

PRODUCT MONOGRAPH

Pr **INVIRASE**[®]

Saquinavir capsules 200 mg

(as saquinavir mesylate)

Saquinavir film-coated tablets 500mg

(as saquinavir mesylate)

Pharmaceutical standard professed

HIV Protease Inhibitor / Antiretroviral Agent

Hoffmann-La Roche Limited
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Table of Contents

PART III: CONSUMER INFORMATION.....3

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Pr INVIRASE®
saquinavir mesylate

This leaflet is part III of a three-part “Product Monograph” published when INVIRASE was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about INVIRASE. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

What the medication is used for:

In adults and adolescents over the age of 16 years, INVIRASE (saquinavir mesylate) in combination with low dose Norvir® (ritonavir) and other anti-HIV drugs is used for the treatment of HIV, the virus that causes AIDS. INVIRASE belongs to a class of drugs called protease (pronounced PRO-tee-ase) inhibitors.

What it does:

As you may know, the immune system is the body's main defence against infection. The immune system includes special cells that recognize and destroy harmful bacteria and viruses. As HIV grows, it destroys these cells -- leaving fewer immune cells, and a greater risk of infection. INVIRASE works by fighting HIV as it grows inside cells by blocking an enzyme (protease) that HIV needs to reproduce.

INVIRASE is not a cure for HIV and/or AIDS, though it may help to slow the progression of HIV disease in your body. While taking INVIRASE however, you may continue to acquire illnesses associated with advanced HIV infection (i.e. opportunistic infections).

It is important to remember that there is NO evidence which suggests that INVIRASE can prevent the transmission of HIV. INVIRASE is NOT therefore a substitute for other measures which have been proven effective in this regard. To avoid transmission of HIV, you should not donate blood, share needles, or engage in unprotected sexual activity (i.e. without a condom).

When it should not be used:

- INVIRASE must not be used unless taken with Norvir (ritonavir);
- INVIRASE should not be used if you are sensitive to saquinavir or to any other component contained in the capsule or tablet (see “What the non-medicinal ingredients are”);
- INVIRASE/ritonavir should not be used if you have a history of problems with the electrical activity of the heart known as QT prolongation or electrolyte imbalances (especially low potassium)

- INVIRASE/ritonavir should not be used if you have severe liver problems;
- INVIRASE/ritonavir should not be used if you are taking or plan on taking any of the following medications:

Drug Class	Drugs within Class Not to be Taken with INVIRASE/Norvir (ritonavir)
Alpha 1- adrenoreceptor antagonist	Alfuzosin
Antiarrhythmics	Cordarone® (amiodarone), Tambocor® (flecainide), procainamide, Rythmol® (propafenone), bepridil, quinidine, sotalol, lidocaine (systemic), Dofetilide
Antihistamines	Seldane® (terfenadine)*, Hismanal® (astemizole)*
Antiinfectives	Clarithromycin, Erythromycin, Halofantrine
Antimigraines	Ergot medications (eg Dihydroergotamine, ergonovine, ergotamine, methylergonovine)
Antimycobacterial Agents	Rifampin
Antidepressants	Trazodone
Antipsychotics	Lurasidone, Pimozide, Quetiapine, Clozapine, Haloperidol, Chlorpromazine, Sertindole, Thioridazine, Ziprasidone
GI Motility Agents	Prepulsid® (cisapride)*
HIV protease inhibitors (PIs)	Atazanavir
Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTI)	Rilpivirine
HMG-CoA Reductase Inhibitors (Statins)	Simvastatin, Lovastatin
Immunosuppressant	Tacrolimus
PDE5 Inhibitors	Sildenafil (for pulmonary arterial hypertension)
Sedative/Hypnotics	Midazolam (oral), triazolam
Tyrosine kinase inhibitors	Dasatinib, Sunitinib

Other medicinal products that are substrate of CYP3A4	Disopyramide Quinine
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*No longer marketed in Canada

INVIRASE causes increased blood levels of these medicines. This can lead to serious or life-threatening reactions such as irregular heartbeat or prolonged sedation. Rifampin, in combination with INVIRASE and ritonavir, may also cause severe liver problems.

Taking INVIRASE with St. John's Wort (*Hypericum perforatum*), a herbal product sold as a dietary supplement, or products containing St. John's Wort is not recommended. Taking St. John's Wort may decrease INVIRASE levels and lead to increased viral load and possible resistance to INVIRASE or cross-resistance to other antiretroviral drugs.

Your doctor may want to change your medicine if you are taking Mycobutin[®] (rifabutin) or Sustiva[®] (efavirenz) since these drugs substantially reduce the level of INVIRASE in the blood.

What the medicinal ingredient is:

The medicinal ingredient found in both INVIRASE capsules and INVIRASE tablets is saquinavir mesylate.

What the non-medicinal ingredients are:

INVIRASE capsules contain the following non-medicinal ingredients: lactose, magnesium stearate, microcrystalline cellulose, povidone, sodium starch glycolate, and talc. The capsule shells are made from gelatin, indigotine, iron oxide, and titanium dioxide.

INVIRASE tablets contain the following non-medicinal ingredients: croscarmellose sodium, lactose, magnesium stearate, microcrystalline cellulose, and povidone K30. Each film coat contains hypromellose, iron oxide red, iron oxide yellow, talc, titanium dioxide, and triacetin.

If you know you have an allergy or have had a serious reaction to any of the ingredients, such as lactose, you must not use INVIRASE.

What dosage forms it comes in:

INVIRASE is available as a 200 mg hard gelatin capsule and as a 500 mg film coated tablet.

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

- INVIRASE must not be used unless it is taken with Norvir (ritonavir).
- Serious or life-threatening interactions may occur when using INVIRASE in combination with other medications (see "ABOUT THIS MEDICATION: When it should not be used").

- Invirase should not be used if you have a history of problems with the electrical activity of the heart known as QT prolongation or electrolyte imbalances (especially low potassium).
- INVIRASE/ritonavir should not be used if you have severe liver problems.

Before you use INVIRASE talk to your doctor or pharmacist if:

- you have ever had a bad reaction to saquinavir (INVIRASE), any component of the capsules or tablet, or any other brand of protease inhibitor;
- you have a history of problems with the electrical activity of the heart including QT prolongation, heart block, or family history of sudden death at a young age;
- you have lactose intolerance. This product contains lactose;
- you have a problem with your liver or kidneys;
- you have hemophilia;
- you have diabetes. Diabetes may be worsened by medicines in the same class as INVIRASE and your dosage of diabetes medicine may have to be adjusted;
- you have been told that you have high blood cholesterol or triglyceride levels;
- you have any other illnesses besides HIV infection;
- you are using Iopinavir/ritonavir, erythromycin or methadone;
- you are taking or plan on taking ANY other drugs (including herbal preparations, especially St. John's Wort and garlic, drugs you purchase without prescriptions, and those not prescribed by your doctor); or
- you are pregnant, plan to become pregnant, breastfeeding or plan to breastfeed.

Your doctor may have you take an ECG (electrocardiogram) before treatment with INVIRASE.

This information will help you and your physician decide if the potential benefits of treating your condition with INVIRASE outweigh the possible risks.

No studies have been conducted on the ability to drive or operate machinery while taking INVIRASE. There is no evidence that INVIRASE may alter your ability to drive and use machines.

INTERACTIONS WITH THIS MEDICATION

There are many medications that may interact with INVIRASE. If you are taking or plan on taking any other medications (prescription or non-prescription, including herbal preparations), tell your doctor or pharmacist.

Special attention is warranted when using INVIRASE with HMG-CoA reductase inhibitors (cholesterol lowering medications), nasal steroids such as Flonase[®] (fluticasone propionate), PDE5 inhibitors (medicines used to treat

erectile dysfunction), bosentan (a medication used to treat pulmonary arterial hypertension), colchicine (anti-gout medication), Celsentri (maraviroc) (another HIV medicine) and vincamine (peripheral vasodilator).

Caution should be taken when taking INVIRASE with digoxin. Your doctor may want to monitor the levels of digoxin in your blood and the dose of digoxin may need to be decreased.

Caution should be taken when taking INVIRASE with fentanyl and alfentanil (opioid analgesic), salmeterol (used to treat asthma or chronic obstructive pulmonary disease), as well as when taking INVIRASE with halofantrine or pentamidine (anti-infective medications). Taking INVIRASE/ritonavir with the anti-infective medication fusidic acid is not recommended.

Caution should be taken when taking INVIRASE with antifungals (e.g. itraconazole, miconazole, fluconazole), antibiotics (e.g. quinupristin, dalfopristin), dapsone (antimycobacterial), calcium channel blockers (e.g. diltiazem, felodipine, nifedipine), ibutilide (antiarrhythmic), nefazodone (antidepressant), tipranavir/ritonavir combination (protease inhibitor) and omeprazole (proton pump inhibitor). Your doctor may monitor you more closely. Taking INVIRASE/ritonavir with nelfinavir (protease inhibitor) is not recommended.

If you are taking an estrogen-based oral contraceptive (e.g. ethinyl estradiol) to prevent pregnancy, you should use an additional or different type of contraception measures

Special attention is also warranted when taking drugs such as: antidepressants, anticoagulants, anticonvulsants (carbamazepine, phenytoin, phenobarbital), and antiarrhythmics. In any of these instances your doctor may need to change your dose and monitor you more closely.

Drugs that should **not** be taken with INVIRASE are discussed in the section above entitled "ABOUT THIS MEDICATION: When it should not be used".

PROPER USE OF THIS MEDICATION

Usual Dose – Adults and adolescents over 16 years of age:

Your doctor has prescribed INVIRASE after carefully studying your case, because he/she believes that you may benefit from this medication. This may not be true for other patients with HIV infection, even those who exhibit symptoms similar to yours. **As with any prescription drug, INVIRASE should only be taken on the advice of a physician. Do not give your INVIRASE to any other person.**

The standard recommended dose of INVIRASE is 1000 mg (5 x 200 mg capsules or 2 x 500 mg tablets) two times daily with Norvir (ritonavir) 100 mg two times daily, in

combination with other antiretroviral agents.

For some patients who have received no prior treatment for HIV and are starting to take INVIRASE for the first time, the recommended starting dose is 500 mg two times daily with ritonavir 100 mg two times daily for the first 7 days of treatment. After 7 days, the recommended dose of INVIRASE is 1000 mg two times daily with ritonavir 100 mg two times daily.

INVIRASE must be taken with meals or up to 2 hours after a meal, but it is easiest to remember if you take it with your meals. When INVIRASE is taken without food, the amount of INVIRASE in the blood is lower and may not fight HIV as well.

INVIRASE capsules and tablets should be swallowed unchewed, with water or some other non-alcoholic drink. You should avoid excessive consumption of alcohol during your treatment with INVIRASE. **Follow the advice of your doctor. Do not discontinue therapy or alter your dosing without consulting your doctor.**

Overdose:

In case of drug overdose, contact a health care practitioner, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

Missed Dose:

The missed dose should be taken as soon as you remember, then just carry on with your regular dosing schedule. However, do not take 2 doses at the same time. If you are unsure what to do, consult your doctor or pharmacist.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

As with any drug, the beneficial effects of INVIRASE may be accompanied by unwanted effects (also known as side-effects or adverse events). It is often difficult to determine whether these adverse events are the result of taking INVIRASE, an effect of your HIV-infection, or a side-effect from other drugs being used to treat the HIV-infection. **It is very important however, to inform your physician of any change in your condition.**

People treated with INVIRASE in combination with Norvir (ritonavir) may have side effects. The majority of these have been described as mild. In clinical studies of patients who received saquinavir in combination with Norvir and other HIV drugs the side effects seen most often were: nausea, diarrhea, body fat changes, vomiting, tiredness, and stomach pain.

Regular blood testing to detect any abnormalities with your liver, pancreas or blood is a recommended part of your therapy with INVIRASE. These abnormalities do not always cause side effects that you can detect yourself, so it is very important to adhere to the blood testing schedule recommended by your doctor.

In hemophiliacs, there have been reports of increased bleeding episodes among patients treated with INVIRASE or other drugs of this class (protease inhibitors). If you suffer from hemophilia, remember to report all bleeding episodes to your doctor.

When INVIRASE is taken with ritonavir, some patients may experience large increases in triglyceride and lipid levels. The long-term chance of getting complications such as heart attack and stroke due to increases in triglyceride and cholesterol levels caused by protease inhibitors is not known at this time.

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. Side effects known to be associated with other drugs used to treat HIV may still occur when INVIRASE is used in combination with these medicines. However, INVIRASE does not appear to increase the frequency or severity of the unwanted effects. These side effects (associated with drugs such as ddC and AZT) include skin rash, inflammation or sores in the mouth and disturbances of the nerves (especially in the hands and feet). These disturbances may take the form of numbness, pins and needles, or shooting/burning pain in the hands and feet.

Changes in your heart rhythm and the electrical activity of your heart have been seen with INVIRASE. These changes may be observed on an ECG (electrocardiogram) and can lead to serious heart problems. Your risk for these problems may be higher if you:

- already have a history of abnormal heart rhythm or other types of heart disease
- take other medicines that can affect your heart rhythm while you take INVIRASE.

Tell your doctor right away if you have any of these symptoms while taking INVIRASE:

- dizziness
- lightheadedness
- fainting
- sensation of abnormal heartbeats

Changes in your immune system (Immune Reconstitution Inflammatory Syndrome) can happen when you start taking HIV medicines. Your immune system may get stronger and begin to fight infections that have been hidden in your body for a long time, or you could develop an autoimmune disease in which your immune system reacts against your own body (e.g. Grave’s disease (which affects the thyroid gland), Guillain-Barre syndrome (which affects the nervous system) or polymyositis (which affects the muscles) and it may develop at any time, sometimes months later after the start of HIV therapy). Sometimes symptoms can be severe, so if you develop high temperature (fever), joint or muscle pain, redness, rash, swelling, or fatigue or any new

symptoms contact your doctor straight away.

If you are concerned about these or any other unexpected effects experienced while taking INVIRASE, talk to your doctor or pharmacist.

Common Side Effects

Common side effects include: nausea, diarrhea, vomiting, flatulence (gas), indigestion, tiredness, fat tissue increase, headache, dry skin, rash, and itching. If these symptoms become bothersome, contact your doctor.

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM			
Symptom / effect Common (at least 1 %)	Talk with your doctor or pharmacist		Stop taking drug and call your doctor or pharmacist
	Only if severe	In all cases	
● Decreased number of red blood cells		✓	
● Selective loss of body fat		✓	
● Abdominal pain (upper and lower)		✓	
● Weakness		✓	
● Allergic reactions (with symptoms such as shortness of breath, wheezing or difficulty breathing; swelling of the face, lips, tongue or other parts of the body; rash, itching or hives on the skin)		✓	
● Increase of liver enzymes in blood		✓	
● Increase in blood fatty acids		✓	
● Weight loss		✓	
● Reduced appetite or total aversion to food		✓	
● High levels of the sugar glucose in the blood		✓	
● High cholesterol levels		✓	
● Dizziness		✓	
● Tingling, numbness, unusual sensations, weakness, or burning pain		✓	

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

HOW TO STORE IT

Always keep your INVIRASE in its original package and store it between 15 and 30°C. **Keep this and any other**

drugs out of sight and out of reach from children. Do not use this medicine after the expiry date ("EXP") shown on the outside of the package.

REPORTING SUSPECTED SIDE EFFECTS

You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways:

- **Report online** at www.healthcanada.gc.ca/medeffect
- **Call toll-free** at 1-866-234-2345
- **Complete a Canada Vigilance Reporting Form and:**
 - Fax toll-free to 1-866-678-6789, or
 - Mail to: **Canada Vigilance Program
Health Canada
Postal Locator 1908C
Ottawa, Ontario
K1A 0K9**

Postage paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available on the MedEffect™ Canada Web site at www.healthcanada.gc.ca/medeffect.

NOTE: Should you require information related to the management of the side effect, please contact your health professional. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

This brochure does not contain all known information about INVIRASE. If you have any further questions or concerns about your treatment with INVIRASE, please contact your doctor or pharmacist.

This document plus the full product monograph, prepared for health professionals can be found at:

www.rochecanada.com

or by contacting the sponsor, Hoffmann-La Roche Limited, at: 1-888-762-4388.

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