Norvir (ritonavir)

Norvir soft-gelatin capsules are white and imprinted with the Abbott corporate logo on one side. Norvir is also available in a liquid formulation.

Also known as: RTV, ABT-358

Background and description. Norvir is a protease inhibitor. The US Food and Drug Administration (FDA) approved Norvir in March 1996. Norvir is indicated in combination with other antiretrovirals for the treatment of HIV infection. The drug is manufactured by Abbott Laboratories. In recent years, Norvir has been used in small doses to increase the levels of other drugs in the body thereby boosting potency. The small levels of Norvir used do not provide activity against HIV, but rather slow down the metabolism of other drugs. One example of this strategy is Kaletra, which is a coformulation of a protease inhibitor "lopinavir" with Norvir. However, this strategy can be used with other protease inhibitors including Crixivan, Viracept, Reyataz, and Agenerase (including the newer formulation: Lexiva). Usually the standard dosing of the main drug is lowered to account for the Norvir boost.

Dose. If used as the only protease inhibitor in a regimen, the recommended dose of Norvir is 600 mg (six 100 mg capsules) twice a day. Dosing with other protease inhibitors as a boosting agent may vary, but several boosted regimens use 100 mg or 200 mg of Norvir once or twice a day with another protease inhibitor. Pediatric dosing is also available.

Food restrictions. Food is not required, but it does improve Norvir's pharmacokinetics somewhat and makes the drug more tolerable.

Storage. Abbott recommends that patients store Norvir capsules in the refrigerator; however, refrigeration is not necessary if the capsules are used within 30 days, protected from light and kept at a temperature less than 77°F. Norvir solution should be kept at room temperature and not refrigerated. Abbott is working on a new form of Norvir that would not require refrigeration.

Patient assistance. Abbott Laboratories provides a patient assistance program. For more information, call 800.659.9050.

Side effects and toxicity. Side effects most commonly produced by Norvir include asthenia (weakness), nausea, diarrhea, vomiting, anorexia, abdominal pain, taste perversion and circumoral paresthesia (numbness around the mouth). Metabolic (lipid and glucose) and morphologic (fat accumulation and fat atrophy) abnormalities have been associated with protease inhibitors in general. Norvir levels are lower in patients with moderate liver impairment. No specific dose adjustment is recommended, but careful monitoring is suggested.

Drug interactions. When mixed with Norvir, certain antihistamines, sedative hypnotics, and antiarrhythmics may produce serious or life-threatening reactions. The following drugs should **not** be combined with Norvir: Vascor (bepridil), Cordarone (amiodarone), Tambocor (flecainide), Rythmol (propafenone), Quinidex (quinidine), Zocor (simvastatin), Mevacor (lovastatin), Propulsid (cisapride), Clozaril (clozapine), Versed (midazolam), Halcion (triazolam), Voriconazole (VFEND), fluticasone (an ingredient in Flonase), alfuzosin (for prostate problems), DHE 45 (dihydroergotamine) and other ergot derivatives such as Wigraine and Cafergot, and St. John's wort (*Hypericum perforatum*).

Lipid-lowering drugs such as Lipitor (atorvastatin), Pravachol (pravastatin) or Lescol (fluvastatin) should be used with caution. Caution should also be used if co-administering Xanax (alprazolam) because Norvir may inhibit clearance of Xanax from the body. When taken with Norvir, the dose of Mycobutin (rifabutin) should be reduced to 150 mg once daily. No more than 200 mg daily of Nizoral (ketoconazole) should be given to a patient receiving Norvir. Levels of methadone are reduced in the presence of Norvir and may require dose adjustment. Also, a lower dose of Desyrel (trazodone) should be given in patients also taking Norvir. Because Norvir decreases the level of oral contraceptives, an additional or alternative method of birth control should be used. Norvir interacts with Coumadin (warfarin); initial frequent monitoring is recommended in patients taking both of these drugs. Finally, when co-administered with Norvir, dose reductions are required for Viagra (sildenafil), Cialis (tadalafil), and Levitra (vardenafil).

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Additional info:

Resistance and cross-resistance. Mutations at positions 82, 84, and 54 are associated with resistance to Norvir. High-level cross-resistance between Norvir and other protease inhibitors has been observed.

Clinical data. Abbott 247 randomized 1090 treatment experienced patients with a mean baseline CD4 T cell count of 32 cells/mm^3 to add Norvir or placebo to each patient's baseline antiviral regimen. The incidence of disease progression or death during the double-blind phase of the study was 26% for patients receiving Norvir versus 42% for patients receiving placebo. This difference was statistically significant. At week 24, patients randomized to the Norvir arm of the study had a mean CD4 T cell increase of approximately 50 cells/mm^3 and a mean decrease in viral load of approximately 0.6 log.

Norvir was the first protease inhibitor to demonstrate a decrease in disease progression or death when administered to patients with advanced HIV infection. Although it is one of the most potent protease inhibitors on the market, the drug's side effect profile prevents its widespread use as the anchor in a 3-drug regimen. The drug holds continued promise in its role as a pharmacokinetic booster of other protease inhibitors. However some researchers caution that the low doses used for boosting may generate resistance, thus leaving this strategy as a better option for patients whose virus already harbors resistance to Norvir.

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