

Fortovase or Invirase (saquinavir)



The 500-mg Invirase tablets are beige and imprinted with "ROCHE" on one side and "SQV 500" on the other side.



Also known as: Ro 31-8959, saquinavir mesylate, SQV

Background and description. This drug is a protease inhibitor manufactured by F. Hoffmann-La Roche Ltd. and distributed by Roche Laboratories Inc. The US Food & Drug Administration (FDA) approved it in its first formulation (the hard-gel formulation Invirase) for use in combination with nucleoside reverse transcriptase inhibitors (NRTIs) in December 1995. Invirase was the first FDA-approved protease inhibitor. Subsequently, the FDA approved a new soft-gel formulation (Fortovase) in November 1997.

The maker of this drug has recently announced that the Fortovase (soft-gel) formulation will no longer be available after 2005. The preferred way to administer this drug is as Norvir-boosted Invirase (see below).

Dose. The soft-gel Fortovase is dosed at 1200 mg (six 200 mg capsules) 3 times a day. The hard-gel Invirase is only recommended when combined with Norvir. As of December 2003, the approved dosing with Norvir is 1000 mg of Fortovase or Invirase with 100 mg of Norvir twice a day. The hard-gel formulation achieves higher therapeutic drug levels than the soft-gel formulation when combined with Norvir. In December 2004, the FDA approved a new 500-mg tablet formulation of Invirase.

Food restrictions. Soft-gel Fortovase should be taken with a meal or up to 2 hours after a meal. Combining Fortovase or Invirase with Norvir eliminates the food effect.

Storage. Fortovase soft-gel capsules should be refrigerated at 36° to 46°F in tightly closed bottles until dispensed. Refrigerated capsules remain stable until the expiration date printed on the label. Once brought to room temperature capsules should be used within 3 months. The Invirase hard-gel capsules may be stored at room temperature.

Patient assistance. Roche offers a patient assistance program for those who qualify. For more information call 800.282.7780.

Side effects and toxicity. The most common side effects seen with Fortovase/Invirase are gastrointestinal disturbances including nausea, bloating, and diarrhea. Elevated liver function has been noted as well. Metabolic (lipid and glucose) and morphologic (fat accumulation and fat atrophy) abnormalities have been associated with protease inhibitors in general.

Drug interactions. Fortovase/Invirase should **not** be taken with the following: Propulsid (cisapride), Halcion (triazolam), Versed (midazolam), ergot derivatives such as Wigraine and Cafergot, Zocor (simvastatin), Mevacor (lovastatin), Rifadin or Rimactane (rifampin), Mycobutin (rifabutin), Sustiva, and Crixivan. The use of St. John's Wort (*Hypericum perforatum*) is not recommended while taking either Fortovase or Invirase.

Lipid-lowering drugs such as Lipitor (atorvastatin), Pravachol (pravastatin), or Lescol (fluvastatin) should be used with caution when combined with Fortovase/Invirase. Dose reductions of Viagra (sildenafil), Cialis (tadalafil), and Levitra (vardenafil) are recommended when taken with Fortovase/Invirase. When combining Fortovase with Viracept consideration should be given to dosing 750 mg Viracept with 800 mg of Fortovase 3 times a day. Rescriptor increases the levels of Fortovase with a mild decrease in Rescriptor levels. An increase in liver toxicities has been observed with this combination and patients with hepatitis B or C should be monitored carefully, especially during the first 6 weeks of administration. Norvir increases the levels of Fortovase by 3 fold or higher.

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Additional info:

Resistance and cross-resistance. Resistance to Invirase has been generally associated with mutations at positions 48 and 90. Resistance and treatment failure with Fortovase has been generally associated with mutations at positions 48, 54, and 82. In addition, a mutation at position 90 can occur with Fortovase. Resistance to Invirase or Fortovase results in potential cross-resistance to other protease inhibitors.

Clinical data. Early trials studied saquinavir as monotherapy, in combination with Retrovir and Hivid and in high doses. All of these trials produced small virologic benefits. Invirase received approval on the basis of ACTG 229, a study comparing the combination of Invirase and Hivid versus monotherapy of either, in Retrovir-experienced patients. FDA approval was based on surrogate marker data, but longer-term follow-up confirmed the clinical benefit of Invirase.

Subsequent studies found Fortovase to have an 8 fold greater increase in drug exposure than Invirase. In a study comparing Fortovase/NRTIs versus Invirase/NRTIs, on-treatment analysis showed that at 16 weeks 67% of patients in the Fortovase arm compared to 37% of patients in the Invirase arm had viral load levels below 400 copies/mL. The mean viral load decreases were 2.0 log in the Fortovase group as compared to 1.6 log in the Invirase group.

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