HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use INVIRASE safely and effectively. See full prescribing information for INVIRASE.

INVIRASE® (saquinavir mesylate) capsules and tablets, for oral use
Initial U.S. Approval: 1995

----------RECENT MAJOR CHANGES----------

Dosage and Administration, Recommended Dose (2.1)	02/2016
Contraindications (4)	09/2016
Warnings and Precautions (5)	12/2015
QT Interval Prolongation (5.3)	02/2016

----------INDICATIONS AND USAGE----------
INVIRASE is an HIV-1 protease inhibitor indicated for the treatment of HIV-1 infection in combination with ritonavir and other antiretroviral agents in adults (over the age of 16 years). (1)

----------DOSAGE AND ADMINISTRATION----------

- **INVIRASE must be administered in combination with ritonavir.** (2)
- Adults (over the age of 16 years): INVIRASE 1000 mg twice daily (5 x 200 mg capsules or 2 x 500 mg tablets) in combination with ritonavir 100 mg twice daily. (2.1)
- Treatment-naïve patients initiating treatment with INVIRASE/ritonavir: First 7 days of treatment: INVIRASE 500 mg twice daily with ritonavir 100 mg twice daily. After 7 days: INVIRASE 1000 mg twice daily with ritonavir 100 mg twice daily. (2.1)
- See Full Prescribing Information for dosing recommendations for patients switching immediately from treatment with another protease inhibitor taken with ritonavir or from a non-nucleoside reverse transcriptase inhibitor based regimen, without a wash-out period. (2.1)
- INVIRASE and ritonavir should be taken within 2 hours after a meal. (2.1)

----------DOSAGE FORMS AND STRENGTHS----------

200 mg capsules and 500 mg film-coated tablets (3)

----------CONTRAINDICATIONS----------

- Patients with congenital or documented acquired QT prolongation, patients with refractory hypokalemia or hypomagnesemia, or those on concomitant therapy with other drugs that prolong the QT interval. (4)
- INVIRASE is contraindicated in patients with complete atrioventricular (AV) block without implanted pacemakers, or patients who are at high risk of complete AV block. (4)
- INVIRASE is contraindicated in patients with clinically significant hypersensitivity (e.g., anaphylactic reaction, Stevens-Johnson syndrome) to saquinavir, saquinavir mesylate, or any of its ingredients. (4)
- INVIRASE when administered with ritonavir is contraindicated in patients with severe hepatic impairment. (4)
- Coadministration of INVIRASE/ritonavir with CYP3A substrates for which increased plasma levels may result in serious or life-threatening reactions. (4)
- Coadministration of INVIRASE/ritonavir with rifampin due to the risk of severe hepatotoxicity. (4)

----------WARNINGS AND PRECAUTIONS----------

- The concomitant use of INVIRASE/ritonavir and certain other drugs may result in known or potentially significant drug interactions. Consult the full prescribing information prior to and during treatment for potential drug interactions. (5.1, 7.3)
- QT and PR interval prolongations have been observed in a healthy volunteer study. Use with caution in patients with preexisting conduction system abnormalities and certain heart diseases. (5.2, 5.3, 12.2)
- Patients on INVIRASE therapy may develop new onset or exacerbations of diabetes mellitus (5.4), hyperglycemia (5.4), elevated cholesterol and/or triglyceride concentrations (5.7), redistribution/accumulation of body fat (5.9), and immune reconstitution syndrome (5.10). Monitor cholesterol and triglycerides prior to therapy and periodically thereafter. (5.7)
- 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. (5.5)
- Hemophilia: Spontaneous bleeding may occur and additional factor VII may be required. (5.6)
- Various degrees of cross-resistance have been observed. (5.11)

----------ADVERSE REACTIONS----------

The most common adverse reactions are nausea, vomiting, diarrhea, fatigue, pneumonia, lipodystrophy and abdominal pain. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Genentech at 1-888-835-2555 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------DRUG INTERACTIONS----------

- INVIRASE/ritonavir is a potent inhibitor of CYP3A, significantly increasing the exposure of drugs primarily metabolized by CYP3A. (7.1)
- Coadministration of INVIRASE/ritonavir with drugs that induce CYP3A may result in decreased plasma concentrations of saquinavir and reduced efficacy. (7.2)
- Certain drugs or drug classes should not be coadministered with INVIRASE/ritonavir based on drug interaction studies or predicted drug interactions. (5.1, 7.2, 7.3)

----------USE IN SPECIFIC POPULATIONS----------

- Pregnancy: Use during pregnancy only if the potential benefit justifies the potential risk to the fetus. (8.1)
- Nursing Mothers: Do not breastfeed if HIV-1-infected mothers are receiving INVIRASE therapy. (8.3)
- Pediatric Use: Pediatric dose recommendations that are both reliably effective and below thresholds of concern with respect to QT and PR prolongation could not be determined (8.4)
- Geriatric Use: Caution should be exercised due to greater frequency of decreased hepatic, renal or cardiac function in elderly population. (8.5)
- Impaired Renal Function: No initial dose adjustment is necessary for patients with renal impairment. (8.6)
- Impaired Hepatic Function: No dose adjustment is necessary for patients with mild or moderate hepatic impairment. (8.7)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 09/2016

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

Product identification in this document includes: INVIRASE in reference to saquinavir mesylate; saquinavir 200 mg soft gel capsule formulation[1] in reference to saquinavir active base.

1 INDICATIONS AND USAGE

INVIRASE in combination with ritonavir and other antiretroviral agents is indicated for the treatment of HIV-1 infection in adults (over the age of 16 years).

The following points should be considered when initiating therapy with INVIRASE:

- The twice daily administration of INVIRASE in combination with ritonavir is supported by safety data from the MaxCmin 1 trial *[see Adverse Reactions (6.1)]* and pharmacokinetic data *[see Clinical Pharmacology (12.3)]*.
- The efficacy of INVIRASE with ritonavir has not been compared against the efficacy of antiretroviral regimens currently considered standard of care.
- The number of baseline primary protease inhibitor mutations affects the virologic response to INVIRASE/ritonavir.

2 DOSAGE AND ADMINISTRATION

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

Cobicistat is not interchangeable with ritonavir to increase systemic exposure of saquinavir *[see Warnings and Precautions (5)]*.

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[1] The term "saquinavir soft gel capsules" used in this label refers to the drug product formerly marketed as "Fortovase" (saquinavir 200 mg soft gel capsule formulation). This formulation has been withdrawn from the market.

2.1 Recommended Dose

- The standard recommended dose of INVIRASE is 1000-mg twice daily (5 x 200-mg capsules or 2 x 500-mg tablets) in combination with ritonavir 100-mg twice daily.
- For treatment-naïve patients initiating treatment with INVIRASE/ritonavir, the recommended starting dose of INVIRASE is 500-mg twice daily with ritonavir 100-mg twice daily for the first 7 days of treatment. After 7 days, the recommended dose of INVIRASE is 1000-mg twice daily with ritonavir 100-mg twice daily *[see Warnings and Precautions (5.3) and Clinical Pharmacology (12.2)]*.
- Patients switching immediately (no washout period) from treatment with another ritonavir containing regimen or from a non-nucleoside reverse transcriptase inhibitor based regimen (not including delavirdine, rilpivirine) should initiate and continue INVIRASE at the standard recommended dose of 1000-mg twice daily with ritonavir 100-mg twice daily. For patients switching from a regimen containing delavirdine or rilpivirine, the recommended dose is 500-mg twice daily with ritonavir 100-mg twice daily for the first 7 days of treatment *[see Warnings and Precautions (5.3) and Drug Interactions (7.3)]*.
- Ritonavir should be taken at the same time as INVIRASE.
- INVIRASE and ritonavir should be taken within 2 hours after a meal.
- For patients already taking ritonavir 100-mg twice daily as part of their antiretroviral regimen, no additional ritonavir is needed.
- Pediatric dose recommendations that are both reliably effective and below thresholds of concern for QT and PR interval prolongation could not be determined.

2.2 Administration for Patients Unable to Swallow Capsules

Open the INVIRASE capsules and place the contents into an empty container. Add 15 mL of either sugar syrup or sorbitol syrup (for patients with Type 1 diabetes or glucose intolerance) **OR** 3 teaspoons of jam to the contents of INVIRASE capsules that are in the container. Stir with a spoon for 30 to 60 seconds. Administer the full amount prepared for each dose. Suspensions should be at room temperature before administering.

3 DOSAGE FORMS AND STRENGTHS

Capsules: 200 mg
Film-coated tablets: 500 mg

4 CONTRAINDICATIONS

QT interval prolongation and torsades de pointes have been reported rarely with INVIRASE/ritonavir use. 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 (5.3) and Clinical Pharmacology (12.2)]*.

INVIRASE 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 (5.2)]*.

INVIRASE is contraindicated in patients with clinically significant hypersensitivity (e.g., anaphylactic reaction, Stevens-Johnson syndrome) to saquinavir, saquinavir mesylate, or any of its ingredients.

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

Coadministration of INVIRASE/ritonavir is contraindicated with drugs that are CYP3A substrates for which increased plasma levels may result in serious or life-threatening reactions. These drugs and potentially related adverse events are listed in **Table 1**.

Table 1 Drugs That Are Contraindicated With INVIRASE/ritonavir

Drug Class	Drugs Within Class That Are Contraindicated With INVIRASE/ritonavir	Clinical Comment
Alpha 1-adrenoreceptor antagonist	Alfuzosin	Potentially increased alfuzosin concentrations can result in hypotension.
Antiarrhythmics	Amiodarone, bepridil, dofetilide, flecainide, lidocaine (systemic), propafenone, quinidine	Potential for serious and/or life-threatening cardiac arrhythmia.
Antidepressant	Trazodone	Increased trazodone concentrations can result in potentially life threatening cardiac arrhythmia.
Anti-infectives	Clarithromycin, erythromycin, halofantrine, pentamidine	Potential for serious and/or life-threatening cardiac arrhythmia.
Antimycobacterial Agents	Rifampin	Rifampin should not be administered in patients taking INVIRASE/ritonavir as part of an ART regimen due to the risk of severe hepatocellular toxicity.
Antipsychotics	Lurasidone Chlorpromazine, clozapine, haloperidol, mesoridazine, phenothiazines, pimozide, sertindole, thioridazine, ziprasidone	Potential for serious and/or life-threatening reactions. Potential for serious and/or life threatening reactions such as cardiac arrhythmias.
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.
GI Motility Agent	Cisapride	Potential for serious and/or life threatening reactions such as cardiac arrhythmias.
HIV-1 Protease Inhibitor	Atazanavir	Potential for serious and/or life-threatening cardiac arrhythmia.
HMG-CoA Reductase Inhibitors	Lovastatin, Simvastatin	Potential for myopathy including rhabdomyolysis.
Immunosuppressant	Tacrolimus	Potential for serious and/or life-threatening cardiac arrhythmia.
PDE5 Inhibitors	Sildenafil (Revatio®)[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 INVIRASE/ritonavir.
Sedative/Hypnotics	Triazolam, orally administered midazolam	Potential for serious and/or life threatening reactions such as prolonged or increased sedation or respiratory depression. Triazolam and orally administered midazolam are

		extensively metabolized by CYP3A4. Coadministration of triazolam or orally administered midazolam with INVIRASE/ritonavir may cause large increases in the concentration of these benzodiazepines.
Other drugs that are CYP3A substrates	Dapsone Disopyramide Quinine	Potential for serious and/or life-threatening cardiac arrhythmia.

5 WARNINGS AND PRECAUTIONS

INVIRASE must be used in combination with ritonavir. Please refer to the ritonavir full prescribing information for additional precautionary measures.

INVIRASE is not recommended for use in combination with cobicistat. Dosing recommendations for this combination have not been established. Cobicistat is also not recommended in combination with regimens containing ritonavir due to similar effects of cobicistat and ritonavir on CYP3A. Please refer to the cobicistat full prescribing information for additional precautionary measures.

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

5.1 Risk of Serious Adverse Reactions Due to Drug Interactions

Initiation of INVIRASE/ritonavir, a CYP3A inhibitor, in patients receiving medications metabolized by CYP3A or initiation of medications metabolized by CYP3A in patients already receiving INVIRASE/ritonavir, may increase plasma concentrations of medications metabolized by CYP3A. Initiation of medications that inhibit or induce CYP3A may increase or decrease concentrations of INVIRASE/ritonavir, respectively. These interactions may lead to:

- Clinically significant adverse reactions potentially leading to severe, life threatening, or fatal events from greater exposures of concomitant medications.
- Clinically significant adverse reactions from greater exposures of INVIRASE/ritonavir.
- Loss of therapeutic effect of INVIRASE/ritonavir and possible development of resistance.

See **Table 3** for steps to prevent or manage these possible and known significant drug interactions, including dosing recommendations *[see Drug Interactions (7)]*. Consider the potential for drug interactions prior to and during INVIRASE/ritonavir therapy; review concomitant medications during INVIRASE/ritonavir therapy; and monitor for the adverse reactions associated with the concomitant medications *[see Contraindications (4) and Drug Interactions (7)]*.

5.2 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 (5.3)]*.

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 (12.2)]*.

5.3 QT Interval Prolongation

Saquinavir/ritonavir causes dose-dependent QT prolongation. Torsades de pointes have 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

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