

PRODUCT MONOGRAPH

Pr AGENERASE™

amprenavir

50 mg and 150 mg capsules

Antiretroviral Agent

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Date of Preparation:
October 30, 2001

Date of Revision:
June 27, 2005

Submission Control No: 097413

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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	Capsules/ 50 and 150 mg	d-alpha tocopheryl polyethylene glycol 1000 succinate (TPGS), polyethylene glycol 400 (PEG 400), propylene glycol, d-sorbitol and sorbitans solution, gelatin, glycerin, and titanium dioxide.

INDICATIONS AND CLINICAL USE

AGENERASE™ (amprenavir) is indicated for:

- 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 naïve patients, AGENERASE™ is less effective than indinavir.

CONTRAINDICATIONS

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

- Due to the potential risk of toxicity from the high propylene glycol content of AGENERASE™ oral solution, that formulation is contraindicated in infants and children younger than 4 years of age, pregnant women, patients with hepatic or renal failure, and patients treated with disulfiram or metronidazole. Consult the Product Monograph for AGENERASE™ oral solution for full information.
- AGENERASE™ in combination with ritonavir is contraindicated in patients with severe hepatic impairment.
- 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

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™ (amprenavir). 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 P450 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.

Because of the potential toxicity from the large amount of the excipient propylene glycol contained in AGENERASE™ oral solution, that formulation is contraindicated in certain patient populations and should be used with caution in others. Consult the Product Monograph for AGENERASE™ oral solution for full information.

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 150 mg capsule contains 109 IU vitamin E. The maximum daily dose of AGENERASE™ capsules corresponds to vitamin E intake of approximately 1750 IU/day.

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

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

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. Please see the Product Monograph for AGENERASE™ oral solution for full information.

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™ capsules are 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 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.

Given the vitamin E content of AGENERASE™ capsules, patients should be advised that supplemental vitamin E is not recommended.

Carcinogenesis and Mutagenesis

Data from long term carcinogenicity studies with amprenavir have 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 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 relationship between protease inhibitor therapy and these events has 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

There are no adequate and well-controlled studies in pregnant women. Animal reproduction studies are not always predictive of human response, therefore administration of AGENERASE™ in pregnancy should be considered only if the benefit to the mother outweighs the possible risk to the fetus.

AGENERASE™ oral solution is contraindicated during pregnancy due to the potential risk of toxicity to the fetus from the high propylene glycol content.

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

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.

AGENERASE™ oral solution is contraindicated in infants and children below the age of 4 years due to the potential risk of toxicity from the large amount of the excipient propylene glycol. Please see the Product Monograph for AGENERASE™ oral solution for full information.

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

Geriatrics (65 years of age)

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 $\geq 1\%$ of Patients				
Adverse Events by body system	Study 3001		Study 3006	
	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%

* 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 practices. Because they are 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 in 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.

Pharmacokinetic Parameters for Amprenavir in the Presence of the Coadministered Drug			Coadministered 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 of 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		
<ul style="list-style-type: none">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.
<ul style="list-style-type: none">Itraconazole	Plasma concentrations may be affected.	Itraconazole may have its plasma concentrations increased by amprenavir. Itraconazole may increase serum concentrations of amprenavir.
<ul style="list-style-type: none">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.
<ul style="list-style-type: none">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		
<ul style="list-style-type: none">Protease inhibitors (PIs) – Ritonavir	The pharmacokinetic parameters of amprenavir are affected when both drugs are administered in combination.	<p>The AUC, C_{min} and C_{max} of amprenavir were increased by 131%, 484% and 33%, respectively, when ritonavir (200mg twice daily) was given in combination with amprenavir (1200mg twice daily) in adults.</p> <p>When given in combination in adults, reduced doses of both medicinal products should be used (see DOSAGE & ADMINISTRATION section).</p> <p>In clinical trials, doses of amprenavir 600mg twice daily and ritonavir 100mg twice daily have been used; confirming safety and efficacy of this regimen. Amprenavir oral solution and ritonavir oral solution should not be coadministered (see AGENERASE™ Oral Solution Product Monograph).</p> <p>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.</p>

Table 3: Established or Potential Drug-Drug Interactions

Proper name	Effect	Clinical comment
Nucleoside analogue reverse transcriptase inhibitors (NRTIs)		
<ul style="list-style-type: none">Didanosine	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.
<ul style="list-style-type: none">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™.
<ul style="list-style-type: none">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.
<ul style="list-style-type: none">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).
<ul style="list-style-type: none">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.

Table 3: Established or Potential Drug-Drug Interactions

Proper name	Effect	Clinical comment
<ul style="list-style-type: none">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.
<ul style="list-style-type: none">HMG-CoA reductase inhibitors	May increase the risk of myopathy including rhabdomyolysis.	<p>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.</p> <p>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.</p>
<ul style="list-style-type: none">Methadone	<p>The pharmacokinetic parameters of both drugs are affected when administered in combination.</p> <p>Coadministration may result in possible methadone underdosing.</p>	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.
<ul style="list-style-type: none">Steroids	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.
<ul style="list-style-type: none">St. John's Wort	May result in reduced plasma concentrations of amprenavir.	Patients on AGENERASE™ should not use products containing St. John's Wort (<i>Hypericum perforatum</i>) since it may result in reduced plasma concentrations of amprenavir (see WARNINGS AND PRECAUTIONS section).

Table 3: Established or Potential Drug-Drug Interactions

Proper name	Effect	Clinical comment
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.

Formulations of AGENERASE™ provide high daily doses of vitamin E. Each 150 mg capsule contains 109 IU vitamin E. The maximum daily dose of AGENERASE™ capsules corresponds to vitamin E intake of approximately 1750 IU/day.

AGENERASE™ is available as an oral solution for use in patients unable to swallow capsules (see Product Monograph for AGENERASE™ oral solution for complete information). Patients should discontinue AGENERASE™ oral solution as soon as they are able to swallow the capsule formulation (see CONTRAINDICATIONS and WARNINGS AND PRECAUTIONS sections). 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.

Recommended Dose and Dosage Adjustment

Adults and Adolescents greater than 12 years of age

The recommended oral dose in adults and adolescents greater than 12 years of age is 600 mg of AGENERASE™ (four 150 mg capsules) twice a day plus 100 mg of ritonavir twice a day in combination with other antiretroviral agents. The full prescribing information for ritonavir must be consulted prior to initiation of therapy with AGENERASE™ and ritonavir.

If AGENERASE™ is used with other antiretroviral agents, excluding ritonavir, 1200 mg (eight 150 mg capsules) of AGENERASE™ twice a day should be used.

Children from 4 to 12 years

At present, the use of AGENERASE™ in children is not recommended although dosing recommendations are provided for information (see ACTIONS AND CLINICAL PHARMACOLOGY, Pediatric Patients section).

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

For subjects with hepatic impairment, pharmacokinetic data are available for the use of AGENERASE™ capsules without the boosting effect of ritonavir.

AGENERASE™ capsules should be used with caution in patients with moderate or severe hepatic impairment.

Patients with a Child-Pugh score ranging from 5 to 8 should receive a reduced dose of 450 mg twice daily, and patients with a Child-Pugh score ranging from 9 to 12 should receive 300 mg twice daily. These dosing regimens will provide plasma amprenavir levels comparable to those achieved in healthy subjects given a 1200 mg dose twice daily without concomitant administration of ritonavir (see ACTIONS AND CLINICAL PHARMACOLOGY, Adults with Impaired Hepatic Function section).

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

Patients with Renal Impairment

No initial dose adjustment is considered necessary in patients with renal impairment.

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. Although no data is available, administration of activated charcoal may be used to aid in removal of unabsorbed drug.

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: $6.18 \pm 2.92 \mu\text{g/mL}$, fasted: $9.72 \pm 2.75 \mu\text{g/mL}$), T_{max} (fed: $1.51 \pm 0.68\text{h}$, fasted: $1.05 \pm 0.63\text{h}$), and AUC (fed: $22.06 \pm 11.6 \mu\text{g}\cdot\text{h/mL}$, fasted: $28.05 \pm 10.1 \mu\text{g}\cdot\text{h/mL}$).

AGENERASE™ may be taken with or without food, but should not be taken with a high-fat meal (see DOSAGE AND ADMINISTRATION section).

Special Populations and Conditions

Adults With Impaired Renal Function

This population has not been studied. The renal elimination of unchanged amprenavir represents < 3% of the administered dose.

Adults with Impaired Hepatic Function

AGENERASE™ has been studied in adult patients with impaired hepatic function using a single oral dose of 600mg. The $AUC_{0-\infty}$ was significantly greater in patients with moderate cirrhosis ($25.76 \pm 14.68 \mu\text{g}\cdot\text{h/mL}$) compared with healthy volunteers ($12.00 \pm 4.38 \mu\text{g}\cdot\text{h/mL}$). The $AUC_{0-\infty}$ and C_{max} were significantly greater in patients with severe cirrhosis ($AUC_{0-\infty}$: $38.66 \pm 16.08 \mu\text{g}\cdot\text{h/mL}$; C_{max} : $9.43 \pm 2.61 \mu\text{g/mL}$) compared with healthy volunteers ($AUC_{0-\infty}$: $12.00 \pm 4.38 \mu\text{g}\cdot\text{h/mL}$; C_{max} : $4.90 \pm 1.39 \mu\text{g/mL}$). Patients with impaired hepatic function require dosage adjustment (see DOSAGE AND ADMINISTRATION section).

Pediatric Patients

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.

At present, the use of AGENERASE™ in children is not recommended, however, if AGENERASE™ capsules are used in this population, an oral dose of 20 mg/kg twice a day or 15 mg/kg three times a day, in combination with other antiretroviral agents, up to a maximum daily dose of 400 mg should be used.

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.

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.

AGENERASE™ oral solution is contraindicated in infants and children below the age of 4 years due to the potential risk of toxicity from the large amount of the excipient propylene glycol. Please see the Product Monograph for AGENERASE™ oral solution for full information.

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.

STORAGE AND STABILITY

Capsules

AGENERASE™ capsules should be stored between 15° and 30°C.

SPECIAL HANDLING INSTRUCTIONS

Not applicable.

DOSAGE FORMS, COMPOSITION AND PACKAGING

AGENERASE™ (amprenavir) capsules, 50 mg, are oblong, opaque off-white to cream-coloured soft gelatin capsules printed with "GX CC1" on one side. They are available in bottles of 480 capsules.

AGENERASE™ capsules, 150 mg, are oblong, opaque off-white to cream-coloured soft gelatin capsules printed with "GX CC2" on one side. They are available in bottles of 240 capsules.

Composition

Capsules

AGENERASE™ capsules are available for oral administration in strengths of 50 and 150 mg. Each capsule contains the active ingredient amprenavir and the inactive ingredients d-alpha tocopheryl polyethylene glycol 1000 succinate (TPGS), polyethylene glycol 400 (PEG 400), and propylene glycol. The capsule shell contains the inactive ingredients d-sorbitol and sorbitans solution, gelatin, glycerin, and titanium dioxide. The soft gelatin capsules are printed with edible red ink.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

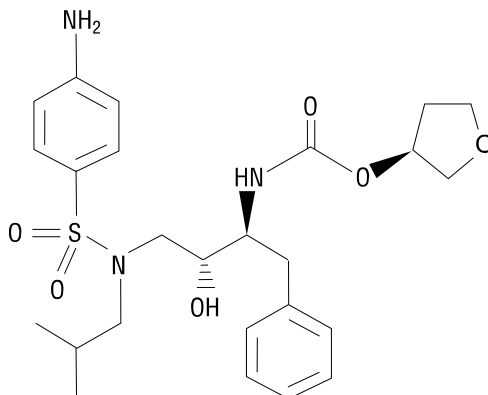
Drug Substance

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: C₂₅H₃₅N₃O₆S 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 (V_z/F) is approximately 430 L 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 0.6 nM. 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 (IC₅₀) 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 IC₅₀. 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 I54I/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 fecal 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 μ g•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 mortality also led 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).

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 F₁ or F₂ pups following oral administration to F₀ 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™ capsules contain 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:

AGENERASE™ contains the active ingredient amprenavir.

What the important nonmedicinal ingredients are:

Each capsule contains the inactive ingredients vitamin E (d-alpha tocopheryl polyethylene glycol 1000 succinate (TPGS)), polyethylene glycol 400 (PEG 400), and propylene glycol. The capsule shell contains the inactive ingredients d-sorbitol and sorbitans solution, gelatin, glycerin, and titanium dioxide. The soft gelatin capsules are printed with edible red ink.

What dosage forms it comes in:

Each bottle of AGENERASE™ 50 mg capsules contains 480 capsules. Each bottle of AGENERASE™ 150 mg capsules contains 240 capsules.

WARNINGS AND PRECAUTIONS**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™ capsules because serious or life-threatening problems could occur: astemizole, cisapride, diazepam, ergot medications, flurazepam, midazolam, pimozone, terfenadine, or triazolam.

You should also not take rifampin with AGENERASE™ capsules because this drug reduces the effectiveness of AGENERASE™.

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.

Use Of This Medicine During Pregnancy and Breast Feeding

If you are pregnant, or planning on becoming pregnant soon, or if you are breast feeding please inform your doctor before taking any medicines. The safe use of AGENERASE™ in human pregnancy has not been established. Your doctor will advise whether you should continue to take AGENERASE™.

The active substance amprenavir in AGENERASE™ is likely to be found in human breast milk. There are no safety data available following treatment with AGENERASE™ in babies. Mothers with HIV should not breast feed their infants because HIV in the breast milk can infect the infant.

Driving and Operating Machinery

There is no information currently available that suggests taking AGENERASE™ affects the ability to drive or operate machinery.

INTERACTIONS WITH THIS MEDICATION

Some drugs change the usefulness and safety of AGENERASE™. It is important that you tell your doctor about all the medicines you're 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, lidocaine (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 interact with the hormones in the contraceptive pill, injection or patch. If you are taking oral hormonal contraceptives, it is recommended that you use an alternative method to prevent pregnancy while taking AGENERASE™.

PROPER USE OF THIS MEDICATION

Usual dose:

Take AGENERASE™ as your doctor has advised you.

AGENERASE™ capsules should be swallowed whole with water.

AGENERASE™ 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™ capsules. If you are unsure about how to take it, ask your doctor or pharmacist.

The recommended oral dose in adults and adolescents greater than 12 years of age is 600 mg of AGENERASE™ (four 150 mg capsules) twice a day plus 100 mg of ritonavir twice a day in combination with other antiretroviral agents.

If AGENERASE™ is used with other antiretroviral agents, excluding ritonavir, 1200 mg (eight 150 mg capsules) of AGENERASE™ twice a day should be used.

The combined use of AGENERASE™ and ritonavir is not recommended in children.

An oral solution (15 mg/mL) is available for the treatment of patients unable to swallow capsules. **Do not** switch to oral solution without talking to your Doctor.

If you have a liver problem your dose may be reduced. In patients with more severe forms of liver disease, AGENERASE™ capsules should not be taken together with ritonavir.

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, rash, tingling sensation around the mouth, fatigue, mood disorders, 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.

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.

This leaflet was prepared by GlaxoSmithKline Inc.

Last revised: June 14, 2005

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HOW TO STORE IT

Store AGENERASE™ capsules between 15° and 30°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://www.gsk.ca> or by contacting the sponsor, GlaxoSmithKline Inc., at:

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