



# fact sheet

## APTIVUS capsules/oral solution

### What is APTIVUS?

APTIVUS is a protease inhibitor co-administered with ritonavir (APTIVUS/r), which is indicated for combination antiretroviral treatment of HIV-1 infected patients who are treatment-experienced and infected with HIV-1 strains resistant to more than one protease inhibitor. APTIVUS must be co-administered with ritonavir to exert its therapeutic effect.

This indication is based on analyses of plasma HIV-1 RNA levels in two controlled studies of APTIVUS/r of 48 weeks duration in treatment-experienced adults and one open-label 48-week study in pediatric patients age 2 to 18 years. The adult studies were conducted in clinically advanced, 3-class antiretroviral (NRTI, NNRTI, PI) treatment-experienced adults with evidence of HIV-1 replication despite ongoing antiretroviral therapy

The following points should be considered when initiating therapy with APTIVUS/r:

- The use of APTIVUS/r in treatment-naïve patients is not recommended
- The use of other active agents with APTIVUS/r is associated with a greater likelihood of treatment response
- Genotypic or phenotypic testing and/or treatment history should guide the use of APTIVUS/r. The number of baseline primary protease inhibitor mutations affects the virologic response to APTIVUS/r
- Use caution when prescribing APTIVUS/r to patients with elevated transaminases, hepatitis B or C co-infection or patients with mild hepatic impairment
- Liver function tests should be performed at initiation of therapy with APTIVUS/r and monitored frequently throughout the duration of treatment
- The drug-drug interaction potential of APTIVUS/r when co-administered with other drugs must be considered prior to and during APTIVUS/r use
- Use caution when prescribing APTIVUS/r in patients who may be at risk for increased bleeding or who are receiving medications known to increase the risk of bleeding
- APTIVUS should not be used in children under 2 years of age
- The risk-benefit of APTIVUS/r has not been established in pediatric patients less than 2 years of age.

There are no study results demonstrating the effect of APTIVUS/r on clinical progression of HIV.

APTIVUS/r does not cure HIV or help prevent passing HIV to others.

### What is the recommended dosage for APTIVUS?

The approved adult dose of APTIVUS is 500 mg taken with 200 mg of ritonavir, twice daily.

Prescribers should calculate the appropriate dose of APTIVUS for each individual child based on body weight (kg) or body surface area (BSA, m<sup>2</sup>) and should not exceed the recommended adult dose. Before prescribing APTIVUS 250 mg capsules, children should be assessed for the ability to swallow capsules. If a child is unable to reliably swallow an APTIVUS capsule, the APTIVUS oral solution formulation should be prescribed. The recommended pediatric dose of APTIVUS is 14 mg/kg with 6 mg/kg ritonavir (or 375

mg/m<sup>2</sup> co-administered with ritonavir 150 mg/m<sup>2</sup>) taken twice daily not to exceed a maximum dose of APTIVUS 500 mg co-administered with ritonavir 200 mg twice daily. For children who develop intolerance or toxicity and cannot continue with APTIVUS 14 mg/kg with 6 mg/kg ritonavir, physicians may consider decreasing the dose to APTIVUS 12 mg/kg with 5 mg/kg ritonavir (or APTIVUS 290 mg/m<sup>2</sup> co-administered with 115 mg/m<sup>2</sup> ritonavir) taken twice daily provided their virus is not resistant to multiple protease inhibitors. Body surface area can be calculated as follows:

$$\text{Mosteller Formula: } \text{BSA (m}^2\text{)} = \sqrt{\frac{\text{Height (cm)} \times \text{Wt (kg)}}{3600}}$$

APTIVUS must be co-administered with ritonavir to boost the therapeutic levels of APTIVUS; otherwise, levels of APTIVUS will be insufficient to inhibit HIV replication. APTIVUS/r must be taken in combination with other anti-HIV medications.

**Can APTIVUS be combined with new anti-HIV medications?**

While BI has not done pharmacokinetic studies on APTIVUS with recently approved antiretroviral drugs and those in development, the companies developing them have in many cases. In adult patients APTIVUS/r may be co-administered with the 2 recently approved agents according to 24-week data from their package inserts: the CCR5 inhibitor, maraviroc, and the integrase inhibitor, raltegravir.

- Dose maraviroc at 300 mg BID when combining with APTIVUS/r
  - APTIVUS/r induces CYP3A enzymes that are responsible for maraviroc metabolism
  - **No dosage adjustments necessary**
- Dose raltegravir at 400 mg BID when combining with APTIVUS/r
  - APTIVUS/r reduces plasma concentrations of raltegravir
  - In clinical studies, because there was no efficacy difference between the subgroup who received APTIVUS/r and those who did not, **no dosage adjustment of raltegravir is needed when combining with APTIVUS/r**
  - Approximately 100 subjects received raltegravir with APTIVUS/r in clinical trials resulting in comparable efficacy to patients not receiving APTIVUS/r
- APTIVUS should not be co-administered with etravirine

The studies supporting these dosage recommendations were conducted by Tibotec Pharmaceuticals Limited, Pfizer Inc. and Merck and Co. Inc. Please consult with the appropriate company for more information.

**What is the most important safety information about APTIVUS?**

**Important Safety Information for APTIVUS**

- APTIVUS/r has been associated with reports of clinical hepatitis and hepatic decompensation, including some fatalities. Extra vigilance is warranted in patients with chronic hepatitis B or hepatitis C co-infection, as these patients have an increased risk of hepatotoxicity. Patients with signs or symptoms of clinical hepatitis should discontinue APTIVUS/r treatment and seek medical evaluation.
- APTIVUS/r has been associated with reports of both fatal and non-fatal intracranial hemorrhage (ICH).
- All patients should be followed closely with clinical and laboratory monitoring, especially those with chronic hepatitis B or C co-infection, as these patients have an increased risk of hepatotoxicity. Liver function tests should be performed prior to initiating therapy with APTIVUS/r, and frequently throughout the duration of treatment.

- Treatment-experienced patients with chronic hepatitis B or hepatitis C co-infection or elevations in transaminases are at approximately 2-fold risk for developing Grade 3 or 4 transaminases elevations or hepatic decompensation. In the RESIST trials, Grade 3 and 4 increases in hepatic transaminases were observed in 10.3 percent (10.9/100 PEY) of patients receiving APTIVUS/r through week 48. In a study of treatment-naïve patients, 20.3 percent (21/100 PEY) experienced Grade 3 or 4 hepatic transaminases elevations while receiving APTIVUS/r through week 48.
- APTIVUS/r is contraindicated in patients with moderate or severe (Child-Pugh Class B or C, respectively) hepatic impairment.
- The drug-drug interaction potential of APTIVUS/r when co-administered with multiple classes of drugs must be considered prior to and during APTIVUS/r use.
- APTIVUS/r is contraindicated with amiodarone, bepridil, flecainide, propafenone, quinidine, rifampin, dihydroergotamine, ergonovine, ergotamine, methylergonovine, cisapride, St. John's wort, lovastatin, simvastatin, pimozide, midazolam (oral) and triazolam due to the potential for serious and/or life-threatening events or loss of efficacy.
- A drug interaction study in healthy subjects has shown that ritonavir significantly increases plasma fluticasone propionate exposures. Concomitant use of APTIVUS/r and fluticasone propionate may produce systemic corticosteroid side effects, including Cushing's syndrome and adrenal suppression. APTIVUS/r should not be taken with fluticasone propionate, inhaled or intranasally administered, unless the potential benefit to the patient outweighs the risk.
- Caution should be used when prescribing sildenafil, tadalafil, and vardenafil with APTIVUS/r because concentrations of these drugs may increase.
- Caution should be used when prescribing carbamazepine, phenobarbital and/or phenytoin. APTIVUS may be less effective due to decreased tipranavir plasma concentrations.
- Caution should be used when prescribing valproic acid. Valproic acid may be less effective due to decreased valproic acid plasma concentrations.
- Use caution when prescribing APTIVUS/r in patients who may be at risk of increased bleeding from trauma, surgery or other medical conditions, or who are receiving medications known to increase the risk of bleeding such as antiplatelet agents and anticoagulants, or who are taking supplemental high doses of vitamin E.
- Patients taking APTIVUS oral solution should be advised not to take supplemental vitamin E greater than a standard multivitamin as APTIVUS oral solution contains 116 IU/mL of vitamin E which is higher than the Reference Daily Intake (adults 30 IU, pediatrics approximately 10 IU).
- Rash, including urticarial rash, maculopapular rash, and possible photosensitivity, has been reported in patients receiving APTIVUS/r. In some, rash was accompanied by joint pain or stiffness, throat tightness, or generalized pruritus. In controlled clinical trials, rash (all grades, all causality) was observed in 10 percent of females and in 8 percent of males receiving APTIVUS/r through 48 weeks of treatment. The median time to onset of rash was 53 days and the median duration of rash was 22 days. The discontinuation rate for rash in clinical trials was 0.5 percent. In an uncontrolled compassionate use program (n=3,920), cases of rash, some of which were severe, accompanied by myalgia, fever, erythema, desquamation, and mucosal erosions were reported. In the pediatric clinical trial, the frequency of rash (all grades, all causality) through 48 weeks of treatment was 21 percent. Most of these patients had mild rash and 5 percent had moderate rash. Overall, 3 percent interrupted APTIVUS treatment due to rash and the discontinuation rate for rash was 0.9 percent. Discontinue and initiate appropriate treatment if severe skin rash develops.

**What is the most important safety information about APTIVUS? (continued)**

- APTIVUS should be used with caution in patients with a known sulfonamide allergy.
- New onset diabetes mellitus, exacerbation of pre-existing diabetes mellitus, hyperglycemia and increased bleeding (in patients with hemophilia) have been reported in patients taking protease inhibitors. A causal relationship between protease inhibitors and these events has not been established.
- Immune reconstitution syndrome has been reported in patients treated with combination antiretroviral therapy, including APTIVUS/r.
- Redistribution and/or accumulation of body fat have been observed in patients receiving antiretroviral therapy. A causal relationship has not been established.
- Treatment with APTIVUS/r has resulted in large increases in total cholesterol and triglycerides, which should be monitored prior to and during APTIVUS/r therapy.
- Because the potential for HIV cross-resistance among protease inhibitors has not been fully explored in APTIVUS/r-treated patients, it is unknown what effect therapy with APTIVUS will have on the activity of subsequently administered protease inhibitors.
- APTIVUS must be co-administered with ritonavir to exert its therapeutic effect. Failure to correctly co-administer APTIVUS with ritonavir will result in reduced plasma levels of tipranavir that will be insufficient to achieve the desired antiviral effect and will alter some drug interactions.
- Please refer to the complete ritonavir prescribing information for a description of ritonavir contraindications and additional information on precautionary measures.
- In adults, the most frequent adverse reactions (incidence greater than 4 percent) were diarrhea, nausea, fever, vomiting, fatigue, headache, and abdominal pain. In pediatric patients (age 2 to 18 years) the most frequent adverse reactions were generally similar to those seen in adults. However, rash was more frequent in pediatric patients than in adults.
- APTIVUS should not be used in children under 2 years of age.

Please consult the [Full Prescribing Information](#), including boxed WARNINGS, and [Important Safety Information](#) for *APTIVUS*, as well as information on the [RESIST](#) Trials.

**How long has APTIVUS been available in the U.S.?**

APTIVUS/r received accelerated approval for use in the United States by the Food and Drug Administration in June 2005. APTIVUS/r was granted full (traditional) approval in the United States in October 2007. Full approval was based on 48-week analyses of the phase 3 RESIST studies.

The U.S. FDA granted approval of APTIVUS capsules/oral solution with dosing information for treatment-experienced pediatric patients infected with HIV-1 in June 2008. The oral solution formulation, which is a new dosage form of APTIVUS, was also approved for treatment-experienced adults.

**For additional information**

APTIVUS is distributed by Boehringer Ingelheim Pharmaceuticals Inc. For additional information, please contact Susan Holz, Public Affairs & Communications at, [susan.holz@boehringer-ingelheim.com](mailto:susan.holz@boehringer-ingelheim.com) or visit [www.aptivus.us](http://www.aptivus.us).