroviral agents reduces HIV in your blood. Response to treatment with AGENERASE™ varies between patients. Your doctor will be monitoring the effectiveness of your treatment. AGENERASE™ does not cure AIDS or kill the virus, but may help to prevent further damage to the immune system by slowing the production of new viruses.

When it should not be used:
AGENERASE™ must not be taken if you are allergic to the active substance amprenavir, any of the other ingredients found in AGENERASE™, or sulfonamide containing drugs. If you are not sure please consult with your doctor.

AGENERASE™ oral solution contains a large quantity of vitamin E. Avoid taking vitamin E supplements or any products containing vitamin E.

You should not use products containing St. John's Wort (*Hypericum perforatum*) because co-administration may reduce the effectiveness of AGENERASE™.

What the medicinal ingredient is:
Each millilitre of AGENERASE™ 15 mg/mL oral solution contains 15 mg of amprenavir.

What the important nonmedicinal ingredients are:
AGENERASE™ 15 mg/mL oral solution contains the non-medicinal ingredients acesulfame potassium, artificial grape/bubblegum flavour, citric acid (anhydrous), vitamin E (d-alpha tocopheryl polyethylene glycol 1000 succinate (TPGS)), menthol, natural peppermint flavour, polyethylene glycol 400 (PEG 400), propylene glycol, saccharin sodium, sodium chloride and sodium citrate (dihydrate).

AGENERASE™ capsules and AGENERASE™ oral solution are not interchangeable on a milligram per milligram basis.

What dosage forms it comes in:
Each bottle contains 240 mL of AGENERASE™ 15 mg/mL oral solution.

WARNINGS AND PRECAUTIONS

AGENERASE™ oral solution should not be used in infants and children below the age of 4 years, pregnant women, patients with liver or kidney failure, and patients receiving disulfiram or metronidazole.

AGENERASE™ oral solution contains a large amount of propylene glycol, a liquid needed to dissolve amprenavir.

Because of the possible side effects of the large amount of propylene glycol, AGENERASE™ oral solution should be used only when AGENERASE™ capsules or other protease inhibitor formulations are not options.

You should not switch from AGENERASE™ capsules to AGENERASE™ oral solution without talking to your doctor.

If you are a woman or a patient of Asian origin or Aboriginal, or if you have liver or kidney disease, you may be at increased risk of side effects from the large amount of propylene glycol in AGENERASE™ oral solution.

Medications not to be taken while taking AGENERASE™
Protease inhibitors, including AGENERASE™, may interact with other drugs, including those you take without a prescription. Before you take AGENERASE™, tell your doctor about any drugs that you are taking or planning to take, including nonprescription drugs.

You should not take any of the following medications with AGENERASE™ oral solution because serious or life-threatening problems could occur: astemizole, cisapride, diazepam, ergot medications, flurazepam, midazolam, pimozide, terfenadine, or triazolam.

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.

Drinking alcoholic beverages is not recommended while taking AGENERASE™ oral solution because it may increase side effects related to propylene glycol content.

Special Warnings
AGENERASE™ helps to control the amount of HIV found in your blood but is not a cure for HIV infection. You will need to take AGENERASE™ every day. Do not stop taking AGENERASE™ without first talking to your doctor.

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

You may continue to develop other infections and other illnesses associated with HIV disease. You should therefore keep in regular contact with your doctor while taking AGENERASE™.

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 hemophilia taking protease inhibitors.

AGENERASE™ oral solution should be used with caution if you have limited liver enzyme activity, kidney impairment or a genetically lower ability to metabolize alcohol (e.g. of Asian origin) due to adverse reactions that may be related to the propylene glycol in the solution.

Use Of This Medicine During Pregnancy and Breast Feeding
AGENERASE™ oral solution should not be used by pregnant women. Talk to your doctor if you are pregnant or if you become pregnant while taking AGENERASE™ oral solution.

Mothers with HIV should not breastfeed their infants because HIV in the breast milk can infect the infant.

Driving and Operating Machinery
There is no information currently available that suggests that taking AGENERASE™ affects the ability to drive or operate machinery, however it is suggested that you do not drive or operate machinery until you know how you react to AGENERASE™ oral solution.

INTERACTIONS WITH THIS MEDICATION

Some drugs may change the usefulness and safety of AGENERASE™. It is important that you tell your doctor about all the medicines you are taking or planning to take, including all those that you have bought yourself. This is very important, as using more than one medicine at the same time can strengthen or weaken the effect of the medicine, causing in some cases serious medical conditions.

AGENERASE™ may interact with other medicines you are being treated with. Some of the medicines that can interact with amprenavir include: amiodarone, phenobarbital, phenytoin, lidociane (systemic), tricyclic antidepressants, warfarin, sildenafil, cholesterol-lowering drugs, and quinidine.

If you are taking antacids (or didanosine) you should take AGENERASE™ at least 1 hour before or after antacid (or didanosine) use.

AGENERASE™ may also interact with the hormones in the contraceptive pill, injection or patch. If you are taking hormonal contraceptives, it is recommended that you use an alternative method to prevent pregnancy while you are taking AGENERASE™.

PROPER USE OF THIS MEDICATION

Usual dose:
Take AGENERASE™ oral solution exactly as your doctor prescribes it. AGENERASE™ oral solution can be taken with or without food. However, you should not take AGENERASE™ with a high-fat meal because this could reduce the effectiveness of AGENERASE™ oral solution. If you are unsure about how to take it, ask your doctor or pharmacist.

Overdose:
You should immediately contact either your doctor, your hospital emergency department or the nearest poison control centre.

Missed Dose:
If you forget to take AGENERASE™, take it as soon as you remember. Then continue as before.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

The following undesirable effects are thought to be related to treatment with AGENERASE™; nausea, diarrhea, mood disorders, rash, tingling sensation around the mouth, fatigue, headache, abdominal pain and vomiting.

Changes in body fat have been seen in some patients taking antiretroviral therapy. These changes may include increased amount of fat in the upper back and neck ("buffalo hump"), breasts, and around the trunk. Loss of fat from the legs, arms, and face may also happen. The cause and long-term health effects of these conditions are not known at this time.

Possible side effects from the large amount of propylene glycol in AGENERASE™ oral solution include seizures, drowsiness, fast heart rate, and kidney and blood abnormalities.

Your doctor will test your blood regularly to check for increases in liver enzymes and blood fats. These have been reported in patients taking AGENERASE™.

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 undesirable effect, even those not mentioned in this leaflet. If you feel ill in any other way that you do not understand, tell your doctor or pharmacist.

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

If you have a severe skin rash, check with your doctor and he may advise you to stop taking AGENERASE™.

This is not a complete list of side effects. For any unexpected effects while taking AGENERASE™, contact your doctor or pharmacist.

HOW TO STORE IT

Store AGENERASE™ oral solution between 5° to 25°C.

Do not take AGENERASE™ after the expiry date on the container.

As with all medications, keep AGENERASE™ out of reach of children.

REPORTING SUSPECTED SIDE EFFECTS

To monitor drug safety, Health Canada collects information on serious and unexpected effects of drugs. If you suspect you have had a serious or unexpected reaction to this drug you may notify Health Canada by:

toll-free telephone: 866-234-2345
toll-free fax 866-678-6789
By email: cadrmp@hc-sc.gc.ca

By regular mail:
National AR Centre
Marketed Health Products Safety and Effectiveness Information Division
Marketed Health Products Directorate
Tunney's Pasture, AL 0701C
Ottawa ON K1A 0K9

NOTE: Before contacting Health Canada, you should contact your physician or pharmacist.

MORE INFORMATION

Remember: AGENERASE™ is for you. Never give it to someone else. It may harm them even if their symptoms are the same as yours.

This leaflet does not tell you everything about AGENERASE™. If you have any questions or are not sure about anything, then ask your doctor or pharmacist. You may need to read this leaflet again. Please do not throw this leaflet away until you are no longer taking AGENERASE™.

This document plus the full product monograph, prepared for health professionals can be found at:
http://gsk.ca
or by contacting the sponsor, GlaxoSmithKline Inc., at:
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Mississauga, Ontario
L5N 6L4
1-800-387-7374

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