

Saquinavir mesylate

MAXIMUNE Tablets

COMPOSITION

Each film-coated tablet contains
Saquinavir mesylate IP equivalent to
Saquinavir IP...500 mg
Colour: Red oxide of Iron

DOSAGE FORM

Oral, film-coated tablet

DESCRIPTION

Saquinavir has been made available in various formulations – 200 mg hard gelatin capsules, 200 mg soft gelatin capsules and 500 mg tablets. The 200 mg hard gelatin capsule and the 500 mg tablet are bioequivalent. The soft gelatin formulation has greater bioavailability. However the soft gelatin formulation has been withdrawn from the market.

PHARMACOLOGY

Pharmacodynamics

Saquinavir is an inhibitor of HIV protease. HIV protease is an enzyme required for the proteolytic cleavage of viral polyprotein precursors into individual functional proteins found in infectious HIV. Saquinavir is a peptide-like substrate analogue that binds to the protease active site and inhibits the activity of the enzyme. Saquinavir inhibition prevents cleavage of the viral polyproteins resulting in the formation of immature non-infectious virus particles.

QTcS interval was evaluated in a randomized, placebo and active (moxifloxacin 400 mg once daily) controlled crossover study in 59 healthy adults, with ECG measurements on Day 3. The maximum mean (95% upper confidence bound) differences in QTcS interval from placebo after baseline-correction were 18.9 (22.0) and 30.2 (33.4) ms for 1000/100 mg twice daily and suprathreshold 1500/100 mg twice daily of saquinavir/ritonavir, respectively. There is a delayed effect between QTc interval change and drug concentrations, with the maximum placebo-adjusted baseline-corrected QTcS observed at about 12-20 h post-dose. Saquinavir /ritonavir 1500/100 mg twice daily resulted in a Day 3 mean C_{max} of saquinavir approximately 1.4-fold higher than the mean C_{max} observed on Day 3 with the approved therapeutic dose in healthy volunteers (within the same study). QTcS in this study was $QT/RR^{0.319}$ for males and $QT/RR^{0.337}$ for females, which are similar to Fridericia's correction ($QTcF=QT/RR^{0.3333}$).

PR and QRS interval prolongations were also noted in subjects receiving saquinavir /ritonavir in the same study on Day 3. The maximum mean (95% upper confidence bound) difference from placebo in the PR interval after baseline-correction were 28.6 (31.6) and 38.4 (41.4) ms for 1000/100 mg twice daily and supratherapeutic 1500/100 mg twice daily saquinavir/ritonavir respectively. The maximum mean (95% upper confidence bound) difference from placebo in QRS interval after baseline correction were 2.9 (3.9) and 4.4 (5.3) ms for 1000/100 mg twice daily and supratherapeutic 1500/100 mg twice daily saquinavir /ritonavir respectively. In this study using healthy subjects, PR interval prolongation of >200 ms was also observed in 40% and 47% of subjects receiving saquinavir/ritonavir 1000/100 mg bid and 1500/100 mg bid, respectively, on Day 3. Three (3%) of subjects in the active control moxifloxacin arm and 5% in the placebo arm experienced PR prolongation of >200 ms.

Pharmacokinetics

The pharmacokinetics of saquinavir/ritonavir 1000/100 mg twice daily have been evaluated in HIV infected patients and healthy subjects. Steady-state saquinavir AUC, Cmax, and Cmin in healthy subjects are approximately 50% higher than observed in HIV infected patients.

Absorption and Bioavailability in Adults

Similar bioavailability was demonstrated when saquinavir mesylate 500 mg film coated tablet (2 x 500 mg) and saquinavir mesylate 200 mg capsule (5 x 200 mg) were administered with low-dose ritonavir (100 mg) under fed conditions. The ratio of mean exposures (90% confidence intervals) of tablets vs. capsules were 1.10 (1.04-1.16) for AUC_{0-α} and 1.19 (1.14 – 1.25) for C_{max}.

Absolute bioavailability of saquinavir administered as saquinavir mesylate averaged 4% (CV 73%, range: 1% to 9%) in 8 healthy volunteers who received a single 600-mg dose (3 x 200 mg) of saquinavir mesylate following a high-fat breakfast (48 g protein, 60 g carbohydrate, 57 g fat; 1006 kcal). The low bioavailability is thought to be due to a combination of incomplete absorption and extensive first-pass metabolism.

Saquinavir mesylate tablets in combination with ritonavir at doses of 1000/100 mg bid or 400/400 mg bid provides saquinavir systemic exposures over a 24-hour period similar to or greater than those achieved with saquinavir soft gelatin capsules 1200 mg t.i.d.

Table1: Pharmacokinetic Parameters of Saquinavir at Steady-State After Administration of Different Regimens in HIV-1 Infected Patients

Dosing Regimen	N	AUC ^T (ng·h/mL)	AUC _{24h} (ng·h/mL)	Cmin (ng/mL)
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Saquinavir 600 mg tid (arithmetic mean, %CV)	10	866 (62)	2598	79
Saquinavir soft gel capsules (FORTOVASE) 1200 mg tid (arithmetic mean)	31	7249	21747	216
Saquinavir 1000 mg bid + ritonavir 100 mg bid (geometric mean and 95% CI)	24	14607 (10218-20882)	29214	371 (245-561)
Saquinavir soft gel capsules 1000 mg bid + ritonavir 100 mg bid (geometric mean and 95% CI)	24	19085 (13943-26124)	38170	433 (301-622)

[†] is the dosing interval (i.e., 8h if three times daily and 12h if twice daily)

Food effect

The mean 24-hour AUC after a single 600-mg oral dose (6 x 100 mg) in healthy volunteers (n=6) was increased from 24 ng.h/mL (CV 33%), under fasting conditions, to 161 ng.h/mL (CV 35%) when saquinavir mesylate tablets was given following a high-fat breakfast (48 g protein, 60 g carbohydrate, 57 g fat; 1006 kcal). Saquinavir 24-hour AUC and C_{max} (n=6) following the administration of a higher calorie meal (943 kcal, 54 g fat) were on average 2 times higher than after a lower calorie, lower fat meal (355 kcal, 8 g fat). The effect of food has been shown to persist for up to 2 hours. Saquinavir/ritonavir should be taken within 2 hours after a meal.

Distribution in Adults

The mean steady-state volume of distribution following intravenous administration of a 12-mg dose of saquinavir (n=8) was 700 L (CV 39%), suggesting saquinavir partitions into tissues. Saquinavir was approximately 98% bound to plasma proteins over a concentration range of 15 to 700 ng/mL. In 2 patients receiving saquinavir mesylate 600 mg t.i.d, cerebrospinal fluid concentrations were negligible when compared to concentrations from matching plasma samples.

Metabolism and Elimination in Adults

In vitro studies using human liver microsomes have shown that the metabolism of saquinavir is cytochrome P450 mediated with the specific isoenzyme, CYP3A4, responsible for more than 90% of the hepatic metabolism. Based on *in vitro* studies, saquinavir is rapidly metabolised to a range of mono- and di-hydroxylated inactive compounds. In a mass balance study using 600 mg ¹⁴C-saquinavir mesylate (n=8), 88% and 1% of the orally administered radioactivity was recovered in feces and urine, respectively, within 5 days of dosing. In mass balance studies, 13% of circulating radioactivity in plasma was attributed to unchanged drug after oral administration and the remainder attributed to saquinavir metabolites. Following intravenous administration, 66% of circulating radioactivity was attributed to unchanged drug and the remainder attributed to

saquinavir metabolites, suggesting that saquinavir undergoes extensive first-pass metabolism.

Systemic clearance of saquinavir was rapid, 1.14 L/h/kg (CV 12%) after intravenous doses of 6, 36 and 72 mg. The mean residence time of saquinavir was 7 hours (n = 8).

Special Population

Renal Impairment

Saquinavir pharmacokinetics in patients with hepatic or renal impairment has not been investigated (see Warnings and Precautions). Only 1% of saquinavir is excreted in the urine, so the impact of renal impairment on saquinavir elimination should be minimal.

Hepatic Impairment

The effect of hepatic impairment on the steady state pharmacokinetics of saquinavir/ritonavir (1000/100 mg bid for 14 days) was investigated in 7 HIV-1-infected patients with moderate liver impairment (6 with Child-Pugh score of 7 and 1 with Child-Pugh score of 9). The study included a control group consisting of 7 HIV-1-infected patients with normal hepatic function matched with hepatically impaired patients for age, gender, weight and tobacco use. The mean (% coefficient of variation in parentheses) values for saquinavir AUC₀₋₁₂ and C_{max} were 24.3 (102%) µg·hr/mL and 3.6 (83%) µg/mL, respectively, for HIV-1-infected patients with moderate hepatic impairment. The corresponding values in the control group were 28.5 (71%) µg·hr/mL and 4.3 (68%) µg/mL. The geometric mean ratio (ratio of pharmacokinetic parameters in hepatically impaired patients to patients with normal liver function) (90% confidence interval) was 0.7 (0.3 to 1.6) for both AUC₀₋₁₂ and C_{max}, which suggests approximately 30% reduction in saquinavir exposure in patients with moderate hepatic impairment. No dose adjustment is warranted for saquinavir in HIV-1-infected patients with mild or moderate hepatic impairment (see **WARNINGS AND PRECAUTIONS**)

Gender, Race and Age

A gender difference was observed, with females showing higher saquinavir exposure than males (mean AUC increase of 56%, mean C_{max} increase of 26%), in the relative bioavailability study comparing saquinavir mesylate 500 mg film-coated tablets to the saquinavir mesylate 200 mg hard gelatin capsules in combination with ritonavir. There was no evidence that age and body weight explained the gender difference in this study. A clinically significant difference in safety and efficacy between men and women has not been reported with the approved dosage regimen (saquinavir 1000-mg/ritonavir 100-mg bid).

The effect of race on the pharmacokinetics of saquinavir has not been investigated.

Pediatric Patients

The pharmacokinetics of saquinavir mesylate have not been sufficiently investigated in pediatric patients.

Geriatric Patients

The pharmacokinetics of saquinavir mesylate have not been sufficiently investigated in patients > 65 years of age.

INDICATIONS

MAXIMUNE in combination with ritonavir and other antiretroviral agents is indicated for the treatment of HIV infection.

DOSAGE AND ADMINISTRATION

MAXIMUNE must be used in combination with ritonavir, because it significantly inhibits saquinavir's metabolism to provide increased plasma saquinavir levels.

Adults (over the age of 16 years)

- **MAXIMUNE** 1000-mg b.i.d (2 x 500-mg tablets) in combination with ritonavir 100-mg bid.
- Ritonavir should be taken at the same time as **MAXIMUNE**
- **MAXIMUNE** and ritonavir should be taken within 2 hours after a meal.

Concomitant Therapy: MAXIMUNE with Lopinavir/Ritonavir

When administered with lopinavir/ritonavir 400/100 mg b.i.d, the appropriate dose of **MAXIMUNE** is 1000 mg b.i.d (with no additional ritonavir).

CONTRAINDICATIONS

MAXIMUNE must be used in combination with ritonavir, which significantly inhibits saquinavir's metabolism and provides increased plasma saquinavir levels.

Do not use in patients with congenital long QT syndrome, those with refractory hypokalemia or hypomagnesemia, and in combination with drugs that both increase saquinavir plasma concentrations and prolong the QT interval (see **WARNINGS AND PRECAUTIONS**).

MAXIMUNE is contraindicated in patients with complete atrioventricular (AV) block without implanted pacemakers, or patients who are at high risk of complete AV block (see **WARNINGS AND PRECAUTIONS**).

MAXIMUNE is contraindicated in patients with clinically significant hypersensitivity to saquinavir or to any of the components contained in the tablet.

MAXIMUNE/ritonavir should not be administered concurrently with terfenadine, cisapride, astemizole, pimozide, triazolam, midazolam or ergot derivatives. Inhibition of CYP3A4 by saquinavir could result in elevated plasma

concentrations of these drugs, potentially causing serious or life-threatening reactions, such as cardiac arrhythmias or prolonged sedation (see **WARNINGS AND PRECAUTIONS: Drug Interactions**).

MAXIMUNE/ritonavir should not be given together with rifampin, due to the risk of severe hepatocellular toxicity if the three drugs are given together (see **WARNINGS AND PRECAUTIONS: Drug Interactions**).

MAXIMUNE when administered with ritonavir is contraindicated in patients with severe hepatic impairment.

MAXIMUNE should not be administered concurrently with drugs listed in Table 2 (also see **WARNINGS AND PRECAUTIONS: Drug Interactions**, Table 3).

Table 2: Drugs That Are Contraindicated With MAXIMUNE/Ritonavir

Drug Class	Drugs Within Class That Are Contraindicated With MAXIMUNE	Clinical Comment
Alpha 1-adrenoreceptor antagonist	Alfuzosin	Potentially increased alfuzosin concentrations can result in hypotension.
Antiarrhythmics	Amiodarone, bepridil, flecainide, dofetilide, propafenone, lidocaine (systemic), quinidine,	Potential for serious and/or life-threatening cardiac arrhythmia.
Antidepressant	Trazodone	Increased trazodone concentrations can result in potentially life-threatening cardiac arrhythmia.
HMG-CoA Reductase Inhibitors	Lovastatin, Simvastatin	Potential for myopathy including rhabdomyolysis.
Ergot Derivatives	Dihydroergotamine, ergonovine, ergotamine, methylergonovine	Potential for serious and life threatening reactions such as ergot toxicity characterized by peripheral vasospasm and ischemia of the extremities and

		other tissues.
Antimycobacterial Agents	Rifampin	Rifampin should not be administered in patients taking ritonavir-boosted saquinavir part of an ART regimen due to the risk of severe hepatocellular toxicity.
GI Motility Agent	Cisapride	Potential for serious and/or life threatening reactions such as cardiac arrhythmias.
PDE5 Inhibitors	Sildenafil (for treatment of pulmonary arterial hypertension)	Increased potential for sildenafil-associated adverse events (which include visual disturbances, hypotension, prolonged erection, and syncope). A safe and effective dose has not been established when used with saquinavir/ritonavir.
Neuroleptics	Pimozide	Potential for serious and/or life threatening reactions such as cardiac arrhythmias.
Sedative/Hypnotics	Triazolam, midazolam	Potential for serious and/or life threatening reactions such as prolonged or increased sedation or respiratory depression.

		<p>Triazolam and orally administered midazolam are extensively metabolized by CYP3A4. Coadministration of triazolam and orally administered midazolam with saquinavir/ritonavir may cause large increases in the concentration of these benzodiazapines.</p>
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WARNINGS AND PRECAUTIONS

ALERT: Find out about medicines that should not be taken with **MAXIMUNE**. **MAXIMUNE** should always be co-administered with ritonavir.

General

If a serious or severe toxicity occurs during treatment with **MAXIMUNE**, **MAXIMUNE** should be interrupted until the etiology of the event is identified or the toxicity resolves. At that time, resumption of treatment with full-dose **MAXIMUNE** may be considered. For antiretroviral agents used in combination with saquinavir mesylate, physicians should refer to the complete product information for these drugs for dose adjustment recommendations and for information regarding drug-associated adverse reactions.

The combination **MAXIMUNE**/ritonavir is a potent inhibitor of CYP3A and may significantly increase the exposure of drugs primarily metabolized by CYP3A. See Table 1 for a listing of drugs that are contraindicated for use with **MAXIMUNE** /ritonavir due to potentially life-threatening adverse events or significant drug interactions [see **Contraindications**]. See Table 3 for established and other potentially significant drug interactions [see **Drug Interactions**].

PR Interval Prolongation

Saquinavir/ritonavir prolongs the PR interval in a dose-dependent fashion. Cases of second or third degree atrioventricular block have been reported rarely. Patients with underlying structural heart disease, pre-existing conduction system abnormalities, cardiomyopathies and ischemic heart disease may be at increased risk for developing cardiac conduction abnormalities. ECG monitoring is recommended in these patients (see **WARNINGS AND PRECAUTIONS**).

The impact on the PR interval of co-administration of saquinavir/ritonavir with other drugs that prolong the PR interval (including calcium channel blockers, beta-adrenergic blockers, digoxin and atazanavir) has not been evaluated. As a result, co-administration of saquinavir/ritonavir with these drugs should be undertaken with caution, particularly with those drugs metabolized by CYP3A, and clinical monitoring is recommended (see **CLINICAL PHARMACOLOGY**).

QT Interval Prolongation

Saquinavir/ritonavir causes dose-dependent QT prolongation. Torsades de pointes has been reported rarely post-marketing. Avoid saquinavir/ritonavir in patients with long QT syndrome. ECG monitoring is recommended if therapy is initiated in patients with congestive heart failure, bradyarrhythmias, hepatic impairment and electrolyte abnormalities. Correct hypokalemia or hypomagnesemia prior to initiating saquinavir/ritonavir and monitor these electrolytes periodically during therapy. Do not use in combination with drugs that both increase saquinavir plasma concentrations and prolong the QT interval (see **Tables 1**) (see **CLINICAL PHARMACOLOGY**).

Patients initiating therapy with ritonavir-boosted Saquinavir.

An ECG should be performed prior to initiation of treatment. Patients with a QT interval > 450 msec should not receive ritonavir-boosted Saquinavir. For patients with a QT interval < 450 msec, an on-treatment ECG is suggested after approximately 3 to 4 days of therapy; patients with a QT interval > 480 msec or prolongation over pre-treatment by > 20 msec should discontinue ritonavir-boosted Saquinavir.

Patients requiring treatment with medications with the potential to increase the QT interval and concomitant ritonavir-boosted Saquinavir.

Such combinations should only be used where no alternative therapy is available and the potential benefits outweigh the potential risks. An ECG should be performed prior to initiation of the concomitant therapy, and patients with a QT interval > 450 msec should not initiate the concomitant therapy. If baseline QT interval < 450 msec, an on-treatment ECG should be performed after 3-4 days of therapy. For patients demonstrating a subsequent increase in QT interval to > 480 msec or increase by > 20 msec after commencing concomitant therapy, the physician should use best clinical judgment to discontinue either ritonavir-boosted Saquinavir or the concomitant therapy or both.

A cardiology consult is recommended if drug discontinuation or interruption is being considered on the basis of ECG assessment.

Diabetes Mellitus and Hyperglycemia

New onset diabetes mellitus, exacerbation of preexisting diabetes mellitus and hyperglycemia have been reported during postmarketing surveillance in HIV-infected patients receiving protease-inhibitor therapy. Some patients required either initiation or dose adjustments of insulin or oral hypoglycemic agents for the 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 a causal relationship between protease-inhibitor therapy and these events has not been established.

Hepatotoxicity

In patients with underlying hepatitis B or C, cirrhosis, chronic alcoholism and/or other underlying liver abnormalities, there have been reports of worsening liver disease.

Hemophilia

There have been reports of spontaneous bleeding in patients with hemophilia A and B treated with protease inhibitors. In some patients additional factor VIII was required. In the majority of reported cases treatment with protease inhibitors was continued or restarted. A causal relationship between protease inhibitor therapy and these episodes has not been established.

Hyperlipidemia

Elevated cholesterol and/or triglyceride levels have been observed in some patients taking saquinavir in combination with ritonavir. Marked elevation in triglyceride levels is a risk factor for development of pancreatitis. Cholesterol and triglyceride levels should be monitored prior to initiating combination dosing regimen of **MAXIMUNE**/ritonavir, and at periodic intervals while on such therapy. In these patients, lipid disorders should be managed as clinically appropriate.

Lactose Intolerance

Each capsule contains lactose (anhydrous) 63.3 mg. This quantity should not induce specific symptoms of intolerance.

Fat Redistribution

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

Immune Reconstitution Syndrome

Immune reconstitution syndrome has been reported in patients treated with combination antiretroviral therapy, including saquinavir mesylate. During the initial phase of combination antiretroviral treatment, patients whose immune system responds may develop an inflammatory response to indolent or residual opportunistic infections (such as *Mycobacterium avium* infection, cytomegalovirus, *Pneumocystis jirovecii* pneumonia (PCP), or tuberculosis), which may necessitate further evaluation and treatment.

Resistance/Cross-resistance

Varying degrees of cross-resistance among protease inhibitors have been observed. Continued administration of **MAXIMUNE** therapy following loss of viral suppression may increase the likelihood of cross-resistance to other protease inhibitors.

Drug Interactions

Several drug interaction studies have been completed with both saquinavir mesylate hard and soft gelatin capsules. Because ritonavir is co-administered, prescribers should refer to the prescribing information for ritonavir regarding drug interactions associated with this drug.

Potential for MAXIMUNE to Affect Other Drugs

The combination saquinavir/ritonavir is a potent inhibitor of CYP3A and may significantly increase the exposure of drugs primarily metabolized by CYP3A. See Table 1 for a listing of drugs that are contraindicated for use with **MAXIMUNE** /ritonavir due to potentially life-threatening adverse events or significant drug interactions (see **CONTRAINDICATIONS**). **See Table 3 for established and other potentially significant drug interactions.**

Potential for Other Drugs to Affect MAXIMUNE

The metabolism of saquinavir is mediated by cytochrome P450, with the specific isoenzyme CYP3A4 responsible for 90% of the hepatic metabolism. Additionally, saquinavir is a substrate for P-Glycoprotein (Pgp). Therefore, drugs that affect CYP3A4 and/or Pgp, may modify the pharmacokinetics of saquinavir. Similarly, saquinavir might also modify the pharmacokinetics of other drugs that are substrates for CYP3A4 or Pgp.

Drugs that are contraindicated specifically due to the expected magnitude of interaction and potential for serious adverse events are listed in Table 1 under **CONTRAINDICATIONS**. Additional drugs that are not recommended for co-administration with saquinavir mesylate and ritonavir are included in Table 2. These recommendations are based on either drug interaction studies or predicted interactions due to the expected magnitude of interaction and potential for serious events or loss of efficacy.

Established and Other Potentially Significant Drug Interactions

Based on the finding of dose-dependent prolongations of QT and PR intervals in healthy volunteers receiving **MAXIMUNE**/ritonavir, additive effects on QT and/or PR interval prolongation may occur with certain members of the following drug classes: antiarrhythmics class IA or class III, neuroleptics, antidepressive agents, PDE5 inhibitors (when used for pulmonary arterial hypertension), antimicrobials, antihistaminics and others. This effect might lead to an increased risk of ventricular arrhythmias, notably torsades de pointes. Therefore, concurrent

administration of these agents with **MAXIMUNE** /ritonavir is contraindicated (see **CONTRAINDICATIONS**).

Table 3: Established and Other Potentially Significant Drug Interactions: Alteration in Dose or Regimen May Be Recommended Based on Drug Interaction Studies or Predicted Interaction (Information in the table applies to saquinavir mesylate /ritonavir)

Concomitant Drug Class: Drug Name	Effect on Concentration of Saquinavir or Concomitant Drug	Clinical Comment
HIV-Antiviral Agents		
Non-nucleoside reverse transcriptase inhibitors: Delavirdine ^b	↑ Saquinavir Effect on delavirdine is not well established	Appropriate doses of the combination with respect to safety and efficacy have not been established
Non-nucleoside reverse transcriptase inhibitors: Efavirenz ^a , nevirapine ^b	↓ Saquinavir ↓ Efavirenz	Appropriate doses of the combination of efavirenz or nevirapine and saquinavir mesylate /ritonavir with respect to safety and efficacy have not been established.
HIV-1 protease inhibitors: Atazanavir ^a	Saquinavir mesylate /ritonavir ↑ Saquinavir ↑ Ritonavir ↔ Atazanavir	No data are available on the combination of saquinavir mesylate /ritonavir 100 mg bid with atazanavir 300 mg od. Appropriate dosing recommendations for this combination, with respect to efficacy and safety, have not been established.
HIV-1 protease inhibitors: Indinavir ^b	↑ Saquinavir Effect on indinavir is not well established. Saquinavir mesylate /ritonavir Interaction has not been evaluated.	Appropriate doses of the combination of indinavir and saquinavir mesylate /ritonavir with respect to safety and efficacy have not been established.
HIV-1 protease	↔ Saquinavir	Evidence from several

inhibitors: Lopinavir/ritonavir ^a	↔ Lopinavir ↓ Ritonavir	clinical trials indicates that saquinavir concentrations achieved with the saquinavir and lopinavir/ritonavir combination are similar to those achieved following saquinavir/ritonavir 1000/100 mg. The recommended dose for this combination is saquinavir 1000 mg plus lopinavir/ritonavir 400/100 mg bid.
HIV protease inhibitor: Tipranavir/ritonavir ^a	↓ Saquinavir	Combining saquinavir with tipranavir/ritonavir is not recommended.
HIV fusion inhibitors: Enfuvirtide ^a	Saquinavir soft gelatin capsules/ritonavir ↔ enfuvirtide	No clinically significant interaction was noted from a study in 12 HIV-1 patients who received enfuvirtide concomitantly with saquinavir soft gelatin capsules/ritonavir 1000/100 mg bid. No dose adjustments are required
HIV-1 CCR5 antagonist : Maraviroc	↑ maraviroc	Maraviroc dose should be 150 mg b.i.d when co-administered with MAXIMUNE /ritonavir. For further details see complete prescribing information for maraviroc.
Other Agents		
Ibutilide Sotalol		Use with caution. Additive effects on QT and/or PR interval prolongation may occur with saquinavir/ritonavir.[see CONDRINDICATIONS and WARNINGS AND PRECAUTIONS]
Anticoagulants: Warfarin ^b	↑ Warfarin	Concentrations of warfarin may be affected. It is

		recommended that INR (international normalized ratio) be monitored
Anticonvulsants: Carbamazepine ^b , phenobarbital ^b , phenytoin ^b	↓ Saquinavir Effect on carbamazepine, phenobarbital, and phenytoin is not well established Saquinavir mesylate /ritonavir Interaction has not been evaluated	Use with caution, saquinavir may be less effective due to decreased saquinavir plasma concentrations in patients taking these agents concomitantly.
Anti-gout Colchicine	↑ Colchicine	<u>Treatment of gout flares-coadministration of colchicines in patients on Saquinavir/ritonavir:</u> 0.6 mg (1 tablet) x 1 dose, followed by 0.3 mg (half tablet) 1 hour later. Dose to be repeated no earlier than 3 days. <u>Treatment of familial Mediterranean fever (FMF) co-administration of colchicine in patients on saquinavir/ritonavir:</u> Maximum daily dose of 0.6 mg (may be given as 0.3 mg twice a day). <u>Prophylaxis of gout-flares-co-administration of colchicine in patients on MAXIMUNE/ritonavir:</u> If the original colchicine regimen was 0.6 mg twice a day, the regimen should be adjusted to 0.3 mg once a day. If the original colchicine regimen was

		0.6 mg once a day, the regimen should be adjusted to 0.3 mg once every other day. Patients with renal or hepatic impairment should not be given colchicine with saquinavir/ritonavir
Anti-infective: Clarithromycin ^a	↑ Saquinavir ↑ Clarithromycin	Due to the known effect of ritonavir on clarithromycin concentrations, the following dose adjustments are recommended: For patients with renal impairment, the following dosage adjustments should be considered. <ul style="list-style-type: none"> • For patients with CL_{CR} 30 to 60 mL/min the dose of clarithromycin should be reduced by 50%. • For patients with CL_{CR} < 30 mL/min the dose of clarithromycin should be decreased by 75%. No dose adjustment for patients with normal renal function is necessary.
Erythromycin Halofantrine Pentamidine		Use with caution. Additive effects on QT and/or PR interval prolongation may occur with MAXIMUNE /ritonavir [see CONTRAINDICATIONS AND WARNINGS AND PRECAUTIONS]
Antifungals: Ketoconazole ^a , itraconazole ^b	↔ Saquinavir ↔ Ritonavir ↑ Ketoconazole	When saquinavir /ritonavir and ketoconazole are coadministered, plasma

		<p>concentrations of ketoconazole are increased. Hence doses of ketoconazole or itraconazole > 200 mg/day are not recommended.</p>
<p>Antimycobacterial Agents: Rifabutin^a</p>	<p>↓ Saquinavir ↑ Rifabutin ↔ Ritonavir</p>	<p>No dose adjustment of MAXIMUNE/ritonavir (1000/100 mg b.i.d) is required if ritonavir-boosted saquinavir is administered in combination with rifabutin.</p> <p>Dosage reduction of rifabutin by at least 75% of the usual dose of 300 mg/day is recommended (i.e., a maximum dose of 150 mg every other day or three times per week). Increased monitoring for adverse events is warranted in patients receiving the combination.</p> <p>Consider monitoring rifabutin concentrations to ensure adequate exposure.</p>
<p>Benzodiazepines^b: Alprazolam, clorazepate, diazepam, flurazepam</p>	<p>↑ Benzodiazepines</p>	<p>Clinical significance is unknown; however, a decrease in benzodiazepine dose may be needed.</p>
<p>Benzodiazepine^b: Intravenously administered Midazolam</p>	<p>↑ Midazolam</p>	<p>Midazolam is extensively metabolized by CYP3A4. Increases in the concentration of midazolam are expected to be significantly higher with oral than parenteral administration. Therefore, MAXIMUNE should not be given with orally</p>

		administered midazolam [see CONTRAINDICATIONS]. If MAXIMUNE is coadministered with parenteral midazolam, close clinical monitoring for respiratory depression and/or prolonged sedation should be exercised and dosage adjustment should be considered.
Calcium channel blockers^b: Diltiazem, felodipine, nifedipine, nicardipine, nimodipine, verapamil, amlodipine, nisoldipine, isradipine	↑ Calcium channel blockers	Caution is warranted and clinical monitoring of patients is recommended.
Corticosteroids: Dexamethasone ^b	↓ Saquinavir	Use with caution, saquinavir may be less effective due to decreased saquinavir plasma concentrations.

<p>Digitalis Glycosides: Digoxin^a</p>	<p>↑ Digoxin</p> <p>Increases in serum digoxin concentration were greater in female subjects as compared to male subjects when digoxin was coadministered with Saquinavir mesylate /ritonavir.</p>	<p>Concomitant use of saquinavir/ritonavir with digoxin results in a significant increase in serum concentrations of digoxin.</p> <p>Caution should be exercised when MAXIMUNE/ritonavir and digoxin are co-administered; serum digoxin concentrations should be monitored and the dose of digoxin may need to be reduced when co-administered with saquinavir mesylate/ritonavir (see WARNINGS AND PRECAUTIONS).</p>
<p>Endothelin receptor antagonists: Bosentan</p>	<p>↑ Bosentan</p>	<p>Coadministration of bosentan in patients on MAXIMUNE/ritonavir: In patients who have been receiving MAXIMUNE /ritonavir for at least 10 days, start bosentan at 62.5 mg once daily or every other day based upon individual tolerability.</p> <p>Coadministration of MAXIMUNE /ritonavir in patients on bosentan: Discontinue use of bosentan at least 36 hours prior to initiation of MAXIMUNE /ritonavir. After at least 10 days following the initiation of saquinavir/ritonavir, resume bosentan at 62.5 mg once daily or every other day based upon individual tolerability.</p>

<p>Inhaled beta agonist: Salmeterol</p>	<p>↑ Salmeterol</p>	<p>Concurrent administration of salmeterol with MAXIMUNE/ritonavir is not recommended. The combination may result in increased risk of cardiovascular adverse events associated with salmeterol, including QT prolongation, palpitations and sinus tachycardia.</p>
<p>Inhaled/nasal steroid: Fluticasone^b</p>	<p>Saquinavir mesylate /ritonavir ↑ Fluticasone</p>	<p>Concomitant use of fluticasone propionate and saquinavir mesylate /ritonavir may increase plasma concentrations of fluticasone propionate, resulting in significantly reduced serum cortisol concentrations. Co-administration of fluticasone propionate and MAXIMUNE/ritonavir is not recommended unless the potential benefit to the patient outweighs the risk of systemic corticosteroid side effects (see WARNINGS AND PRECAUTIONS).</p>
<p>HMG-CoA reductase inhibitors^b: Rosuvastatin, atorvastatin</p>	<p>↑ Rosuvastatin ↑ Atorvastatin</p>	<p>Use lowest possible dose of atorvastatin or rosuvastatin with careful monitoring or consider other HMG-CoA reductase inhibitors in combination with saquinavir/ritonavir.</p>
<p>Immunosuppressants: Cyclosporine, tacrolimus, rapamycin</p>	<p>↑ Immunosuppressants</p>	<p>Therapeutic concentration monitoring is recommended for immunosuppressant agents when co-administered with</p>

		MAXIMUNE/ritonavir.
Narcotic analgesic: Methadone ^a	↓ Methadone	Dosage of methadone may need to be increased when MAXIMUNE/ritonavir are co-administered. Use with caution. Additive effects on QT and/or PR interval prolongation may occur with MAXIMUNE/ritonavir [see CONTRAINDICATIONS and WARNINGS AND PRECAUTIONS].
Neuroleptics: Clozapine Haloperidol Mesoridazine Phenothiazines Thioridazine Ziprasidone		Use with caution. Additive effects on QT and/or PR interval prolongation may occur with saquinavir/ritonavir [See CONTRAINDICATIONS and WARNINGS AND PRECAUTIONS.]
Oral contraceptives: Ethinyl estradiol ^b	↓ Ethinyl estradiol	Alternative or additional contraceptive measures should be used when estrogen-based oral contraceptives and MAXIMUNE/ritonavir are co-administered.
PDE5 inhibitors (phosphodiesterase type 5 inhibitors): Sildenafil ^a , vardenafil ^b , tadalafil ^b	↑ Sildenafil ↔ Saquinavir ↑ Vardenafil ↑ Tadalafil	Use sildenafil with caution at reduced doses of 25 mg every 48 hours with increased monitoring of adverse events when administered concomitantly with MAXIMUNE/ritonavir. Use vardenafil with caution at reduced doses of no more than 2.5 mg every 72 hours with

		<p>increased monitoring of adverse events when administered concomitantly with MAXIMUNE/ritonavir.</p> <p>Use tadalafil with caution at reduced doses of no more than 10 mg every 72 hours with increased monitoring of adverse events when administered concomitantly with MAXIMUNE/ritonavir.</p>
<p>Tricyclic antidepressants^b: Amitriptyline, imipramine</p>	<p>↑ Tricyclics</p>	<p>Therapeutic concentration monitoring is recommended for tricyclic antidepressants when co-administered with MAXIMUNE/ritonavir</p>
<p>Proton pump inhibitors: Omeprazole^a</p>	<p>↑ Saquinavir</p>	<p>When saquinavir mesylate /ritonavir is co-administered with omeprazole, saquinavir concentrations are increased significantly. If omeprazole or another proton pump inhibitor is taken concomitantly with saquinavir mesylate /ritonavir, caution is advised and monitoring for potential saquinavir toxicities is recommended, particularly gastrointestinal symptoms, increased triglycerides, and deep vein thrombosis.</p>
<p>Herbal Products: St. John's wort^b (hypericum perforatum)</p>	<p>↓ Saquinavir</p>	<p>Coadministration may lead to loss of virologic response and possible resistance to saquinavir or to the class of protease inhibitors.</p>

Garlic Capsules ^b	↓ Saquinavir	Coadministration of garlic capsules and saquinavir is not recommended due to the potential for garlic capsules to induce the metabolism of saquinavir which may result in sub-therapeutic saquinavir concentrations.
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^a See Drug Interactions, Table 1 for interactions.

^b Saquinavir/ritonavir interaction has not been evaluated.

Impaired Renal Function

Renal clearance is only a minor elimination pathway; the principal route of metabolism and excretion for saquinavir is by the liver. Therefore, no initial dose adjustment is necessary for patients with renal impairment. However, patients with severe renal impairment have not been studied, and caution should be exercised when prescribing saquinavir in this population.

Impaired Hepatic Function

No dosage adjustment is necessary for HIV-1-infected patients with mild or moderate hepatic impairment based on limited data. In patients with underlying hepatitis B or C, cirrhosis, chronic alcoholism and/or other underlying liver abnormalities, there have been reports of worsening liver disease (see **CLINICAL PHARMACOLOGY**).

Pregnancy:

Pregnancy Category B

Reproduction studies conducted with saquinavir have shown no embryotoxicity or teratogenicity in both rats and rabbits. Because of limited bioavailability of saquinavir in animals and/or dosing limitations, the plasma exposures (AUC values) in the respective species were approximately 29% (using rat) and 21% (using rabbit) of those obtained in humans at the recommended clinical dose boosted with ritonavir. Clinical experience in pregnant women is limited. Saquinavir should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Lactation

The Centers for Disease Control and Prevention recommend that HIV-infected mothers not breast-feed their infants to avoid risking postnatal transmission of HIV. It is not known whether saquinavir is excreted in human milk. Because of both the potential for HIV transmission and the potential for serious adverse reactions in nursing infants, **mothers should be instructed not to breast feed if they are receiving antiretroviral medications, including MAXIMUNE.**

Pediatric Use

Safety and effectiveness of saquinavir mesylate in HIV-infected pediatric patients younger than 16 years of age have not been established.

Geriatric Use

Clinical studies of saquinavir mesylate did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. In general, caution should be taken when dosing saquinavir mesylate in elderly patients due to the greater frequency of decreased hepatic, renal or cardiac function, and of concomitant disease or other drug therapy.

UNDESIRABLE EFFECTS

The following adverse reactions are discussed in greater detail in other sections of the labeling:

PR Interval Prolongation (see **WARNINGS AND PRECAUTIONS**)

QT Interval Prolongation (see **WARNINGS AND PRECAUTIONS**)

MAXIMUNE must be used in combination with ritonavir, which significantly inhibits saquinavir's metabolism to provide increased plasma saquinavir levels.

Concomitant Therapy with Ritonavir Adverse Reactions

In combination with ritonavir the recommended dose of saquinavir mesylate is 1000 mg two times daily with ritonavir 100 mg two times daily in combination with other antiretroviral agents. Table 4 lists grade 2, 3 and 4 related adverse events that occurred in $\geq 2\%$ of patients receiving saquinavir soft gel capsules with ritonavir (1000/100 mg bid).

Table 4. Grade 2, 3 and 4 Related Adverse Events (All Causality) Reported in $\geq 2\%$ of Adult Patients in the MaxCmin 1 Study of saquinavir soft gel capsules in combination with Ritonavir 1000/100 mg bid

Adverse Events	Saquinavir soft gel capsules 1000 mg plus Ritonavir 100 mg bid (48 weeks) N=148 n (%=n/N)
Endocrine Disorders	
Diabetes mellitus/hyperglycemia	4 (2.7)
Lipodystrophy	8 (5.4)
Gastrointestinal Disorders	
Nausea	16 (10.8)
Vomiting	11 (7.4)
Diarrhea	12 (8.1)
Abdominal Pain	9 (6.1)

Constipation	3 (2.0)
General Disorders and Administration Site Conditions	
Fatigue	9 (6.1)
Fever	5 (3.4)
Musculoskeletal Disorders	
Back Pain	3 (2.0)
Respiratory Disorders	
Pneumonia	8 (5.4)
Bronchitis	4 (2.7)
Influenza	4 (2.7)
Sinusitis	4 (2.7)
Dermatological Disorders	
Rash	5 (3.4)
Pruritus	5 (3.4)
Dry lips/skin	3 (2.0)
Eczema	3 (2.0)

Limited experience is available from three studies investigating the pharmacokinetics of the saquinavir mesylate 500 mg film coated tablet compared to the saquinavir mesylate 200 mg hard gelatin capsule in healthy volunteers (n=140). In two of these studies saquinavir was boosted with ritonavir; in the other study, saquinavir was administered as the single drug. The saquinavir mesylate tablet and the hard gelatin capsule formulations were similarly tolerated. The most common adverse events were gastrointestinal disorders (such as diarrhea). Similar bioavailability was demonstrated and no clinically significant differences in saquinavir exposures were seen. Thus, similar safety profiles are expected between these two saquinavir mesylate formulations.

In a study investigating the drug-drug interaction of rifampin 600 mg/day daily and ritonavir 100 mg/saquinavir mesylate 1000 mg twice daily (ritonavir-boosted saquinavir mesylate) involving 28 healthy volunteers, 11 of 17 healthy volunteers (65%) exposed concomitantly to rifampin and ritonavir-boosted saquinavir mesylate developed severe hepatocellular toxicity presented as increased hepatic transaminases. In some subjects, transaminases increased up to > 20 fold the upper limit of normal and were associated with gastrointestinal symptoms, including abdominal pain, gastritis, nausea, and vomiting. Following discontinuation of all three drugs, clinical symptoms abated and the increased hepatic transaminases normalized (see **CONTRAINDICATIONS**).

Additional Adverse Reactions Reported with Saquinavir mesylate

Additionally, adverse experiences of any intensity, at least remotely related to saquinavir, that were reported from clinical trials using saquinavir mesylate hard or soft gel capsules with or without ritonavir, are listed below by body system:

Blood and lymphatic system disorders: anemia, hemolytic anemia, leukopenia, lymphadenopathy, neutropenia, pancytopenia, thrombocytopenia

Cardiac disorders: heart murmur, syncope

Ear and labyrinth disorders: tinnitus

Eye disorders: visual impairment

Gastrointestinal disorders: abdominal discomfort, ascites, dyspepsia, dysphagia, eructation, flatulence, gastritis, gastrointestinal hemorrhage, intestinal obstruction, mouth dry, mucosal ulceration, pancreatitis

General disorders and administration site conditions: anorexia, asthenia, chest pain, edema, lethargy, wasting syndrome, weight increased

Hepatobiliary disorders: chronic active hepatitis, hepatitis, hepatomegaly, hyperbilirubinemia, jaundice, portal hypertension

Immune system disorders: allergic reaction

Investigations: ALT increase, AST increase, blood creatine phosphokinase increased, increased alkaline phosphatase, GGT increase, raised amylase, raised LDH,

Metabolism and nutrition disorders: increased or decreased appetite, dehydration, hypertriglyceridemia

Musculoskeletal and connective tissue disorders: arthralgia, muscle spasms, myalgia, polyarthritis

Neoplasms benign, malignant and unspecified (incl cysts and polyps): acute myeloid leukemia, Papillomatosis

Nervous system disorders: confusion, convulsions, coordination abnormal, dizziness, dysgeusia, headache, hypoaesthesia, intracranial hemorrhage leading to death, loss of consciousness, paresthesia, peripheral neuropathy, somnolence, tremor

Psychiatric disorders: anxiety, depression, insomnia, libido disorder, psychotic disorder, sleep disorder, suicide attempt

Renal and urinary disorders: nephrolithiasis

Respiratory, thoracic and mediastinal disorders: cough, dyspnea

Skin and subcutaneous tissue disorders: acne, alopecia, dermatitis bullous, drug eruption, erythema, severe cutaneous reaction associated with increased liver function tests, Stevens-Johnson syndrome, sweating increased, urticaria

Vascular disorders: hypertension, hypotension, thrombophlebitis, peripheral vasoconstriction

OVERDOSAGE

No acute toxicities or sequelae were noted in 1 patient who ingested 8 grams of saquinavir mesylate as a single dose. The patient was treated with induction of emesis within 2 to 4 hours after ingestion. A second patient ingested 2.4 grams of saquinavir mesylate in combination with 600 mg of ritonavir and experienced pain in the throat that lasted for 6 hours and then resolved. In an exploratory Phase II study of oral dosing with saquinavir mesylate at 7200 mg/day (1200 mg q4h), there were no serious toxicities reported through the first 25 weeks of treatment.

PACKAGING INFORMATION

MAXIMUNEContainer of 120 tablets.

Last updated: October 2010