

Aptivus (tipranavir)



Aptivus tablets are orange-beige in color with the "TPV 250" written in dark ink on one side. Each tablet contains 250 mg of tipranavir. This medication is designed for patients with drug-resistant HIV, especially those who have taken other protease inhibitors. Aptivus must be taken with Norvir as a boosting agent.



Background. Aptivus (tipranavir) received approval from the US Food and Drug Administration (FDA) in June 2005. The drug is manufactured by Boehringer Ingelheim. Aptivus is a protease inhibitor and must be used in combination with Norvir (ritonavir) and at least two other anti-HIV drugs. Aptivus is only approved for HIV-positive people who have failed other anti-HIV drug regimens (including those containing protease inhibitors).

Dose. Aptivus is supplied in soft gelatin capsules of 250mg. The recommended dose of Aptivus is 500mg (two 250-mg capsules) with 200 mg (two 100-mg capsules) of Norvir twice daily. So, a total of 1000 mg of Aptivus and 400 mg of Norvir is taken each day.

Food restrictions. Aptivus should be taken with food, preferably a complete meal.

Storage. Unopened bottles of Aptivus capsules should be stored in a refrigerator (36°-46°F). Once the bottle is opened, the contents must be used within 60 days. Aptivus can be brought along while traveling if the bottle remains at a temperature of approximately 59°F to 86°F.

Patient assistance. Patient should call 800.274.8651.

Side effects and toxicity. The most common side effects include diarrhea, nausea, vomiting, stomach pain, tiredness, fever, bronchitis, depression, and headache. Women taking birth control pills or hormone replacement therapy may be more likely to get a skin rash.

Serious side effects include liver problems, including liver failure and death. You should stop taking Aptivus/ritonavir treatment and call your doctor immediately if you experience tiredness, general ill feeling or "flu-like" symptoms, loss of appetite, nausea, yellowing of your skin or whites of your eyes, dark colored urine, pale stools (bowel movements), or pain, ache, or sensitivity on your right side below your ribs.

Other serious side effects include rash, increased bleeding in patients with hemophilia, diabetes and high blood sugar (hyperglycemia), worsening of pre-existing diabetes, increased blood fat (lipid) levels, and changes in body fat (lipodystrophy).

When taking Aptivus, caution should be exercised in patients with hemophilia, diabetes, or liver problems, as well as those who are infected with hepatitis B or hepatitis C, who are allergic to sulfa medicines, who are pregnant or plan on becoming pregnant, who are breastfeeding, or who are using estrogens for birth control or hormone replacement. There are no adequate and well-controlled studies of Aptivus in pregnant women for the treatment of HIV infection. Aptivus should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Drug interactions. Aptivus should not be taken with the following: Halcion (triazolam), Versed (midazolam), Hismanal (astemizole), Seldane (terfenadine), Orap (pimozide), Propulsid (cisapride), Pacedone (amiodarone), Vasacor (bepridil), Tambocor (flecainide), Rythmol (propafenone), Quinaglute/Quinidex (quinidine), Rifadin or Rimactane (rifampin), Antabuse (disulfiram), Flagyl (metronidazole), St. John's wort (*Hypericum perforatum*), cholesterol-lowering drugs such as Mevacor (lovastatin) and Zocor (simvastatin), and ergot alkaloids/derivatives (medications to treat migraine headaches, for example Ergostat, Cafergot, etc.). Because Aptivus lowers the levels of birth control pills, an additional or alternative method of birth control should be used.

Also, the following medications may require a dosing change of Aptivus and/or the other medicine, and should be used with caution: HIV medications such as Ziagen, Videx (EC), Retrovir (included in Combivir and Trizivir), Lexiva (or Agenerase), Kaletra, and Fortovase or Invirase; Coumadin (warfarin); antifungals; antimycobacterials such as clarithromycin or rifabutin; calcium-channel blockers, with the exception of Vasacor (bepridil), which cannot be used with Aptivus/Norvir at all; medications to treat diabetes such as Amaryl (glimepiride), Metaglip (glipizide), Glucovance (glyburide), Actos (pioglitazone), Prandin (repaglinide), and Orinase (tolbutamide); Lipitor (atorvastatin); medicines to prevent organ transplant rejection; methadone; Demerol (meperidine); oral contraceptives; and antidepressants such as Prozac (fluoxetine), Paxil (paroxetine), Zoloft (sertraline), and Norpramin (desipramine). Levels of Viagra (sildenafil), Cialis (tadalafil), and Levitra (vardenafil) may be significantly raised in the presence of Aptivus and dose reductions are recommended.

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Additional info:

Resistance and cross resistance. In Phase 3 studies, multiple protease inhibitor-resistant HIV-1 isolates from 59 highly treatment-experienced patients who received Aptivus/Norvir and experienced virologic rebound developed amino acid substitutions that were associated with resistance to Aptivus. The most common amino acid substitutions that developed on 500/200 mg Aptivus/Norvir in greater than 20% of Aptivus/Norvir virologic failure isolates were L33V/I/F, V82T, and I84V. Other substitutions that developed in 10 to 20% of Aptivus/Norvir virologic failure isolates included L10V/I/S, I13V, E35D/G/N, I47V, K55R, V82L, and L89V/M. Aptivus resistance was detected at virologic rebound after an average of 38 weeks of Aptivus/Norvir treatment with a median 14-fold decrease in Aptivus susceptibility. The resistance profile in treatment-naive subjects has not been characterized.

Cross-resistance among protease inhibitors has been observed. Aptivus had less than a 4-fold decreased susceptibility against 90% (94/105) of HIV-1 isolates resistant to Lexiva (or Agenerase), Reyataz, Crixivan, Kaletra, Viracept, Norvir, or Fortovase or Invirase. Aptivus-resistant viruses which emerged in vitro had decreased susceptibility to the protease inhibitors Lexiva (or Agenerase), Reyataz, Crixivan, Kaletra, Viracept, and Norvir but remained sensitive to Fortovase or Invirase.

Clinical data . Studies 1182.12 and 1182.48 are ongoing, randomized, controlled, open-label, multicenter studies in HIV-positive, triple antiretroviral class experienced patients. All patients were required to have previously received at least two protease inhibitor-based antiretroviral regimens and were failing a protease inhibitor-based regimen at the time of study entry with baseline HIV-1 RNA at least 1000 copies/mL and any CD4+ cell count. At least one primary protease gene mutation from among 30N, 46I, 46L, 48V, 50V, 82A, 82F, 82L, 82T, 84V or 90M had to be present at baseline, with not more than two mutations at codons 33, 82, 84 or 90. These studies evaluated treatment response at 24 weeks in a total of 1159 patients receiving either Aptivus co-administered with 200 mg of ritonavir plus optimized background regimen (OBR) versus a control group receiving a ritonavir-boosted protease inhibitor (lopinavir, amprenavir, saquinavir or indinavir) plus OBR. After Week 8, patients in the control group who met the protocol defined criteria of initial lack of virologic response had the option of discontinuing treatment and switching over to Aptivus/Norvir in a separate roll-over study.

Demographics and baseline characteristics were similar in the Aptivus/Norvir arm and control arms. Participants in both studies were mostly Caucasian males with a median baseline CD4 T cell count of 155 cells/mm³ and a median baseline plasma HIV-1 RNA of 4.82 log₁₀ copies/mL. Forty percent of the patients had baseline HIV-1 RNA of ≥ 100,000 copies/mL, 61% had a baseline CD4+ cell count < 200 cells/mm³, and 57% had experienced an AIDS defining Class C event at baseline. Patients had prior exposure to a median of 6 nucleoside reverse transcriptase inhibitors (NRTIs), 1 non-nucleoside reverse transcriptase inhibitor (NNRTI), and 4 protease inhibitors (PIs). A total of 12% of patients had previously used Fuzeon. In baseline patient samples (n=454), 97% of the isolates were resistant to at least one protease inhibitor, 95% of the isolates were resistant to at least one NRTI, and > 75% of the isolates were resistant to at least one NNRTI.

Based on genotypic testing and the patient's medical history, the individually selected (before start of study) protease inhibitor was Kaletra in 50%, Lexiva (or Agenerase) in 26%, Fortovase or Invirase in 20%, and Crixivan in 4% of patients. A total of 86% were possibly resistant or resistant to the pre-selected comparator protease inhibitors. Approximately 25% of patients used Fuzeon during study. There were differences between Studies 1182.12 and 1182.48 in the use of the protease inhibitors and in the use of Fuzeon.

Through 24 weeks of treatment, the proportion of patients in the Aptivus/Norvir arm compared to the comparator PI/Norvir arm with HIV-1 RNA < 400 copies/mL was 34% and 16% respectively, and with HIV-1 RNA < 50 copies/mL was 23% and 9% respectively. Among all randomized and treated patients, the median change from baseline in HIV-1 RNA at the last measurement up to Week 24 was -0.80 log₁₀ copies/mL in patients receiving Aptivus/Norvir versus -0.25 log₁₀ copies/mL in the comparator PI/Norvir arm.

Among all randomized and treated patients, the median change from baseline in CD4 T cell count at the last measurement up to Week 24 was +34 cells/mm³ in patients receiving Aptivus/Norvir (N=582) versus +4 cells/mm³ in the comparator PI/Norvir (N=577) arm. Patients in the Aptivus/Norvir arm achieved a significantly better virologic outcome when Aptivus/Norvir was combined with Fuzeon.

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