Table 9 Established and Other Potentially Significant Drug Interactions: Alterations in Dose or Regimen May be Recommended Based on Drug Interaction Studies or Predicted Interaction (continued)

Concomitant Drug Class: Drug name	Effect on Concentration of Tipranavir or Concomitant Drug	Clinical Comment
	Other Agents for Opportunistic Infections	
Antimycobacterials:		
Clarithromycin	↑ Tipranavir, ↑ Clarithromycin, ↓ 14-hydroxy-clarithromycin metabolite	No dose adjustment of tipranavir or clarithromycin for patients with normal renal function is necessary. For patients with renal impairment the following dosage adjustments should be considered: • For patients with CL_{CR} 30 to 60 mL/min the dose of clarithromycin should be reduced by 50%. For patients with CL_{CR} < 30 mL/min the dose of clarithromycin should be decreased by 75%.
Rifabutin	Tipranavir not changed, ↑Rifabutin ↑ Desacetyl-rifabutin	Single dose study. Dosage reductions of rifabutin by 75% are recommended (e.g. 150 mg every other day). Increased monitoring for adverse events in patients receiving the combination is warranted. Further dosage reduction may be necessary.
	Other Agents Commonly used	
Calcium Channel Blockers: Diltiazem Felodipine Nicardipine Nisoldipine Verapamil	Combination with TPV/ritonavir not studied. Cannot predict effect of TPV/ritonavir on calcium channel blockers that are dual substrates of CYP 3A and P-gp due to conflicting effect of TPV/ritonavir on CYP 3A and P-gp. ↕ Diltiazem ↑ Felodipine (CYP 3A substrate but not P-gp substrate) ↕ Nicardipine ↕ Nisoldipine (CYP 3A substrate but not clear whether it is a P-gp substrate) ↕ Verapamil	Caution is warranted and clinical monitoring of patients is recommended.
Despiramine	Combination with TPV/ritonavir not studied ↑ Despiramine	Dosage reduction and concentration monitoring of despiramine is recommended.

Table 9 Established and Other Potentially Significant Drug Interactions: Alterations in Dose or Regimen May be Recommended Based on Drug Interaction Studies or Predicted Interaction (continued)

Disulfiram/Metronidazole	Combination with TPV/ritonavir not studied	APTIVUS capsules contain alcohol that can produce disulfiram-like reactions when co-administered with disulfiram or other drugs which produce this reaction (e.g. metronidazole).
HMG-CoA reductase inhibitors: Atorvastatin	↑ Tipranavir, ↑ Atorvastatin ↓ Hydroxy-atorvastatin metabolites	Start with the lowest possible dose of atorvastatin with careful monitoring, or consider other HMG-CoA reductase inhibitors. Concomitant use of APTIVUS, co-administered with 200 mg of ritonavir, with lovastatin or simvastatin is not recommended.
Hypoglycemics: Glimepiride Glipizide Glyburide Pioglitazone Repaglinide Tolbutamide	Combination with TPV/ritonavir not studied. ↕ Glimepiride (CYP 2C9) ↕ Glipizide (CYP 2C9) ↕ Glyburide (CYP 2C9) ↕ Pioglitazone (CYP 2C8 and CYP 3A4) ↕ Repaglinide (CYP 2C8 and CYP 3A4) ↕ Tolbutamide (CYP 2C9) The effect of TPV/ritonavir on CYP 2C8 and CYP 2C9 substrates is not known.	Careful glucose monitoring is warranted.
Immunosuppressants: Cyclosporine Sirolimus Tacrolimus	Combination with TPV/ritonavir not studied. Cannot predict effect of TPV/ritonavir on immunosuppressants due to conflicting effect of TPV/ritonavir on CYP 3A and P-gp. ↕ Cyclosporine ↕ Sirolimus ↕ Tacrolimus	More frequent concentration monitoring of these medicinal products is recommended until blood levels have been stabilized.
Narcotic analgesics:		
Meperidine	Combinations with TPV/ritonavir not studied ↓ Meperidine, ↑ Normeperidine	Dosage increase and long-term use of meperidine are not recommended due to increased concentrations of the metabolite normeperidine which has both analgesic activity and CNS stimulant activity (e.g. seizures).
Methadone	↓ Methadone by 50%	Dosage of methadone may need to be increased when co-administered with tipranavir and 200 mg of ritonavir.

Table 9 Established and Other Potentially Significant Drug Interactions: Alterations in Dose or Regimen May be Recommended Based on Drug Interaction Studies or Predicted Interaction (continued)

Oral contraceptives/Estrogens: Ethinyl estradiol	 ↓ Ethinyl estradiol concentrations by 50%	Alternative methods of nonhormonal contraception should be used when estrogen based oral contraceptives are co-administered with tipranavir and 200 mg of ritonavir. Patients using estrogens as hormone replacement therapy should be clinically monitored for signs of estrogen deficiency. Women using estrogens may have an increased risk of non serious rash.
PDE5 inhibitors: Sildenafil Tadalafil Vardenafil	Combinations with TPV/ritonavir not studied. ↑ Sildenafil ↑ Tadalafil ↑ Vardenafil	Concomitant use of PDE5 inhibitors with tipranavir and ritonavir should be used with caution and in no case should the starting dose of: • sildenafil exceed 25 mg within 48 hours • tadalafil exceed 10 mg every 72 hours • vardenafil exceed 2.5 mg every 72 hours
Selective Serotonin-Reuptake Inhibitors: Fluoxetine Paroxetine Sertraline	Combination with TPV/ritonavir not studied ↑ Fluoxetine ↑ Paroxetine ↑ Sertraline	Antidepressants have a wide therapeutic index, but doses may need to be adjusted upon initiation of APTIVUS/ritonavir therapy.
Warfarin	Combination with TPV/ritonavir not studied. Cannot predict the effect of TPV/ritonavir on S-Warfarin due to conflicting effect of TPV and RTV on CYP 2C9	Frequent INR (international normalized ratio) monitoring upon initiation of tipranavir/ritonavir therapy.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Long term animal carcinogenicity bioassays with tipranavir and tipranavir/ritonavir are currently in progress. However, tipranavir showed no evidence of mutagenicity or clastogenicity in a battery of five *in vitro* and *in vivo* tests including the Ames bacterial reverse mutation assay using *S. typhimurium* and *E. coli*, unscheduled DNA synthesis in rat hepatocytes, induction of gene mutation in Chinese hamster ovary cells, a chromosome aberration assay in human peripheral lymphocytes, and a micronucleus assay in mice.

Tipranavir had no effect on fertility or early embryonic development in rats at dose levels up to 1000 mg/Kg/day, equivalent to a C_{max} of 258 μM in females. Based on C_{max} levels in these rats, as well as an exposure (AUC) of 1670 μM·h in pregnant rats from another study, this exposure was

approximately equivalent to the anticipated exposure in humans at the recommended dose level of 500/200 mg tipranavir/ritonavir BID.

Pregnancy

Teratogenic Effects, Pregnancy Category C.

Investigation of fertility and early embryonic development with tipranavir disodium was performed in rats, teratogenicity studies were performed in rats and rabbits, and pre- and post-natal development were explored in rats.

No teratogenicity was detected in reproductive studies performed in pregnant rats and rabbits up to dose levels of 1000 mg/Kg/day and 150 mg/Kg/day tipranavir, respectively, at exposure levels approximately 1.1-fold and 0.1-fold human exposure. At 400 mg/Kg/day and above in rats, fetal toxicity (decreased sternebrae ossification and body weights) was observed, corresponding to an AUC of 1310 μM·h or approximately 0.8-fold human exposure at the recommended dose. In rats and rabbits, fetal toxicity was not noted at 40 mg/Kg/day and 150 mg/Kg/day, respectively, corresponding accordingly to C_{max}/AUC_{0-24h} levels of 30.4 μM/340 μM·h and 8.4 μM/120 μM·h. These exposure levels (AUC) are approximately 0.2-fold and 0.1-fold the exposure in humans at the recommended dose.

In pre- and post-development studies in rats, tipranavir showed no adverse effects at 40 mg/Kg/day (~0.2-fold human exposure), but caused growth inhibition in pups and maternal toxicity at dose levels of 400 mg/Kg/day (~0.8-fold human exposure). No post-weaning functions were affected at any dose level.

There are no adequate and well-controlled studies in pregnant women for the treatment of HIV-1 infection. APTIVUS should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Antiretroviral Pregnancy Registry

To monitor maternal-fetal outcomes of pregnant women exposed to APTIVUS, an Antiretroviral Pregnancy Registry has been established. Physicians are encouraged to register patients by calling (800) 258-4263.

Nursing Mothers

The Centers for Disease Control and Prevention recommend that HIV-infected mothers not breastfeed their infants to avoid risking postnatal transmission of HIV. Because of both the potential for HIV transmission and any possible adverse effects of tipranavir, mothers should be instructed not to breastfeed if they are receiving APTIVUS.

Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

Geriatric Use

Clinical studies of APTIVUS did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. In general, caution should be exercised in the administration and monitoring of APTIVUS in elderly patients reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

ADVERSE REACTIONS

APTIVUS (tipranavir), co-administered with 200 mg of ritonavir, has been studied in a total of 1854 HIV-positive adults as combination therapy in clinical studies. Of these, 1397 patients received the dose of 500/200 mg BID. Seven hundred sixty one (761) adults, including 385 in the 1182.12 and 1182.48 Phase 3 pivotal studies, have been treated for at least 24 weeks.

In 1182.12 and 1182.48 in the APTIVUS/ritonavir arm, the most frequent AEs were diarrhea, nausea, fatigue, headache and vomiting. Adverse events leading to discontinuation were reported by 7.8% of the tipranavir-treated patients and 4.9% of the comparator arm patients.

Due to the need for co-administration of APTIVUS with 200 mg of ritonavir, please refer to ritonavir prescribing information for ritonavir-associated adverse reactions.

The most frequent clinical treatment-emergent adverse events reported in Phase 3 clinical studies (1182.12 and 1182.48) in adults are summarized in Table 10 below. Events of moderate to severe intensity (Grades 2-4) reported in at least 2% of highly treatment-experienced subjects in either treatment group are included.

Table 10 Percentage of Patients with Treatment Emergent Adverse Events of at Least Moderate Intensity (Grades 2-4) in ≥ 2% of Patients in Either Treatment Group[a]

	Phase 3 Studies 1182.12 and 1182.48 (24-weeks)	
	Tipranavir/ritonavir (500/200 mg BID) + OBR (n=746)	Comparator PI/ritonavir[b] + OBR (n=737)
Gastrointestinal Disorders		
Diarrhea	10.9%	9.4%
Nausea	6.7%	4.6%
Vomiting	3.4%	3.0%
Abdominal pain[c]	2.8%	3.7%
General Disorders		
Pyrexia	4.6%	4.3%
Fatigue	4.0%	3.9%
Asthenia	1.5%	2.3%
Infections and Infestations		
Bronchitis	2.9%	1.1%
Nervous System Disorders		
Headache	3.1%	3.1%
Psychiatric Disorders		
Depression	2.0%	3.0%
Insomnia	1.2%	2.6%
Respiratory, Thoracic and Mediastinal Disorders		
Cough	0.8%	2.2%
Skin and Subcutaneous Tissue Disorders		
Rash	2.0%	2.0%

[a]Excludes laboratory abnormalities that were Adverse Events
[b]Comparator PI/RTV: lopinavir/ritonavir 400/100 mg BID, indinavir/ritonavir 800/100 mg BID, saquinavir/ritonavir 1000/100 mg BID, amprenavir/ritonavir 600/100 mg BID
[c]Abdominal pain includes Preferred Terms "Abdominal pain" and "Abdominal pain upper"

Clinically meaningful adverse reactions in < 2% of adult patients (n=1397) treated with APTIVUS/ritonavir 500/200mg in Phase 2 and 3 trials listed below by body system:

Blood and Lymphatic System Disorders: anemia, neutropenia, thrombocytopenia

Gastrointestinal Disorders: abdominal distension, dyspepsia, flatulence, gastroesophageal reflux disease, pancreatitis

General Disorders: influenza like illness, malaise, pyrexia

Hepatobiliary Disorders: hepatitis, hepatic failure

Immune System Disorders: hypersensitivity

Infections and infestations: reactivation of herpes simplex and varicella zoster

Investigations: hepatic enzymes increased, liver function test abnormal, lipase increased, weight decreased

Metabolism and Nutrition Disorders: anorexia, decreased appetite, dehydration, diabetes mellitus, facial wasting, hyperamylasemia, hypercholesterolemia, hyperglycemia

Musculoskeletal and Connective Tissue Disorders: muscle cramp, myalgia

Nervous System Disorders: dizziness, neuropathy peripheral, somnolence

Psychiatric Disorders: insomnia, sleep disorder

Renal and Urinary Disorders: renal insufficiency

Respiratory, Thoracic and Mediastinal Disorders: dyspnea

Skin and Subcutaneous System Disorders: exanthem, lipoatrophy, lipodystrophy acquired, lipohypertrophy, pruritus

Laboratory Abnormalities

Treatment-emergent clinical laboratory abnormalities reported at 24 weeks in Phase 3 clinical studies (1182.12 and 1182.48) in adults are summarized in Table 11 below.

Table 11 Treatment Emergent Laboratory Abnormalities Reported in ≥ 2% of Adult Patients

		Studies 1182.12 and 1182.48 (24-weeks)	
	Limit	APTIVUS/ritonavir (500/200 mg BID) + OBR (n = 732)	Comparator PI/ritonavir + OBR* (n = 726)
Hematology			
WBC count decrease			
Grade 3-4	< 2.0 x 10^3/μL	3.6%	5.4%
Chemistry			
Amylase			
Grade 3-4	> 2 x ULN	2.9%	4.8%
ALT			
Grade 2	> 2.5-5 x ULN	10.7%	5.4%
Grade 3	> 5-10 x ULN	3.1%	1.4%
Grade 4	> 10 x ULN	2.7%	0.4%
AST			
Grade 2	> 2.5-5 x ULN	6.0%	5.8%
Grade 3	> 5-10 x ULN	3.3%	1.0%
Grade 4	> 10 x ULN	0.7%	0.4%
ALT and/or AST			
Grade 2-4	> 2.5 x ULN	17.5%	9.9%
Cholesterol			
Grade 2	> 300 – 400 mg/dL	11.3%	4.3%
Grade 3	> 400 – 500 mg/dL	2.5%	0.3%
Grade 4	> 500 mg/dL	0.8%	0%
Triglycerides			
Grade 2	400 – 750 mg/dL	26.2%	14.7%
Grade 3	> 750 – 1200 mg/dL	12.8%	5.6%
Grade 4	> 1200 mg/dL	6.1%	3.4%

*Comparator PI/RTV: lopinavir/ritonavir 400/100 mg BID, indinavir/ritonavir 800/100 mg BID, saquinavir/ritonavir 1000/100 mg BID, amprenavir/ritonavir 600/100 mg BID

In clinical trials extending up to 48 weeks, the proportion of patients who developed Grade 2-4 ALT and/or AST elevations increased to 24.4% with APTIVUS/ritonavir and to 12.8% with CPI/ritonavir.

OVERDOSAGE

There is no known antidote for tipranavir overdose. Treatment of overdose should consist of general supportive measures, including monitoring of vital signs and observation of the patient's clinical status. If indicated, elimination of unabsorbed tipranavir should be achieved by emesis or gastric lavage. Administration of activated charcoal may also be used to aid in removal of unabsorbed drug. Since tipranavir is highly protein bound, dialysis is unlikely to be beneficial in significant removal of this medicine.

DOSAGE AND ADMINISTRATION

General

The recommended dose of APTIVUS (tipranavir) Capsules is 500 mg (two 250 mg capsules), co-administered with 200 mg of ritonavir, twice daily.

APTIVUS Capsules, co-administered with 200 mg of ritonavir should be taken with food. Bioavailability is increased with a high fat meal.

HOW SUPPLIED

APTIVUS (tipranavir) Capsules 250 mg are pink, oblong soft gelatin capsules imprinted in black with "TPV 250". They are packaged in HDPE unit-of-use bottles with a child resistant closure and 120 capsules. (NDC 0597-0003-02)

APTIVUS capsules should be **stored in a refrigerator 2°-8°C (36°-46°F)** prior to opening the bottle. After opening the bottle, the capsules may be **stored at 25°C (77°F); excursions permitted to 15°-30°C (59°-86°F)** and must be used within 60 days.

Store in a safe place out of the reach of children.

Address medical inquiries to: http://us.boehringer-ingelheim.com, (800) 542-6257 or (800) 459-9906 TTY.

RX ONLY

Distributed by:
Boehringer Ingelheim Pharmaceuticals, Inc.
Ridgefield, CT 06877 USA

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APTIVUS Capsules are covered by U.S. Patents 5,852,195; 6,147,095; 6,169,181 and 6,231,887

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Revision Date: June 21, 2005

Patient Information

Aptivus® (ap' · ti · vəs) (tipranavir) **Capsules, 250 mg**	Boehringer Ingelheim

ALERT: Find out about medicines that should not be taken with Aptivus. Please also read the section "WHO SHOULD NOT TAKE APTIVUS".

Read the Patient Information that comes with APTIVUS before you start taking it and each time you get a refill. There may be new information. This leaflet does not take the place of talking with your doctor about your medical condition or treatment. You should stay under a doctor's care while taking APTIVUS.

What is the most important information I should know about APTIVUS?

Patients taking APTIVUS, together with 200 mg NORVIR® (ritonavir), may develop severe liver disease that can cause death. If you develop any of the following symptoms of liver problems, you should stop taking APTIVUS/ritonavir treatment and call your doctor right away: tiredness, general ill feeling or "flu-like" symptoms, loss of appetite, nausea (feeling sick to your stomach), yellowing of your skin or whites of your eyes, dark (tea-colored) urine, pale stools (bowel movements), or pain, ache, or sensitivity on your right side below your ribs. If you have chronic Hepatitis B or C infection, your doctor should check your blood tests more often because you have an increased chance of developing liver problems.

What is APTIVUS?

APTIVUS is a medicine called a "protease inhibitor" that is used to treat adults with Human Immunodeficiency Virus (HIV). APTIVUS blocks HIV protease, an enzyme which is needed for HIV to make more virus. When used with other anti-HIV medicines, APTIVUS may reduce the amount of HIV in your blood and increase the number of CD4+ cells. Reducing the amount of HIV in the blood may keep your immune system healthy, so it can help fight infection.

APTIVUS is always taken with NORVIR® (ritonavir) and at the same time as NORVIR When you take APTIVUS with NORVIR, you must always use at least 2 other anti-HIV medicines.

Does APTIVUS cure HIV or AIDS?

APTIVUS does not cure HIV infection or AIDS. The long-term effects of APTIVUS are not known at this time. People taking APTIVUS may still get infections or other conditions common in people with HIV (opportunistic infections). It is very important that you stay under the care of your doctor during treatment with APTIVUS.

Does APTIVUS lower the chance of passing HIV to other people?

APTIVUS does not reduce the chance of passing HIV to others through sexual contact, sharing needles, or being exposed to your blood. Continue to practice safer sex. Use a latex or polyurethane condom or other barrier method to lower the chance of sexual contact with any body fluids such as semen, vaginal secretions or blood. Never use or share dirty needles.

Ask your doctor if you have any questions about safer sex or how to prevent passing HIV to other people.

Who should not take APTIVUS?

Do not take APTIVUS if you:

- are allergic to tipranavir or any of the other ingredients in APTIVUS. See the end of this leaflet for a list of major ingredients.
- are allergic to ritonavir (NORVIR®)
- have moderate to severe liver problems
- take any of the following types of medicines because **you could have serious side effects:**
    - Migraine headache medicines called "ergot alkaloids". If you take migraine headache medicines, ask you doctor or pharmacist if any of them are "ergot alkaloids".
    - Halcion® (triazolam)
    - Hismanal® (astemizole)
    - Orap® (pimozide)
    - Propulsid® (cisapride)
    - Seldane® (terfenadine)
    - Versed® (midazolam)
    - Pacenone® (amiodarone)
    - Vascor® (bepridil)
    - Tambocor® (flecainide)
    - Rythmol® (propafenone)
    - Quinaglute dura® (quinidine)

What should I tell my doctor before I take APTIVUS?

Tell your doctor about all of your medical conditions, including if you:

- **have liver problems** or are infected with Hepatitis B or Hepatitis C. These patients may have worsening of their liver disease.
- **are allergic to sulfa medicines.**
- **have hemophilia.** APTIVUS may cause increased bleeding.
- **have diabetes.** APTIVUS may worsen your diabetes or high blood sugar levels.

- **are pregnant or planning to become pregnant.** It is not known if APTIVUS can harm your unborn baby. You and your doctor will need to decide if APTIVUS is right for you. If you take APTIVUS while you are pregnant, talk to your doctor about how you can be in the Antiretroviral Pregnancy Registry.

- **are breast-feeding.** Do not breast-feed if you are taking APTIVUS. You should not breast-feed if you have HIV because of the chance of passing the HIV virus to your baby. Talk with your doctor about the best way to feed your baby.

- **are using estrogens for birth control or hormone replacement.** Women who use estrogens for birth control or hormone replacement have an increased chance of developing a skin rash while taking APTIVUS. If a rash occurs, it is usually mild to moderate, but you should talk to your doctor as you may need to temporarily stop taking either APTIVUS or the other medicine that contains estrogen or female hormones.

Tell your doctor about all the medicines you take including prescription and nonprescription medicines, vitamins and herbal supplements. **APTIVUS and many other medicines can interact. Sometimes serious side effects will happen if APTIVUS is taken with certain other medicines (see "Who should not take APTIVUS?").**

- Some medicines cannot be taken at all with APTIVUS
- Some medicines will require a change in dosage if taken with APTIVUS
- Some medicines will require close monitoring if taken with APTIVUS.

Women taking birth control pills need to use another birth control method. APTIVUS makes birth control pills work less well.

Know all the medicines you take and keep a list of them with you. Show this list to all your doctors and pharmacists anytime you get a new medicine you take. They will tell you if you can take these other medicines with APTIVUS. **Do not start any new medicines while you are taking APTIVUS without first talking with your doctor or pharmacist.** You can ask your doctor or pharmacist for a list of medicines that can interact with APTIVUS.

How should I take APTIVUS?

- Take APTIVUS exactly as your doctor has prescribed. You should check with your doctor or pharmacist if you are not sure. **You must take APTIVUS at the same time as NORVIR® (ritonavir).** The usual dose is 500 mg (two 250 mg capsules) of APTIVUS, together with 200 mg (two 100 mg capsules or 2.5 mL of solution) of NORVIR, twice per day. APTIVUS with NORVIR must be used together with other anti-HIV medicines.

APTIVUS comes in a capsule form and you should **swallow APTIVUS capsules whole. Do not chew the capsules.**

- Always take APTIVUS with food.
- Do not change your dose or stop taking APTIVUS without first talking with your doctor.
- If you take too much APTIVUS, call your doctor or poison control center right away.
- If you forget to take APTIVUS, take the next dose of APTIVUS, together with NORVIR® (ritonavir), as soon as possible. Do not take a double dose to make up for a missed dose.

- It is very important to take all your anti-HIV medicines as prescribed and at the right times of day. This can help your medicines work better. It also lowers the chance that your medicines will stop working to fight HIV (drug resistance).
- When your APTIVUS supply starts to run low, get more from your doctor or pharmacy. This is very important because the amount of virus in your blood may increase if the medicine is stopped for even a short period of time. The HIV virus may develop resistance to APTIVUS and become harder to treat. You should NEVER stop taking APTIVUS or your other HIV medicines without talking with your doctor.

What are the possible side effects of APTIVUS?

APTIVUS may cause serious side effects, including:

- **liver problems, including liver failure and death.** Your doctor should do blood tests to monitor your liver function during treatment with APTIVUS. Patients with liver diseases such as Hepatitis B and Hepatitis C may have worsening of their liver disease with APTIVUS and should have more frequent monitoring blood tests.

- **rash.** Mild to moderate rash, including flat or raised rashes or sensitivity to the sun, have been reported in approximately 10% of subjects receiving APTIVUS. Some patients who developed rash also had joint pain or stiffness, throat tightness, or generalized itching.

- **increased bleeding in patients with hemophilia.** This can happen in patients taking APTIVUS or other protease inhibitor medicines.

- **diabetes and high blood sugar (hyperglycemia).** This can happen in patients taking APTIVUS or other protease inhibitor medicines. Some patients have diabetes before starting treatment with APTIVUS which gets worse. Some patients get diabetes during treatment with APTIVUS. Some patients will need changes in their diabetes medicine. Some patients will need new diabetes medicine.

- **increased blood fat (lipid) levels.** Your doctor should do blood tests to monitor your blood fat (triglycerides and cholesterol) during treatment with APTIVUS. Some patients taking APTIVUS have large increases in triglycerides and cholesterol. The long-term chance of having a heart attack or stroke due to increases in blood fats caused by APTIVUS is not known at this time.

- **changes in body fat.** These changes have happened in patients taking APTIVUS. and other anti-HIV medicines. The changes may include an increased amount of fat in the upper back and neck ("buffalo hump"), breast, and around the back, chest, and stomach area. Loss of fat from the legs, arms, and face may also happen. The cause and long-term health effects of these conditions are not known.

The most common side effects include diarrhea, nausea, vomiting, stomach pain, tiredness and headache. Women taking birth control pills may get a skin rash.

It may be hard to tell the difference between side effects caused by APTIVUS, by the other medicines you are also taking, or by the complications of HIV infection. For this reason it is very important that

you tell your doctor about any changes in your health. You should report any new or continuing symptoms to your doctor right away. Your doctor may be able to help you manage these side effects.

The list of side effects is **not** complete. Ask your doctor or pharmacist for more information.

How should I store APTIVUS?

- Store APTIVUS capsules in a refrigerator at approximately **36°F to 46°F (2°C to 8°C).** Once the bottle is opened, the contents must be used within 60 days. Patients may take the bottle with them for use away from home so long as the bottle remains at a temperature of approximately **59°F to 86°F (15°C to 30°C).** You can write the date of opening the bottle on the label. Do not use after the expiration date written on the bottle.

- **Keep APTIVUS and all medicines out of the reach of children.**

General advice about APTIVUS

Medicines are sometimes prescribed for purposes other than those listed in a Patient Information leaflet. Do not use APTIVUS for a condition for which it was not prescribed. Do not give APTIVUS to other people, even if they have the same condition you have. It may harm them.

This leaflet summarizes the most important information about APTIVUS. If you would like more information, talk with your doctor. You can ask your pharmacist or doctor for information about APTIVUS that is written for health professionals.

For additional information, you may also call Boehringer Ingelheim Pharmaceuticals, Inc. at 1-800-542-6257, or (TTY) 1-800-459-9906. You may also request information through the company website at http://us.boehringer-ingelheim.com.

What are the ingredients in APTIVUS?

Active Ingredient: tipranavir

Major Inactive Ingredients: dehydrated alcohol, polyoxyl 35 castor oil, propylene glycol, mono/diglycerides of caprylic/capric acid and gelatin.

Rx only

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Roche

FUZEON®

(enfuvirtide)

for Injection

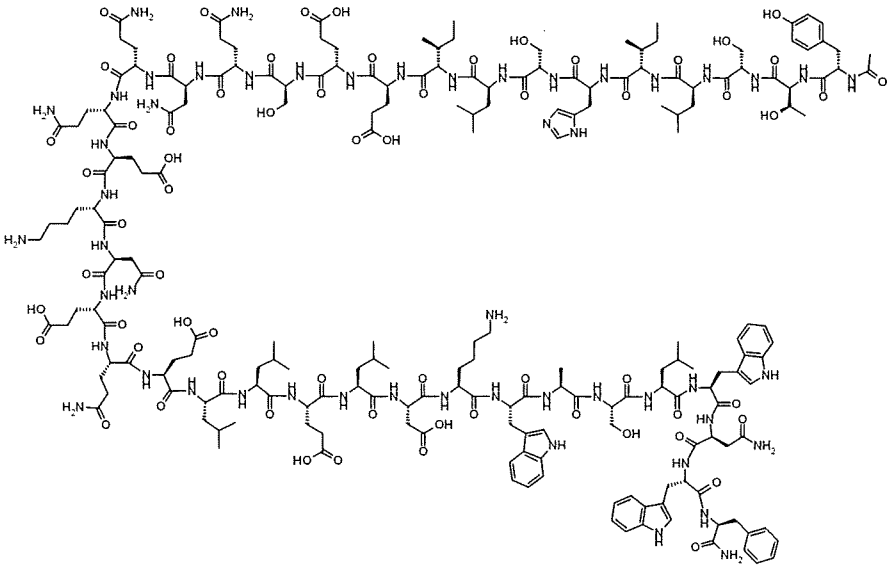
R_x only

DESCRIPTION

FUZEON (enfuvirtide) is an inhibitor of the fusion of HIV-1 with $CD4^+$ cells. Enfuvirtide is a linear 36-amino acid synthetic peptide with the N-terminus acetylated and the C-terminus is a carboxamide. It is composed of naturally occurring L-amino acid residues.

Enfuvirtide is a white to off-white amorphous solid. It has negligible solubility in pure water and the solubility increases in aqueous buffers (pH 7.5) to 85-142 g/100 mL. The empirical formula of enfuvirtide is $C_{204}H_{301}N_{51}O_{64}$, and the molecular weight is 4492. It has the following primary amino acid sequence:

CH_3CO-Tyr-Thr-Ser-Leu-Ile-His-Ser-Leu-Ile-Glu-Glu-Ser-Gln-Asn-Gln-Gln-Glu-Lys-Asn-Glu-Gln-Glu-Leu-Leu-Glu-Leu-Asp-Lys-Trp-Ala-Ser-Leu-Trp-Asn-Trp-Phe-NH_2 and the following structural formula:



The drug product, FUZEON (enfuvirtide) for Injection, is a white to off-white, sterile, lyophilized powder. Each single-use vial contains 108 mg of enfuvirtide for the delivery of 90 mg. Prior to subcutaneous administration, the contents of the vial are reconstituted with 1.1 mL of Sterile Water for Injection giving a volume of approximately 1.2 mL to provide the delivery of 1 mL of the solution. Each 1 mL of the reconstituted solution contains approximately 90 mg of enfuvirtide with approximate amounts of the following excipients: 22.55 mg of mannitol, 2.39 mg of sodium carbonate (anhydrous), and sodium hydroxide and hydrochloric acid for pH adjustment as needed. The reconstituted solution has an approximate pH of 9.0.

MICROBIOLOGY

Mechanism of Action

Enfuvirtide interferes with the entry of HIV-1 into cells by inhibiting fusion of viral and cellular membranes. Enfuvirtide binds to the first heptad-repeat (HR1) in the gp41 subunit of the viral envelope glycoprotein and prevents the conformational changes required for the fusion of viral and cellular membranes.

Antiviral Activity In Vitro

The in vitro antiviral activity of enfuvirtide was assessed by infecting different $CD4^+$ cell types with laboratory and clinical isolates of HIV-1. The IC_{50} values for baseline clinical isolates ranged from 0.089 to 107 nM (0.4 to 480 ng/mL) by the cMAGI assay (n=130) and from 1.56 to 1680 nM (7 to 7530 ng/mL) by a recombinant phenotypic entry assay (n=627). Enfuvirtide was similarly active in vitro against clades A, AE, C, D, E, F, and G (range 5.1 to 10.5 nM), and R5, X4, and dual tropic viruses. Enfuvirtide has no activity against HIV-2.

Enfuvirtide exhibited additive to synergistic effects in cell culture assays when combined with individual members of various antiretroviral classes, including lamivudine, zidovudine, indinavir, nelfinavir, and efavirenz.

Drug Resistance

HIV-1 isolates with reduced susceptibility to enfuvirtide have been selected in vitro. Genotypic analysis of the in vitro-selected resistant isolates showed mutations that resulted in amino acid substitutions at the enfuvirtide binding HR1 domain positions 36 to 38 of the HIV-1 envelope glycoprotein gp41. Phenotypic analysis of site-directed mutants in positions 36 to 38 in an HIV-1 molecular clone showed a 5-fold to 684-fold decrease in susceptibility to enfuvirtide.

In clinical trials, HIV-1 isolates with reduced susceptibility to enfuvirtide have been recovered from subjects failing a FUZEON containing regimen. Posttreatment HIV-1 virus from 277 subjects experiencing protocol defined virological failure at 48 weeks exhibited a median decrease in susceptibility to enfuvirtide of 33.4-fold (range 0.4-6318-fold) relative to their respective baseline virus. Of these, 249 had decreases in susceptibility to enfuvirtide of greater than 4-fold and all but 3 of those 249 exhibited genotypic changes in the codons encoding gp41 HR1 domain amino acids 36 to 45. Substitutions in this region were observed with decreasing frequency at amino acid positions 38, 43, 36, 40, 42, and 45.

Cross-resistance

HIV-1 clinical isolates resistant to nucleoside analogue reverse transcriptase inhibitors (NRTI), non-nucleoside analogue reverse transcriptase inhibitors (NNRTI), and protease inhibitors (PI) were susceptible to enfuvirtide in cell culture.

CLINICAL PHARMACOLOGY

Pharmacokinetics

The pharmacokinetic properties of enfuvirtide were evaluated in HIV-1 infected adult and pediatric patients.

Absorption

Following a 90-mg single subcutaneous injection of FUZEON into the abdomen in 12 HIV-1 infected subjects, the mean (±SD) C_{max} was 4.59 ± 1.5 μg/mL, AUC was 55.8 ± 12.1 μg•h/mL and the median T_{max} was 8 hours

(ranged from 3 to 12 h). The absolute bioavailability (using a 90-mg intravenous dose as a reference) was 84.3% ± 15.5%. Following 90-mg bid dosing of FUZEON subcutaneously in combination with other antiretroviral agents in 11 HIV-1 infected subjects, the mean (±SD) steady-state C_{max} was 5.0 ± 1.7 μg/mL, C_{trough} was 3.3 ± 1.6 μg/mL, AUC_{0-12h} was 48.7 ± 19.1 μg•h/mL, and the median T_{max} was 4 hours (ranged from 4 to 8 h).

Absorption of the 90-mg dose was comparable when injected into the subcutaneous tissue of the abdomen, thigh or arm.

Distribution

The mean (±SD) steady-state volume of distribution after intravenous administration of a 90-mg dose of FUZEON (N=12) was 5.5 ± 1.1 L.

Enfuvirtide is approximately 92% bound to plasma proteins in HIV-infected plasma over a concentration range of 2 to 10 μg/mL. It is bound predominantly to albumin and to a lower extent to α-1 acid glycoprotein.

Metabolism/Elimination

As a peptide, enfuvirtide is expected to undergo catabolism to its constituent amino acids, with subsequent recycling of the amino acids in the body pool.

Mass balance studies to determine elimination pathway(s) of enfuvirtide have not been performed in humans.

In vitro studies with human microsomes and hepatocytes indicate that enfuvirtide undergoes hydrolysis to form a deamidated metabolite at the C-terminal phenylalanine residue, M3. The hydrolysis reaction is not NADPH dependent. The M3 metabolite is detected in human plasma following administration of enfuvirtide, with an AUC ranging from 2.4% to 15% of the enfuvirtide AUC.

Following a 90-mg single subcutaneous dose of enfuvirtide (N=12) the mean ±SD elimination half-life of enfuvirtide is 3.8 ± 0.6 h and the mean ±SD apparent clearance was 24.8 ± 4.1 mL/h/kg. Following 90-mg bid dosing of FUZEON subcutaneously in combination with other antiretroviral agents in 11 HIV-1 infected subjects, the mean ±SD apparent clearance was 30.6 ± 10.6 mL/h/kg.

Special Populations

Hepatic Insufficiency

Formal pharmacokinetic studies of enfuvirtide have not been conducted in patients with hepatic impairment.

Renal Insufficiency

Formal pharmacokinetic studies of enfuvirtide have not been conducted in patients with renal insufficiency. However, analysis of plasma concentration data from subjects in clinical trials indicated that the clearance of enfuvirtide is not affected in patients with creatinine clearance greater than 35 mL/min. The effect of creatinine clearance less than 35 mL/min on enfuvirtide clearance is unknown.

Gender and Weight

Gender

Analysis of plasma concentration data from subjects in clinical trials indicated that the clearance of enfuvirtide is 20% lower in females than males after adjusting for body weight.

Weight

Enfuvirtide clearance decreases with decreased body weight irrespective of gender. Relative to the clearance of a 70-kg male, a 40-kg male will have 20% lower clearance and a 110-kg male will have a 26% higher clearance. Relative to a 70-kg male, a 40-kg female will have a 36% lower clearance and a 110-kg female will have the same clearance.

No dose adjustment is recommended for weight or gender.

Race

Analysis of plasma concentration data from subjects in clinical trials indicated that the clearance of enfuvirtide was not different in Blacks compared to Caucasians. Other pharmacokinetic studies suggest no difference between Asians and Caucasians after adjusting for body weight.

Pediatric Patients

The pharmacokinetics of enfuvirtide have been studied in 23 pediatric subjects aged 6 through 16 years at a dose of 2 mg/kg. Enfuvirtide pharmacokinetics were determined in the presence of concomitant medications including antiretroviral agents. A dose of 2 mg/kg bid (maximum 90 mg bid) provided enfuvirtide plasma concentrations similar to those obtained in adult patients receiving 90 mg bid.

In the 23 pediatric subjects receiving the 2 mg/kg bid dose, the mean ±SD steady-state AUC was 56.3 ± 22.3 μg•h/mL, C_{max} was 6.3 ± 2.4 μg/mL, C_{trough} was 3.1 ± 1.5 μg/mL, and apparent clearance was 40 ± 17 mL/h/kg.

Geriatric Patients

The pharmacokinetics of enfuvirtide have not been studied in patients over 65 years of age.

Drug Interactions

Influence of FUZEON on the Metabolism of Concomitant Drugs

Based on the results from an in vitro human microsomal study, enfuvirtide is not an inhibitor of CYP450 enzymes. In an in vivo human metabolism study (N=12), FUZEON at the recommended dose of 90 mg bid did not alter the metabolism of CYP3A4, CYP2D6, CYP1A2, CYP2C19 or CYP2E1 substrates.

Influence of Concomitant Drugs on the Metabolism of Enfuvirtide

As indicated in Table 1, pharmacokinetic interaction studies were conducted between FUZEON and the following drugs: ritonavir, saquinavir/ritonavir, and rifampin.

Table 1 Effect of Ritonavir, Saquinavir/Ritonavir, and Rifampin on the Steady-State Pharmacokinetics of Enfuvirtide (90 mg bid)*

Coadministered Drug	Dose of Coadministered Drug	N	% Change of Enfuvirtide Pharmacokinetic Parameters[†x] (90% CI)		
			C_{max}	AUC	C_{trough}
Ritonavir	200 mg, q12h, 4 days	12	↑24 (↑9 to ↑41)	↑22 (↑8 to ↑37)	↑14 (↑2 to ↑28)
Saquinavir/ Ritonavir	1000/100 mg, q12h, 4 days	12	⇔	↑14 (↑5 to ↑24)	↑26 (↑17 to↑35)
Rifampin	600 mg, qd, 10 days	12	⇔	⇔	↓15 (↓22 to ↓7)

* All studies were performed in HIV-1+ subjects using a sequential crossover design.
† ↑= Increase; ↓ = Decrease; ⇔ = No Effect (↑ or ↓ <10%)

[x] No interactions were clinically significant.

INDICATIONS AND USAGE

FUZEON in combination with other antiretroviral agents is indicated for the treatment of HIV-1 infection in treatment-experienced patients with evidence of HIV-1 replication despite ongoing antiretroviral therapy.

This indication is based on results from two controlled studies of 48 weeks duration. Subjects enrolled were treatment-experienced adults; many had advanced disease. There are no studies of FUZEON in antiretroviral naive patients.

Description of Clinical Studies

Studies in Antiretroviral Experienced Patients

Studies T20-301 and T20-302 were randomized, controlled, open-label, multicenter trials in HIV-1 infected subjects. Subjects were required to have either (1) viremia despite 3 to 6 months prior therapy with a nucleoside reverse transcriptase inhibitor (NRTI), non-nucleoside reverse transcriptase inhibitor (NNRTI), and protease inhibitor (PI) or (2) viremia and documented resistance or intolerance to at least one member in each of the NRTI, NNRTI, and PI classes.

All subjects received an individualized background regimen consisting of 3 to 5 antiretroviral agents selected on the basis of the subject's prior treatment history and baseline genotypic and phenotypic viral resistance measurements. Subjects were then randomized at a 2:1 ratio to FUZEON 90 mg bid with background regimen or background regimen alone.

After week 8, patients on either treatment arm who met protocol defined criteria for virological failure were permitted to revise their background regimens; those on background regimen alone were also permitted to add FUZEON.

Demographic characteristics for studies T20-301 and T20-302 are shown in Table 2. Subjects had prior exposure to a median of 12 antiretrovirals for a median of 7 years.

Table 2 T20-301 and T20-302 Pooled Subject Demographics

	FUZEON+Background Regimen	Background Regimen
	N=663	N=334
Sex Male Female	 90% 10%	 90% 10%
Race White Black	 89% 8%	 89% 7%
Mean Age (yr) (range)	42 (16-67)	43 (24-82)
Median Baseline HIV-1 RNA (log_{10} copies/mL) (range)	5.2 (3.5-6.7)	5.1 (3.7-7.1)
Median Baseline $CD4^+$ Cell Count ($cells/mm^3$) (range)	89 (1-994)	97 (1-847)

The disposition and efficacy outcomes of studies T20-301 and T20-302 are shown in Table 3.

Table 3 Outcomes at Week 48 (Pooled Studies T20-301 and T20-302)

Outcomes	FUZEON+Background Regimen 90 mg bid N=663	Background Regimen N=334	
Virological Responder (at least 1 log_{10} below baseline)	304 (46%)	61 (18%)	
Virological Non-responder: • Switch • Completed 48 weeks randomized regimen*	 0 191 (29%)	 220 (66%) 12 (4%)	
		Continued Background Regimen (N=112)	Switched to FUZEON (N=220)
Discontinued due to insufficient treatment response#	37 (5%)	13 (12%)	22 (10%)
Discontinued due to adverse	46 (7%)	9 (8%)	13 (6%)