

# Saquinavir (Invirase)

## Summary

Saquinavir is a type of anti-HIV drug called a protease inhibitor. The most common side effects of saquinavir can include nausea, diarrhea, abdominal discomfort, and heartburn. It is usually taken at a dose of 1,000 mg twice daily with food together with another drug ritonavir (Norvir).

## What is saquinavir?

Saquinavir, sold under the brand name Invirase, is a type of anti-HIV drug (antiretroviral) called a protease inhibitor (PI). Saquinavir is used in combination with other anti-HIV drugs to treat (but not cure) HIV.

## How does saquinavir work?

To explain how saquinavir works, we need to first tell you some information about HIV. When HIV infects a cell, it takes control of that cell. HIV then forces the cell to make many more copies of the virus. To make these copies, the cell uses proteins called enzymes. When the activity of these enzymes is reduced the production of HIV slows.

Saquinavir belongs to a group or class of drugs called protease inhibitors. Saquinavir interferes with an enzyme called protease, which is used by HIV-infected cells to make new viruses. Since saquinavir inhibits, or reduces the activity of this enzyme, this drug causes HIV-infected cells to produce fewer viruses.

## How do people with HIV use saquinavir?

Saquinavir is used in combination with several other anti-HIV drugs, usually nukes (nucleoside analogues), and sometimes including drugs from other classes such as non-nukes (non-nucleoside reverse transcriptase inhibitors). Combinations such as this are called antiretroviral therapy, or ART. For more information on ART, see CATIE's *Your Guide to HIV Treatment*.

For many people with HIV, the use of ART has increased their CD4+ cell counts and decreased the amount of HIV in their blood (viral load). These beneficial effects help to reduce the risk of developing a life-threatening infection. Neither saquinavir nor any other anti-HIV medication is a cure for HIV. It is therefore important that you do the following:

- See your doctor regularly so that he/she monitors your health.

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- Continue to practise safer sex and take other precautions so as not to pass HIV on to other people.

## Warning

Patients starting treatment with ritonavir-boosted saquinavir should have a cardiogram (ECG) performed before starting treatment. Saquinavir can affect the electrical activity of the heart and patients should be monitored regularly after starting treatment.

## Side effects

### 1. General

Side effects that can commonly occur with the use of saquinavir are mainly gastrointestinal and include the following: nausea, diarrhea, abdominal discomfort or pain, and heartburn. Less common side effects include unexpected tiredness, headaches, difficulty falling asleep and altered sense of taste.

### 2. Liver enzymes

Because saquinavir is metabolized (processed and broken down) by the liver, blood tests may show increased levels of liver enzymes.

### 3. Bleeding

Women may experience heavier menstrual periods when using protease inhibitors. Hemophiliacs who use protease inhibitors may experience increased bleeding. If you are a hemophiliac who uses saquinavir and has this problem, let your doctor know about it.

### 4. Blood sugar

In some people with HIV who use protease inhibitors, levels of sugar (glucose) in the blood become higher than normal. Prolonged bouts of higher-than-normal blood sugar levels may lead to diabetes. At least one study has found that some HIV-positive women, particularly those who are overweight, may be at increased risk for

diabetes when they use protease inhibitors. Regular monitoring of your blood to assess sugar levels and other measurements will help you and your doctor be aware of changes that might suggest problems with your blood sugar. Although the risk of developing diabetes is generally low, symptoms that may be related to diabetes (increased thirst, increased urination, unexplained weight loss, fatigue and dry, itchy skin) should be discussed with your doctor.

## 5. Lipodystrophy syndrome

HIV lipodystrophy syndrome is the name given to a range of symptoms that can develop over time when people use ART. Some features of the lipodystrophy syndrome include:

- loss of fat just under the skin (subcutaneous fat) in the face, arms, and legs
- bulging veins in the arms and/or legs due to the loss of fat under the skin
- increased waist and belly size
- fat pads at the back of the neck (“buffalo hump”) or at the base of the neck (“horse collar”)
- small lumps of fat in the abdomen
- increased breast size (in women)

Together with these physical changes, lab tests of your blood may detect the following:

- increased levels of fatty substances called triglycerides
- increased levels of LDL-cholesterol (low-density lipoprotein), or “bad” cholesterol
- increased levels of sugar (glucose)
- increased levels of the hormone insulin
- decreased sensitivity to insulin (insulin resistance)
- decreased levels of HDL-cholesterol (high-density lipoprotein), or “good” cholesterol

The precise causes of the HIV lipodystrophy syndrome are not clear and are difficult to understand because in some people with HIV, there

may be one or more aspects of the syndrome taking place. For instance, some people may experience fat wasting, others fat gain, and others may experience both fat gain and wasting. What is becoming increasingly clear is that unfavourable changes in the lab readings of glucose, cholesterol, and triglycerides over a period of several years increase the risk of diabetes and cardiovascular disease. So far, however, the many benefits of ART are much greater than the increased risk of cardiovascular disease or other side effects.

Maintaining a normal weight, eating a healthy diet, exercising regularly and quitting smoking are all important in helping you to reduce your risk of diabetes, heart disease, and other complications. Regular visits to your doctor for checkups and blood tests are a vital part of staying healthy. If necessary, your doctor can prescribe lipid-lowering therapy.

Researchers are studying the lipodystrophy syndrome to try to discover ways of helping people with HIV avoid or reduce this problem. To find out more about options for managing aspects of the lipodystrophy syndrome, see CATIE's *Practical Guide to HIV Drug Side Effects*.

## 6. Pregnancy

Like many anti-HIV medicines, the long-term effect of saquinavir on the human fetus is not known. In experiments on rats, no toxicity was seen in doses five times greater than used in people. Because animal studies are not always predictive of what happens in humans, the manufacturer (Hoffmann-La Roche) cautions that this drug should only be used by pregnant women if the benefits to the mother outweigh the risk to the fetus. Therefore, if you are pregnant or wish to become pregnant, talk to your specialist about using saquinavir. The good news is that a recent American study (PACTG 386) suggests that the combination of saquinavir with low-dose ritonavir is safe and effective in pregnancy.

## Drug interactions

Always consult your doctor and pharmacist about taking any other prescription or non-prescription

medication, including herbs, supplements, and street drugs.

Some drugs can interact with saquinavir, increasing or decreasing its levels in your body. Increased drug levels can cause you to experience side effects or make pre-existing side effects worse. On the other hand, if drug levels become too low, HIV can develop resistance and your future treatment options may be reduced.

It may also be necessary to avoid drugs that do not affect saquinavir drug levels, but cause similar side effects.

If you must take a drug that has the potential to interact with your existing medications, your doctor can do the following:

- adjust your dose of either your anti-HIV drugs or other medications
- prescribe different anti-HIV drugs for you

## Drug interactions for saquinavir

The following drugs interact or have the potential to interact with saquinavir. These lists are not exhaustive.

The manufacturer recommends that the following drugs should not be taken by people using saquinavir, because this could lead to serious (or life-threatening) interactions.

- antihistamines – astemizole (Hismanal), terfenadine (Seldane)
- antibiotics – rifampin (Rifadin, Rofact)
- anti-psychotic drugs – pimozide (Orap)
- antidepressants – trazodone
- drugs for abnormal heart rhythms – amiodarone (Codarone), bepridil (Vasacor), flecainide (Tambocor), propafenone (Rhythmol), quinidine, procainamide, sotalol, lidocaine
- gastrointestinal motility agents – cisapride (Prepulsid)
- herbs – St. John's wort, garlic (raw or capsule formulations)

- lipid-lowering agents – lovastatin (Mevacor), simvastatin (Zocor).
- migraine drugs (Ergot derivatives) – dihydroergotamine (Migranal), Ergomar (ergotamine), ergonovine, methylergonovine
- sedatives – midazolam (Versed), triazolam (Halcion)
- drugs to treat erectile dysfunction – sildenafil (Viagra), tadalafil (Cialis), vardenafil (Levitra). Taking saquinavir with any of these drugs can lead to dangerous side effects and even death. Talk to your doctor if you have erectile dysfunction about how you might use these drugs safely
- Drugs to treat benign prostatic hyperplasia (BPH) – alfuzosin

The following drugs can *increase* levels of saquinavir in your body:

- antibiotics – clarithromycin (Biaxin)
- antifungal agents – ketoconazole (Nizoral)
- antiulcer drugs – ranitidine (Zantac)
- non-nukes (NNRTIs) – delavirdine (Rescriptor)
- HIV protease inhibitors – atazanavir (Reyataz), indinavir (Crixivan), nelfinavir (Viracept) all raise levels of saquinavir in the blood

The following drugs can *decrease* levels of saquinavir in the blood:

- antibiotics – rifabutin (Mycobutin), rifampin (Rifater)
- antiseizure drugs – carbamazepine (Tegretol), phenobarbital, phenytoin
- corticosteroids – dexamethasone

Saquinavir can *increase* levels of the following drugs:

- benzodiazepines – including alprazolam (Xanax), diazepam (Valium), flurazepam (Dalmane)
- calcium channel blockers – including felodipine (Plendil, Renedil), nifedipine (Adalat), nifedipine

- lipid-lowering drugs – atorvastatin (Lipitor)
- transplant drugs – cyclosporine (Neoral)
- tricyclic antidepressants – including amitriptyline (Elavil), nortriptyline

Saquinavir can *decrease* levels of the following drugs:

- oral contraceptive hormones – ethinyl estradiol
- narcotics – methadone

## Resistance and cross-resistance

Over time, as new copies of HIV are made in the body, the virus changes its structure. These changes are called mutations and can cause HIV to resist the effects of anti-HIV drugs, which means those drugs will no longer work for you. Combining saquinavir with at least two other anti-HIV drugs delays the development of drug resistance.

To reduce the risk of developing drug resistance, all anti-HIV drugs should be taken every day exactly as prescribed and directed. If doses are delayed, missed, or not taken as prescribed, levels of saquinavir in the blood may fall too low. If this happens, resistant virus can develop. If you find you are having problems taking your medications as directed, speak to your doctor and nurse about this. They can find ways to help you.

When HIV becomes resistant to one drug in a class, it sometimes becomes resistant to other drugs in that class. This is called cross-resistance. Feel free to talk with your doctor about your current and future treatment options. To help you decide what these future therapies might be, at some point your doctor can have a small sample of your blood analysed using resistance testing. Should HIV in your body become resistant to saquinavir, your doctor, with the help of resistance testing, can help put together a new treatment regimen for you.

## Dosage and formulations

Because saquinavir is not well absorbed on its own and it is almost always taken in combination with another drug, called ritonavir (Norvir), which 'boosts' the absorption of saquinavir.

When saquinavir is taken with ritonavir, it raises the level of saquinavir in the blood compared to when saquinavir is taken alone. It also prolongs the time saquinavir remains in the blood. Combining saquinavir with ritonavir allows for twice-daily dosing. Both drugs should be taken at the same time.

In some cases saquinavir may be combined with other PIs such as lopinavir (in Kaletra) or atazanavir (Reyataz), particularly in the case of people with HIV who are treatment-experienced.

Saquinavir is available as 500 mg tablets and 200 mg hard gelatin capsules. The usual standard adult dose of saquinavir is 1,000 mg (2 tablets or 5 capsules) with 100 mg ritonavir, both drugs taken two times a day within 2 hours of a meal. Avoid grapefruit juice when taking saquinavir. Formulations can change, and dosages may need to be customized. All medications should always be taken as prescribed and directed.

## Availability

Saquinavir is licensed in Canada for the treatment of HIV infection in adults, in combination with other anti-HIV drugs. Your doctor can tell you more about the availability and coverage of saquinavir in your region. CATIE's online module *Federal, Provincial and Territorial Drug Access Programs* also contains information about Canadian drug coverage.

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## Disclaimer

Decisions about particular medical treatments should always be made in consultation with a qualified medical practitioner knowledgeable about HIV- and hepatitis C-related illness and the treatments in question.

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