



DARUNAVIR (Prezista)

Summary

Darunavir is a type of anti-HIV drug called a protease inhibitor. Common side effects of darunavir can include nausea, diarrhea and headache. It is taken at a dose of 600 mg twice daily along with 100 mg of ritonavir (Norvir) also twice daily. Both drugs need to be taken with food.

What is darunavir?

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

How does darunavir work?

To explain how darunavir 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. In order to make these copies, the cell uses proteins called enzymes. When the activity of these enzymes is reduced or blocked, production of HIV slows or stops.

Darunavir belongs to a group or class of drugs called protease inhibitors. Darunavir interferes with an enzyme called protease, which is used by HIV-infected cells to make new viruses. Since darunavir inhibits, or reduces the activity of this enzyme, this drug causes HIV-infected cells to slow down or stop producing new viruses.

How do people with HIV/AIDS use darunavir?

Darunavir 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 highly active antiretroviral therapy, or HAART. For more information on HAART, see CATIE's *Practical Guide to HAART for People Living with HIV/AIDS* at www.catie.ca/PG_HAART_e.nsf.

For many people with HIV/AIDS (PHAs), the use of HAART 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 darunavir nor any other anti-HIV medication is a cure for HIV/AIDS. It is therefore important that you do the following:

- see your doctor regularly so that he/she monitors your health
- continue to practise safer sex and take other precautions so as not to pass HIV on to other people and to protect yourself from new strains of HIV and other germs



Warnings

1. Pregnancy

The safety of darunavir in pregnant women has not been studied. The manufacturer notes that darunavir “should be used during pregnancy only if the potential benefit justifies the potential risk.”

2. Liver and pancreas health

In controlled clinical trials, a small proportion of darunavir users, about 2%, have developed severely or dangerously elevated levels of the following in their blood:

- alkaline phosphatase – a liver enzyme
- pancreatic amylase – an enzyme produced by the pancreas gland
- pancreatic lipase – an enzyme produced by the pancreas gland

This increase in liver enzymes suggests that damage to important organs such as the liver and pancreas is occurring. It is important to discuss your lab test results with your doctor(s) and nurse.

In clinical trials, about 0.5% of darunavir users have developed liver damage. Since darunavir has been approved, reports of liver injury have emerged. Some of these cases of liver injury have been fatal. Liver injury has occurred among darunavir users with the following profile:

- advanced HIV infection
- having complications including co-infection with hepatitis B or hepatitis C virus
- taking multiple medications
- developing the immune reconstitution syndrome

Before beginning therapy with darunavir, you need to have levels of your liver enzymes checked with a blood test. If your liver enzymes are elevated before you begin darunavir, you will need to have their levels frequently monitored after you start taking darunavir.

If your liver enzymes levels increase while you are on darunavir, this suggests that liver damage is occurring. Your doctor may therefore have to stop giving you darunavir and use a different medication.

The following signs or symptoms can appear when liver damage is occurring:

- unexpected tiredness
- loss of appetite
- nausea
- yellowing of the skin and whites of the eyes
- dark urine
- tender liver
- swollen liver or spleen

If you develop any of these signs or symptoms, tell your doctor right away.

Darunavir should not be used in people with severe liver damage.

Side effects

1. General

Common side effects that have been reported by some darunavir users include the following:

- nausea
- diarrhea
- constipation
- rash
- headache
- lack of energy

Most of these side effects were either mild or moderate in severity. Also, if they did occur, these side effects happened early in the course of darunavir therapy.

2. Rash

Rash can be a side effect of darunavir, occurring early in the course of therapy. However, this is usually mild and can clear within two or three weeks. In cases of severe



rash, or rash of moderate intensity that is accompanied by other symptoms, it is important to contact your doctor right away.

In clinical trials, fewer than 1% of darunavir users developed a severe or life-threatening rash (Stevens-Johnson syndrome).

3. Lipodystrophy syndrome

The HIV lipodystrophy syndrome is the name given to a range of symptoms that can develop over time when people use HAART regimens. 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 PHAs 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 HAART 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 PHAs 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* at www.catie.ca/sideeffects_e.nsf.

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 darunavir, 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.

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 with darunavir

Below are lists of actual and potential drug interactions. These lists are not exhaustive.

The manufacturer recommends that the following drugs should not be taken by darunavir users, because this could lead to serious or life-threatening reactions:

- anesthetics – lidocaine
- anti-anxiety agents – midazolam (**Versed**), triazolam (**Halcion**), diazepam (**Valium**), flurazepam (**Dalmane**)
- antidepressants – tricyclic antidepressants such as imipramine, amitriptyline
- antihistamines – astemizole (**Hismanal**), terfenadine (**Seldane**)
- anti-malaria drugs – halofantrine (**Halfan**)
- anti-psychotic drugs – pimozide (**Orap**)

- blood thinning agents – warfarin (**Coumadin**)
- gastrointestinal motility agents – cisapride (**Prepulsid**)
- drugs for abnormal heart rhythms – amiodarone (**Codarone**), bepridil (**Vascor**), lidocaine, quinidine
- migraine medications (ergot derivatives) including the following – dihydroergotamine (**Migranal**), ergotamine (**Ergomar**), ergonovine

The following drugs can *increase* levels of darunavir in the blood:

- HIV protease inhibitors – lopinavir/ritonavir (**Kaletra**), saquinavir (**Invirase**)
- antibiotics – clarithromycin (**Biaxin**)
- anti-fungal agents – ketoconazole (**Nizoral**), itraconazole (**Sporanox**), voriconazole (**Vfend**)

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

- antibiotics / anti-tuberculosis medications

– rifampin, rifampicin. These drugs should not be used with darunavir.

- herbs – St. John's wort (hypericin, hyperforin)
- anti-seizure medications – phenytoin (**Dilantin**), carbamazepine (**Tegretol**), phenobarbital

Darunavir can *increase* levels of the following drugs in the blood:

- antibiotics – rifabutin (**Mycobutin**). If rifabutin must be used, the manufacturer of darunavir recommends that a dose of rifabutin 150 mg every other day be used. Regular blood tests are necessary to ensure that bone marrow damage does not occur.
- anti-fungal agents – itraconazole (**Sporanox**), ketoconazole (**Nizoral**)
- corticosteroids – including dexamethasone, fluticasone propionate (**Advair**, **Flonase**, **Flovent**). This group of medications should be used with caution in people taking darunavir.
- erectile dysfunction (ED) medications – sildenafil (Viagra), vardenafil (**Levitra**) and tadalafil (**Cialis**). When taken by users of darunavir, these medications can reach very high levels in the blood, causing dangerous side effects. If you have difficulty getting or maintaining an erection, speak to your doctor about how you might safely use these ED medications.
- non-nukes (NNRTIs) – nevirapine (**Viramune**)
- lipid-lowering medications commonly called statins – atorvastatin (**Lipitor**). The manufacturer of darunavir recommends that atorvastatin be initiated at a dose of 10 mg/day and this dose may be gradually increased.
- transplant medications – levels of the following may be increased in users of darunavir: cyclosporine (**Neoral**), rapamycin (**Sirolimus**, **Rapamune**), tacrolimus (**Prograf**)



Darunavir can *decrease* the levels of the following drugs:

- antidepressants – paroxetine (**Paxil**), sertraline (**Zoloft**)
- narcotics – methadone; monitoring for signs of methadone withdrawal and adjusting the dose may become necessary in some people also using darunavir
- hormones – estrogens and proestrogens may interact with darunavir

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 darunavir 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 darunavir 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 darunavir, your doctor, with the help of resistance testing, can help put together a new treatment regimen for you.

Dosage and formulations

Darunavir (**Prezista**) is available as 300 mg tablets. Darunavir is not well absorbed on its own and it is always taken in combination with another drug, called ritonavir (**Norvir**), which ‘boosts’ the absorption of darunavir.

For adults, the recommended dose of darunavir is 600 mg with 100 mg of ritonavir, twice daily. Both medicines must be taken with food to ensure proper absorption.

Formulations can change, and dosages may need to be customized. All medications should always be taken as prescribed and directed.

Availability

Darunavir is licensed in Canada for the treatment of HIV infection in adults whose previous therapy has failed. Darunavir must be taken in combination with other anti-HIV drugs. Your doctor can tell you more about the availability and coverage of darunavir in your region. CATIE’s online module Federal, Provincial and Territorial Drug Access Programs (on CATIE’s website at www.catie.ca/eng/Publications/drugaccess/drugaccessIndex.shtml) also contains information about Canadian drug coverage.

Credits

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Disclaimer

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

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