## HIGHLIGHTS OF PRESCRIBING INFORMATION

**These highlights do not include all the information needed to use APTIVUS safely and effectively. See full prescribing information for APTIVUS.**

**APTIVUS® (tipranavir) capsules**
**APTIVUS® (tipranavir) oral solution**
**Initial U.S. Approval: 2005**

**WARNING: HEPATOTOXICITY and INTRACRANIAL HEMORRHAGE**

***See full prescribing information for complete boxed warning.***

- **Clinical hepatitis and hepatic decompensation including some fatalities. Extra vigilance is warranted in patients with chronic hepatitis B or hepatitis C co-infection (5.1)**
- **Fatal and non-fatal intracranial hemorrhage (5.2)**

**----------RECENT MAJOR CHANGES----------**

| | |
|---|---|
| Indications and Usage (1) | 06/2008 |
| Dosage and Administration (2) | 06/2008 |
| Warnings and Precautions | |
| Hepatic Impairment and Toxicity (5.1) | 10/2007 |
| Drug Interactions (5.3) | 10/2007 |
| Effects on Platelet Aggregation and Coagulation (5.4) | 06/2008 |
| Vitamin E Intake (5.5) | 06/2008 |
| Rash (5.6) | 06/2008 |

**----------INDICATIONS AND USAGE----------**

APTIVUS, a protease inhibitor, co-administered with ritonavir, 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 (1)

- Do not use APTIVUS/ritonavir in treatment-naïve patients (1)

**----------DOSAGE AND ADMINISTRATION----------**

- Adults: 500 mg APTIVUS, co-administered with 200 mg ritonavir, twice daily with or without food (2.1)
- Pediatric patients (age 2 to 18 years): Dosing is based on body weight or body surface area not to exceed adult dose (2.2)
- Store unopened bottles of APTIVUS capsules in the refrigerator (16)
- Do not freeze or refrigerate APTIVUS oral solution (16)

**----------DOSAGE FORMS AND STRENGTHS----------**

Capsules: 250 mg (3)
Oral solution: 100 mg/mL (3)

**----------CONTRAINDICATIONS----------**

- Patients with moderate or severe (Child-Pugh Class B or C) hepatic impairment (4.1, 5.1)
- Use with drugs highly dependent on CYP 3A for clearance or are potent CYP 3A inducers (4.2, 5.3, 7)

**----------WARNINGS AND PRECAUTIONS----------**

- Hepatic Impairment: Discontinue for signs and symptoms of clinical hepatitis or asymptomatic increases in ALT/AST > 10 times ULN or asymptomatic increases in ALT/AST 5-10 times ULN with concomitant increases in total bilirubin. Monitor liver function tests prior to therapy and frequently thereafter (5.1)
- Intracranial Hemorrhage/Platelet Aggregation and Coagulation: Use with caution in patients at risk for increased bleeding or who are receiving medications that increase the risk of bleeding (5.2, 5.4)
- Drug Interactions: Consider drug-drug interaction potential to reduce risk of serious or life-threatening adverse reactions (5.3)
- Rash: Discontinue and initiate appropriate treatment if severe skin reaction occurs or is suspected (5.6). Use with caution in patients with a known sulfonamide allergy (5.7)
- Patients may develop new onset or exacerbations of diabetes mellitus, hyperglycemia (5.8), immune reconstitution syndrome (5.9), redistribution/accumulation of body fat (5.10), and elevated lipids (5.11). Monitor cholesterol and triglycerides prior to therapy and periodically thereafter
- Hemophilia: Spontaneous bleeding may occur, and additional factor VIII may be required (5.12)

**----------ADVERSE REACTIONS----------**

- In adults the most frequent adverse reactions (incidence > 4%) were diarrhea, nausea, pyrexia, vomiting, fatigue, headache, and abdominal pain (6.1).
- 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 (6.2).

**To report SUSPECTED ADVERSE REACTIONS, contact Boehringer Ingelheim Pharmaceuticals, Inc. at (800) 542-6257 or (800) 459-9906 TTY, or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.**

**----------DRUG INTERACTIONS----------**

Co-administration of APTIVUS can alter the concentrations of other drugs and other drugs may alter the concentration of tipranavir. The potential for drug-drug interactions must be considered prior to and during therapy (4.2, 5.3, 7).

**----------USE IN SPECIFIC POPULATIONS----------**

The risk-benefit has not been established in pediatric patients <2 years of age. (8.4)

**See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.**

**Revised: 6/2008**

## FULL PRESCRIBING INFORMATION: CONTENTS*

* Sections or sub-sections omitted from the full prescribing information are not listed.

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**FULL PRESCRIBING INFORMATION**

**WARNING: HEPATOTOXICITY and INTRACRANIAL HEMORRHAGE**

**Hepatotoxicity:**

**Clinical hepatitis and hepatic decompensation, including some fatalities, have been reported. Extra vigilance is warranted in patients with chronic hepatitis B or hepatitis C co-infection, as these patients have an increased risk of hepatotoxicity** [*see Warnings and Precautions (5.1)*].

**Intracranial Hemorrhage:**

**Both fatal and non-fatal intracranial hemorrhage have been reported** [*see Warnings and Precautions (5.2)*].

## 1 INDICATIONS AND USAGE

APTIVUS, co-administered with ritonavir, 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 (PI).

This indication is based on analyses of plasma HIV-1 RNA levels in two controlled studies of APTIVUS/ritonavir 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/ritonavir:

- The use of APTIVUS/ritonavir in treatment-naïve patients is not recommended [*see Warnings and Precautions (5.1)*].
- The use of other active agents with APTIVUS/ritonavir is associated with a greater likelihood of treatment response [*see Clinical Pharmacology (12.4) and Clinical Studies (14)*].
- Genotypic or phenotypic testing and/or treatment history should guide the use of APTIVUS/ritonavir [*see Clinical Pharmacology (12.4)*]. The number of baseline primary protease inhibitor mutations affects the virologic response to APTIVUS/ritonavir [*see Clinical Pharmacology (12.4)*].
- Use caution when prescribing APTIVUS/ritonavir to patients with elevated transaminases, hepatitis B or C co-infection or patients with mild hepatic impairment [*see Warnings and Precautions (5.1)*].
- Liver function tests should be performed at initiation of therapy with APTIVUS/ritonavir and monitored frequently throughout the duration of treatment [*see Warnings and Precautions (5.1)*].
- The drug-drug interaction potential of APTIVUS/ritonavir when co-administered with other drugs must be considered prior to and during APTIVUS/ritonavir use [*see Contraindications (4.2) and Drug Interactions (7)*].
- Use caution when prescribing APTIVUS/ritonavir in patients who may be at risk for increased bleeding or who are receiving medications known to increase the risk of bleeding [*see Warnings and Precautions (5.4)*].
- The risk-benefit of APTIVUS/ritonavir has not been established in pediatric patients <2 years of age.

There are no study results demonstrating the effect of APTIVUS/ritonavir on clinical progression of HIV-1.

## 2 DOSAGE AND ADMINISTRATION

APTIVUS must be co-administered with ritonavir to exert its therapeutic effect. Failure to correctly co-administer APTIVUS with ritonavir will result in plasma levels of tipranavir that will be insufficient to achieve the desired antiviral effect and will alter some drug interactions.

APTIVUS must be co-administered with ritonavir and can be taken with or without food [*see Effects of Food on Oral Absorption (12.3)*].

APTIVUS may be administered as either capsules or oral solution to either pediatric or adult patients.

### 2.1 Adults

The recommended adult dose of APTIVUS is 500 mg (two 250 mg capsules or 5 mL oral solution) co-administered with 200 mg of ritonavir, twice daily.

### 2.2 Pediatric Patients (age 2 to 18 years)

Healthcare professionals should pay special attention to accurate calculation of the dose of APTIVUS, transcription of the medication order, dispensing information and dosing instruction to minimize risk for medication errors, overdose, and underdose.

Prescribers should calculate the appropriate dose of APTIVUS for each individual child based on body weight (kg) or body surface area (BSA, $m^2$) 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/$m^2$ co-administered with ritonavir 150 mg/$m^2$) 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/$m^2$ co-administered with 115 mg/$m^2$ ritonavir) taken twice daily provided their virus is not resistant to multiple protease inhibitors. [*See Adverse Reactions (6.2), Use in Specific Populations (8.4) and Clinical Studies (14.2)*].

Body surface area can be calculated as follows:

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

## 3 DOSAGE FORMS AND STRENGTHS

Capsules: 250 mg, pink, oblong capsules imprinted with TPV 250

Oral solution: 100 mg/mL, yellow, viscous clear liquid with a buttermint-butter toffee flavor

## 4 CONTRAINDICATIONS

### 4.1 Hepatic Impairment

APTIVUS is contraindicated in patients with moderate or severe (Child-Pugh Class B or C, respectively) hepatic impairment [*see Warnings and Precautions (5.1)*].

### 4.2 Drug Interactions

Co-administration of APTIVUS/ritonavir with drugs that are highly dependent on CYP 3A for clearance or are potent CYP 3A inducers are contraindicated (See Table 1). These recommendations are based on either drug interaction studies or they are predicted interactions due to the expected magnitude of interaction and potential for serious events or loss of efficacy. For information regarding clinical recommendations *see Drug Interactions (7.2)*.

**Table 1 Drugs that are Contraindicated with APTIVUS Co-Administered with Ritonavir**

| Drug Class | Drugs within Class that are Contraindicated with APTIVUS Co-administered with Ritonavir | Clinical Comments: |
|---|---|---|
| Antiarrhythmics | Amiodarone, bepridil, flecainide, propafenone, quinidine | Potential for serious and/or life-threatening reactions such as cardiac arrhythmias secondary to increases in plasma concentrations of antiarrhythmics. |
| Antimycobacterials | Rifampin | May lead to loss of virologic response and possible resistance to APTIVUS or to the class of protease inhibitors or other co-administered antiretroviral agents. |
| Ergot derivatives | Dihydroergotamine, ergonovine, ergotamine, methylergonovine | Potential for acute ergot toxicity characterized by peripheral vasospasm and ischemia of the extremities and other tissues. |
| GI motility agent | Cisapride | Potential for cardiac arrhythmias. |
| Herbal Products | St. John's wort (hypericum perforatum) | May lead to loss of virologic response and possible resistance to APTIVUS or to the class of protease inhibitors. |
| HMG CoA reductase inhibitors | Lovastatin, simvastatin | Potential for myopathy including rhabdomyolysis. |
| Neuroleptic | Pimozide | Potential for cardiac arrhythmias. |
| Sedatives/hypnotics | Oral midazolam, triazolam | Prolonged or increased sedation or respiratory depression. |

Due to the need for co-administration of APTIVUS with ritonavir, please refer to the ritonavir prescribing information for a description of ritonavir contraindications.

## 5 WARNINGS AND PRECAUTIONS

Please refer to the ritonavir prescribing information for additional information on precautionary measures.

### 5.1 Hepatic Impairment and Toxicity

Clinical hepatitis and hepatic decompensation, including some fatalities, were reported with APTIVUS co-administered with 200 mg of ritonavir. These have generally occurred in patients with advanced HIV-1 disease taking multiple concomitant medications. A causal relationship to APTIVUS/ritonavir could not be established. Physicians and patients should be vigilant for the appearance of signs or symptoms of hepatitis, such as fatigue, malaise, anorexia, nausea, jaundice, bilirubinuria, acholic stools, liver tenderness or hepatomegaly. Patients with signs or symptoms of clinical hepatitis should discontinue APTIVUS/ritonavir treatment and seek medical evaluation.

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/ritonavir, and frequently throughout the duration of treatment.

If asymptomatic elevations in AST or ALT greater than 10 times the upper limit of normal occur, APTIVUS/ritonavir therapy should be discontinued. If asymptomatic elevations in AST or ALT between 5 – 10 times the upper limit of normal and increases in total bilirubin greater than 2.5 times the upper limit of normal occur, APTIVUS/ritonavir therapy should be discontinued.

Treatment-experienced patients with chronic hepatitis B or hepatitis C co-infection or elevated transaminases are at approximately 2-fold risk for developing Grade 3 or 4 transaminase elevations or hepatic decompensation. In two large, randomized, open-label, controlled clinical trials with an active comparator (1182.12 and 1182.48) of treatment-experienced patients, Grade 3 and 4 increases in hepatic transaminases were observed in 10.3% (10.9/100 PEY) receiving APTIVUS/ritonavir through week 48. In a study of treatment-naïve patients, 20.3% (21/100 PEY) experienced Grade 3 or 4 hepatic transaminase elevations while receiving APTIVUS/ritonavir 500 mg/200 mg through week 48.

Tipranavir is principally metabolized by the liver. Caution should be exercised when administering APTIVUS/ritonavir to patients with mild hepatic impairment (Child-Pugh Class A) because tipranavir concentrations may be increased [*see Clinical Pharmacology (12.3)*].

### 5.2 Intracranial Hemorrhage

APTIVUS, co-administered with 200 mg of ritonavir, has been associated with reports of both fatal and non-fatal intracranial hemorrhage (ICH). Many of these patients had other medical conditions or were receiving concomitant medications that may have caused or contributed to these events. No pattern of abnormal

coagulation parameters has been observed in patients in general, or preceding the development of ICH. Therefore, routine measurement of coagulation parameters is not currently indicated in the management of patients on APTIVUS.

### 5.3 Drug Interactions

See Table 1 for a listing of contraindicated drugs with APTIVUS due to potentially life-threatening adverse events, significant drug interactions, or due to loss of virologic activity [*see Contraindications (4.2)*].

### 5.4 Effects on Platelet Aggregation and Coagulation

APTIVUS/ritonavir should be used with caution 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.

In rats, tipranavir treatment alone induced dose-dependent changes in coagulation parameters, bleeding events and death. Co-administration with vitamin E significantly increased these effects [*see Nonclinical Toxicology (13.2)*]. However, analyses of stored plasma from adult patients treated with APTIVUS capsules and pediatric patients treated with APTIVUS oral solution (which contains a vitamin E derivative) showed no effect of APTIVUS/ritonavir on vitamin K-dependent coagulation factors (Factor II and Factor VII), Factor V, or on prothrombin or activated partial thromboplastin times.

In *in vitro* experiments, tipranavir was observed to inhibit human platelet aggregation at levels consistent with exposures observed in patients receiving APTIVUS/ritonavir.

### 5.5 Vitamin E Intake

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).

### 5.6 Rash

Rash, including urticarial rash, maculopapular rash, and possible photosensitivity, has been reported in subjects receiving APTIVUS/ritonavir. In some cases rash was accompanied by joint pain or stiffness, throat tightness, or generalized pruritus. In controlled adult clinical trials, rash (all grades, all causality) was observed in 10% of females and in 8% of males receiving APTIVUS/ritonavir 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%. In an uncontrolled compassionate use program (n=3920), 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%. Overall, most of the pediatric patients had mild rash and 5 (5%) had moderate rash. Overall 3% of pediatric patients interrupted APTIVUS treatment due to rash and the discontinuation rate for rash in pediatric patients was 0.9%. Discontinue and initiate appropriate treatment if severe skin rash develops.

### 5.7 Sulfa Allergy

APTIVUS should be used with caution in patients with a known sulfonamide allergy. Tipranavir contains a sulfonamide moiety. The potential for cross-sensitivity between drugs in the sulfonamide class and APTIVUS is unknown.

### 5.8 Diabetes Mellitus/Hyperglycemia

New onset diabetes mellitus, exacerbation of pre-existing diabetes mellitus and hyperglycemia have been reported during post-marketing surveillance in HIV-1 infected patients receiving protease inhibitor therapy. Some patients required either initiation or dose adjustments of insulin or oral hypoglycemic agents for treatment of these events. In some cases, diabetic ketoacidosis has occurred. In those patients who discontinued protease inhibitor therapy, hyperglycemia persisted in some cases. Because these events have been reported voluntarily during clinical practice, estimates of frequency cannot be made and a causal relationship between protease inhibitor therapy and these events has not been established.

### 5.9 Immune Reconstitution Syndrome

Immune reconstitution syndrome has been reported in patients treated with combination antiretroviral therapy, including APTIVUS. During the initial phase of combination antiretroviral treatment, patients whose immune system responds may develop an inflammatory response to indolent or residual opportunistic infections (such as *Mycobacterium avium* infection, cytomegalovirus, *Pneumocystis jiroveci* pneumonia, tuberculosis, or reactivation of herpes simplex and herpes zoster), which may necessitate further evaluation and treatment.

### 5.10 Fat Redistribution

Redistribution/accumulation of body fat including central obesity, dorsocervical fat enlargement (buffalo hump), peripheral wasting, facial wasting, breast enlargement, and “cushingoid appearance” have been observed in patients receiving antiretroviral therapy. The mechanism and long-term consequences of these events are currently unknown. A causal relationship has not been established.

### 5.11 Elevated Lipids

Treatment with APTIVUS co-administered with 200 mg of ritonavir has resulted in large increases in the concentration of total cholesterol and triglycerides [*see Adverse Reactions (6)*]. Triglyceride and cholesterol testing should be performed prior to initiating APTIVUS/ritonavir therapy and at periodic intervals during therapy. Lipid disorders should be managed as clinically appropriate; taking into account any potential drug-drug interactions [*see Drug Interactions (7.2)*].

### 5.12 Patients with Hemophilia

There have been reports of increased bleeding, including spontaneous skin hematomas and hemarthrosis in patients with hemophilia type A and B treated with protease inhibitors. In some patients additional Factor VIII was given. In more than half of the reported cases, treatment with protease inhibitors was continued or reintroduced if treatment had been discontinued. A causal relationship between protease inhibitors and these events has not been established.

### 5.13 Resistance/Cross Resistance

Because the potential for HIV-1 cross-resistance among protease inhibitors has not been fully explored in APTIVUS/ritonavir treated patients, it is unknown what effect therapy with APTIVUS will have on the activity of subsequently administered protease inhibitors.

## 6 ADVERSE REACTIONS

The following adverse reactions are described, in greater detail, in other sections:

- Hepatic Impairment and Toxicity [*see Warnings and Precautions (5.1)*]
- Intracranial Hemorrhage [*see Warnings and Precautions (5.2)*]
- Rash [*see Warnings and Precautions (5.6)*]

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

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

### 6.1 Clinical Trials in Adults

APTIVUS, co-administered with ritonavir, has been studied in a total of 6308 HIV-1 positive adults as combination therapy in clinical studies. Of these, 1299 treatment-experienced patients received the dose of 500/200 mg BID. Nine hundred nine (909) adults, including 541 in the 1182.12 and 1182.48 controlled clinical trials, have been treated for at least 48 weeks [*see Clinical Studies (14)*].

In 1182.12 and 1182.48 in the APTIVUS/ritonavir arm, the most frequent adverse reactions were diarrhea, nausea, pyrexia, vomiting, fatigue, headache, and abdominal pain. The 48 Week Kaplan-Meier rates of adverse reactions leading to discontinuation were 13.3% for APTIVUS/ritonavir-treated patients and 10.8% for the comparator arm patients.

Adverse reactions reported in the controlled clinical trials 1182.12 and 1182.48, based on treatment-emergent clinical adverse reactions of moderate to severe intensity (Grades 2 - 4) in at least 2% of treatment-experienced subjects in either treatment group are summarized in Table 2 below.

**Table 2 Adverse Reactions Reported in Randomized, Controlled Clinical Trials (1182.12 and 1182.48) Based on Treatment-Emergent Clinical Adverse Reactions of Moderate to Severe Intensity (Grades 2 - 4) in at least 2% of Treatment-Experienced Subjects in either Treatment Group[a] (48 week Analyses)**

| | Percentage of patients (rate per 100 patient-exposure years) | |
|---|---|---|
| | **APTIVUS/ritonavir (500/200 mg BID) + OBR[c] (n=749; 757.4 patient-exposure years)** | **Comparator PI/ritonavir[b] + OBR (n=737; 503.9 patient-exposure years)** |
| **Blood and Lymphatic Disorders** | | |
| Anemia | 3.3% (3.4) | 2.3% (3.4) |
| Neutropenia | 2.0% (2.0) | 1.0% (1.4) |
| **Gastrointestinal Disorders** | | |
| Diarrhea | 15.0% (16.5) | 13.4% (21.6) |
| Nausea | 8.5% (9.0) | 6.4% (9.7) |
| Vomiting | 5.9% (6.0) | 4.1% (6.1) |
| Abdominal pain | 4.4% (4.5) | 3.4% (5.1) |
| Abdominal pain upper | 1.5% (1.5) | 2.3% (3.4) |
| **General Disorders** | | |
| Pyrexia | 7.5% (7.7) | 5.4% (8.2) |
| Fatigue | 5.7% (5.9) | 5.6% (8.4) |
| **Investigations** | | |
| Weight decreased | 3.1% (3.1) | 2.2% (3.2) |
| ALT increased | 2.0% (2.0) | 0.5% (0.8) |
| GGT increased | 2.0% (2.0) | 0.4% (0.6) |
| **Metabolism and Nutrition Disorders** | | |
| Hypertriglyceridemia | 3.9% (4.0) | 2.0% (3.0) |
| Hyperlipidemia | 2.5% (2.6) | 0.8% (1.2) |
| Dehydration | 2.1% (2.1) | 1.1% (1.6) |
| **Musculoskeletal and Connective Tissue Disorders** | | |
| Myalgia | 2.3% (2.3) | 1.8% (2.6) |
| **Nervous System Disorders** | | |
| Headache | 5.2% (5.3) | 4.2% (6.3) |
| Peripheral neuropathy | 1.5% (1.5) | 2.0% (3.0) |
| **Psychiatric Disorders** | | |
| Insomnia | 1.7% (1.7) | 3.7% (5.5) |
| **Respiratory, Thoracic and Mediastinal Disorders** | | |
| Dyspnea | 2.1% (2.1) | 1.0% (1.4) |
| **Skin and Subcutaneous Tissue Disorders** | | |
| Rash | 3.1% (3.1) | 3.8% (5.7) |

[a] Excludes laboratory abnormalities that were Adverse Events

[b] Comparator PI/ritonavir: 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] Optimized Background Regimen

*Less Common Adverse Reactions*

Other adverse reactions reported in < 2% of adult patients (n=1474) treated with APTIVUS/ritonavir 500/200 mg in Phase 2 and 3 clinical trials are listed below by body system:

*Blood and Lymphatic System Disorders:* thrombocytopenia

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

*General Disorders:* influenza like illness, malaise

*Hepatobiliary Disorders:* hepatitis, hepatic failure, hyperbilirubinemia, cytolytic hepatitis, toxic hepatitis, hepatic steatosis

*Immune System Disorders:* hypersensitivity

*Investigations:* hepatic enzymes increased, liver function test abnormal, lipase increased

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

*Musculoskeletal and Connective Tissue Disorders:* muscle cramp

*Nervous System Disorders:* dizziness, intracranial hemorrhage, somnolence

*Psychiatric Disorders:* sleep disorder

*Renal and Urinary Disorders:* renal insufficiency

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

*Laboratory Abnormalities*
Treatment-emergent laboratory abnormalities reported at 48 weeks in the controlled clinical trials 1182.12 and 1182.48 in adults are summarized in Table 3 below.

**Table 3 Treatment-Emergent Laboratory Abnormalities Reported in ≥ 2% of Adult Patients (48 week Analyses)**

| | | Randomized, Controlled Clinical Trials 1182.12 and 1182.48 | |
|---|---|---|---|
| | | Percentage of patients (rate per 100 patient-exposure years) | |
| | Limit | APTIVUS/ritonavir (500/200 mg BID) + OBR (n=738) | Comparator PI/ritonavir + OBR* (n=724) |
| **Hematology** | | | |
| WBC count decrease | | | |
| Grade 3 | < 2.0 x $10^3$/μL | 5.4% (5.6) | 4.8% (7.7) |
| Grade 4 | < 1.0 x $10^3$/μL | 0.3% (0.3) | 1.1% (1.7) |
| **Chemistry** | | | |
| Amylase | | | |
| Grade 3 | > 2.5 x ULN | 5.7% (5.9) | 6.4% (10.4) |
| Grade 4 | > 5 x ULN | 0.3% (0.3) | 0.7% (1.1) |
| ALT | | | |
| Grade 2 | > 2.5-5 x ULN | 14.9% (16.5) | 7.5% (12.4) |
| Grade 3 | > 5-10 x ULN | 5.6% (5.7) | 1.7% (2.6) |
| Grade 4 | > 10 x ULN | 4.1% (4.1) | 0.4% (0.7) |
| AST | | | |
| Grade 2 | > 2.5-5 x ULN | 9.9% (10.5) | 8.0% (13.3) |
| Grade 3 | > 5-10 x ULN | 4.5% (4.6) | 1.4% (2.2) |
| Grade 4 | > 10 x ULN | 1.6% (1.6) | 0.4% (0.6) |
| ALT and/or AST | | | |
| Grade 2-4 | > 2.5 x ULN | 26.0% (31.5) | 13.7% (23.8) |
| Cholesterol | | | |
| Grade 2 | > 300 – 400 mg/dL | 15.6% (17.7) | 6.4% (10.5) |
| Grade 3 | > 400 – 500 mg/dL | 3.3% (3.3) | 0.3% (0.4) |
| Grade 4 | > 500 mg/dL | 0.9% (1.0) | 0.1% (0.2) |
| Triglycerides | | | |
| Grade 2 | 400 – 750 mg/dL | 35.9% (49.9) | 26.8% (51.0) |
| Grade 3 | > 750 – 1200 mg/dL | 16.9% (19.4) | 8.7% (14.6) |
| Grade 4 | > 1200 mg/dL | 8.0% (8.4) | 4.3% (7.0) |

* Comparator PI/ritonavir: 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 controlled clinical trials 1182.12 and 1182.48 extending up to 96 weeks, the proportion of patients who developed Grade 2-4 ALT and/or AST elevations increased from 26% at week 48 to 32.1% at week 96 with APTIVUS/ritonavir. The risk of developing transaminase elevations is greater during the first year of therapy.

**6.2 Clinical Trials in Pediatric Patients**

APTIVUS, co-administered with ritonavir, has been studied in a total of 135 HIV-1 infected pediatric patients age 2 through 18 years as combination therapy. This study enrolled HIV-1 infected, treatment-experienced pediatric patients (with the exception of 3 treatment naïve patients), with baseline HIV-1 RNA of at least 1500 copies/mL. One hundred and ten (110) patients were enrolled in a randomized, open-label 48-week clinical trial (Study 1182.14) and 25 patients were enrolled in other clinical studies including Expanded Access and Emergency Use Programs.

The adverse reactions profile seen in Study 1182.14 was similar to adults. Pyrexia (6.4%), vomiting (5.5%), cough (5.5%), rash (5.5%), nausea (4.5%), and diarrhea (3.6%) were the most frequently reported adverse reactions (Grade 2-4, all causes) in pediatric patients. Rash was reported more frequently in pediatric patients than in adults.

The most common Grade 3-4 laboratory abnormalities were increase in CPK (11%), ALT (6.5%), and amylase (7.5%).

Due to previous reports of both fatal and non-fatal intracranial hemorrhage (ICH), an analysis of bleeding events was performed. At 48 weeks of treatment, the frequency of pediatric patients with any bleeding adverse reactions was 7.5%. No drug related serious bleeding adverse reaction was reported. The most frequent bleeding adverse reaction was epistaxis (3.7%). No other bleeding adverse reaction was reported in frequency of >1%. Additional trial follow-up through 100 weeks showed a cumulative 12% frequency of any bleeding adverse reaction.

## 7 DRUG INTERACTIONS

See also *Contraindications (4.2), Warnings and Precautions (5.3), and Clinical Pharmacology (12.3).*

### 7.1 Potential for APTIVUS/ritonavir to Affect Other Drugs

APTIVUS co-administered with ritonavir at the recommended dose is a net inhibitor of CYP 3A and may increase plasma concentrations of agents that are primarily metabolized by CYP 3A. Thus, co-administration of APTIVUS/ritonavir with drugs highly dependent on CYP 3A for clearance and for which elevated plasma concentrations are associated with serious and/or life-threatening events is contraindicated [*see Contraindications (4.2)*]. Co-administration with other CYP 3A substrates may require a dose adjustment or additional monitoring [*see Drug Interactions (7)*].

Clinically significant drug-drug interactions of APTIVUS co-administered with ritonavir are summarized in Table 4 below.

A phenotypic cocktail study was conducted with 16 healthy volunteers to quantify the influence of 10 days of APTIVUS/ritonavir capsule administration on the activity of hepatic CYP 1A2 (caffeine), 2C9 (warfarin), 2C19 (omeprazole), 2D6 (dextromethorphan) and the activity of intestinal and hepatic CYP3A4/5 (midazolam) and P-glycoprotein (P-gp) (digoxin). This study determined the first-dose and steady-state effects of 500 mg of APTIVUS co-administered with 200 mg of ritonavir twice-daily in capsule form. APTIVUS oral solution co-administered with ritonavir capsules demonstrated similar effects as APTIVUS capsules co-administrated with ritonavir.

There was no net effect on CYP2C9 or hepatic P-gp at first dose or steady state. There was no net effect after first dose on CYP1A2, but there was moderate induction at steady state. There was modest inhibition of CYP2C19 at the first dose, but there was marked induction at steady state. Potent inhibition of CYP2D6 and both hepatic and intestinal CYP3A4/5 activities were observed after first dose and steady state.

Intestinal and hepatic P-gp activity was assessed by administering oral and intravenous digoxin, respectively. The digoxin results indicate P-gp was inhibited after the first dose of APTIVUS/ritonavir followed by induction of P-gp over time. Thus, it is difficult to predict the net effect of APTIVUS administered with ritonavir on oral bioavailability and plasma concentrations of drugs that are dual substrates of CYP 3A and P-gp. The net effect will vary depending on the relative affinity of the co-administered drugs for CYP 3A and P-gp, and the extent of intestinal first-pass metabolism/efflux. An *in vitro* induction study in human hepatocytes showed an increase in UGT1A1 by tipranavir similar to that evoked by rifampin. The clinical consequences of this finding have not been established.

### 7.2 Potential for Other Drugs to Affect Tipranavir

Tipranavir is a CYP 3A substrate and a P-gp substrate. Co-administration of APTIVUS/ritonavir and drugs that induce CYP 3A and/or P-gp may decrease tipranavir plasma concentrations. Co-administration of APTIVUS/ritonavir and drugs that inhibit P-gp may increase tipranavir plasma concentrations. Co-administration of APTIVUS/ritonavir with drugs that inhibit CYP 3A may not further increase tipranavir plasma concentrations, because the level of metabolites is low following steady-state administration of APTIVUS/ritonavir 500/200 mg twice daily.

Clinically significant drug-drug interactions of APTIVUS co-administered with ritonavir are summarized in Table 4 below.

**Table 4 Established and Other Potentially Significant Drug Interactions: Alterations in Dose or Regimen May be Recommended Based on Drug Interaction Studies or Predicted Interaction**

| Concomitant Drug Class: Drug name | Effect on Concentration of Tipranavir or Concomitant Drug | Clinical Comment |
|---|---|---|
| HIV-1 Antiviral Agents | | |
| **Nucleoside reverse transcriptase inhibitors:** | | |
| Abacavir | ↓ Abacavir AUC by approximately 40% | Clinical relevance of reduction in abacavir levels not established. Dose adjustment of abacavir cannot be recommended at this time. |
| Didanosine (EC) | ↓ Didanosine | Clinical relevance of reduction in didanosine levels not established. For optimal absorption, didanosine should be separated from APTIVUS/ritonavir dosing by at least 2 hours. |
| Zidovudine | ↓ Zidovudine AUC by approximately 35%. ZDV glucuronide concentrations were unaltered. | Clinical relevance of reduction in zidovudine levels not established. Dose adjustment of zidovudine cannot be recommended at this time. |
| **Protease inhibitors (co-administered with** | | |

**Table 4 Established and Other Potentially Significant Drug Interactions: Alterations in Dose or Regimen May be Recommended Based on Drug Interaction Studies or Predicted Interaction**

| Concomitant Drug Class: Drug name | Effect on Concentration of Tipranavir or Concomitant Drug | Clinical Comment |
|---|---|---|
| **200 mg of ritonavir):** | | |
| Fosamprenavir<br>Lopinavir<br>Saquinavir | ↓ Amprenavir,<br>↓ Lopinavir,<br>↓ Saquinavir | Combining a protease inhibitor with APTIVUS/ritonavir is not recommended. |
| **Protease inhibitors (co-administered with 100 mg of ritonavir):** | | |
| Atazanavir | ↓ Atazanavir,<br>↑ Tipranavir | |
| Agents for Opportunistic Infections | | |
| **Antifungals:** | | Fluconazole increases tipranavir concentrations but dose adjustments are not needed. Fluconazole doses > 200 mg/day are not recommended.<br><br>Based on theoretical considerations itraconazole and ketoconazole should be used with caution. High doses (>200 mg/day) are not recommended.<br><br>Due to multiple enzymes involved with voriconazole metabolism, it is difficult to predict the interaction. |
| Fluconazole<br>Itraconazole<br>Ketoconazole<br>Voriconazole | ↑ Tipranavir, ↔ Fluconazole<br>↑ Itraconazole (not studied)<br>↑ Ketoconazole (not studied)<br>↕ Voriconazole (not studied) | |
| **Antimycobacterials:** | | |
| Clarithromycin | ↑ Tipranavir, ↑ Clarithromycin,<br>↓ 14-hydroxy-clarithromycin metabolite | No dose adjustment of APTIVUS or clarithromycin for patients with normal renal function is necessary.<br><br>For patients with renal impairment the following dosage adjustments should be considered:<br>• For patients with $CL_{CR}$ 30 to 60 mL/min the dose of clarithromycin should be reduced by 50%.<br>• For patients with $CL_{CR}$ < 30 mL/min the dose of clarithromycin should be decreased by 75%. |
| Rifabutin | Tipranavir not changed, ↑Rifabutin<br>↑ 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 | | |
| **Anticonvulsants:** | | Caution should be used when prescribing carbamazepine, phenobarbital and/or phenytoin. APTIVUS may be less effective due to decreased tipranavir plasma concentration in patients taking these agents concomitantly. |
| Carbamazepine<br>Phenobarbital<br>Phenytoin | ↓ Tipranavir | |
| Valproic Acid | ↓ Valproic Acid | Caution should be used when prescribing valproic acid. Valproic acid may be less effective due to decreased valproic acid plasma concentration in patients taking APTIVUS concomitantly. |
| **Antidepressants:** | | |
| Trazodone | ↑ Trazodone | Concomitant use of trazodone and APTIVUS/ritonavir may increase plasma concentrations of trazodone. Adverse events of nausea, dizziness, hypotension, and |

**Table 4 Established and Other Potentially Significant Drug Interactions: Alterations in Dose or Regimen May be Recommended Based on Drug Interaction Studies or Predicted Interaction**

| Concomitant Drug Class: Drug name | Effect on Concentration of Tipranavir or Concomitant Drug | Clinical Comment |
|---|---|---|
| | | syncope have been observed following co-administration of trazodone and ritonavir. If trazodone is used with a CYP3A4 inhibitor such as APTIVUS/ritonavir, the combination should be used with caution and a lower dose of trazodone should be considered. |
| Desipramine | Combination with APTIVUS/ritonavir not studied<br>↑ Desipramine | Dosage reduction and concentration monitoring of desipramine is recommended. |
| Selective Serotonin-Reuptake Inhibitors:<br><br>Fluoxetine<br>Paroxetine<br>Sertraline | Combination with APTIVUS/ritonavir not studied<br><br>↑ Fluoxetine<br>↑ Paroxetine<br>↑ Sertraline | Antidepressants have a wide therapeutic index, but doses may need to be adjusted upon initiation of APTIVUS/ritonavir therapy. |
| **Benzodiazepines:**<br>**Parenterally administered midazolam** | ↑ Midazolam | Midazolam is extensively metabolized by CYP3A4. Increases in the concentration of midazolam are expected to be significantly higher with oral than parenteral administration. Therefore, APTIVUS should not be given with orally administered midazolam [*see Contraindications (4)*]. If APTIVUS is co-administered with parenteral midazolam, close clinical monitoring for respiratory depression and/or prolonged sedation should be exercised and dosage adjustments should be considered. |
| **Calcium Channel Blockers:**<br><br>Diltiazem<br>Felodipine<br>Nicardipine<br>Nisoldipine<br>Verapamil | Combination with APTIVUS/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.<br>↕ Diltiazem<br>↑ Felodipine (CYP 3A substrate but not P-gp substrate)<br>↕ Nicardipine<br>↕ Nisoldipine (CYP 3A substrate but not clear whether it is a P-gp substrate)<br>↕ Verapamil | Caution is warranted and clinical monitoring of patients is recommended. |
| 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:**<br><br>Atorvastatin<br>Rosuvastatin | ↑ Atorvastatin<br>↓ Hydroxy-atorvastatin metabolites<br>↑ Tipranavir<br>↑ Rosuvastatin | Use the lowest possible dose of atorvastatin or rosuvastatin with careful monitoring, or consider other HMG-CoA reductase inhibitors such as pravastatin or fluvastatin when in concomitant use of APTIVUS, co-administered with 200 mg of ritonavir. |
| **Hypoglycemics:**<br><br>Glimepiride<br>Glipizide<br>Glyburide<br>Pioglitazone<br><br>Repaglinide<br><br>Tolbutamide | Combination with APTIVUS/ritonavir not studied.<br><br>↔ Glimepiride (CYP 2C9)<br>↔ Glipizide (CYP 2C9)<br>↔ Glyburide (CYP 2C9)<br>↕ Pioglitazone (CYP 2C8 and CYP 3A4)<br>↕ Repaglinide (CYP 2C8 and CYP 3A4)<br>↔ Tolbutamide (CYP 2C9)<br><br>The effect of TPV/ritonavir on CYP 2C8 substrate is not known. | Careful glucose monitoring is warranted. |
| **Immunosuppressants:**<br><br>Cyclosporine<br>Sirolimus | Combination with APTIVUS/ritonavir not studied. Cannot predict effect of TPV/ritonavir on immunosuppressants due to conflicting effect of TPV/ritonavir on | Increased frequency of monitoring of plasma levels of immunosuppressant drugs is recommended. |

**Table 4 Established and Other Potentially Significant Drug Interactions: Alterations in Dose or Regimen May be Recommended Based on Drug Interaction Studies or Predicted Interaction**

| Concomitant Drug Class: Drug name | Effect on Concentration of Tipranavir or Concomitant Drug | Clinical Comment |
|---|---|---|
| Tacrolimus | CYP 3A and P-gp.<br>↕ Cyclosporine<br>↕ Sirolimus<br>↕ Tacrolimus | |
| **Inhaled /nasal steroids:**<br>Fluticasone | ↑ Fluticasone | Concomitant use of fluticasone propionate and APTIVUS/ritonavir may increase plasma concentrations of fluticasone propionate, resulting in significantly reduced serum cortisol concentrations. Co-administration of fluticasone propionate and APTIVUS/ritonavir is not recommended unless the potential benefit to the patient outweighs the risk of systemic corticosteroid side effects. |
| **Narcotic analgesics:** | | |
| Meperidine | Combinations with APTIVUS/ritonavir not studied<br>↓ 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<br>↓ S-Methadone >↓ R-Methadone | Dosage of methadone may need to be increased when co-administered with APTIVUS and 200 mg of ritonavir. |
| **Oral contraceptives/Estrogens:**<br>Ethinyl estradiol | ↓ Ethinyl estradiol concentrations by 50% | Alternative methods of nonhormonal contraception should be used when estrogen based oral contraceptives are co-administered with APTIVUS 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. |
| **Proton Pump Inhibitors:**<br>Omeprazole | ↓ omeprazole ↔ tipranavir | Dosage of omeprazole may need to be increased when co-administered with APTIVUS and ritonavir. |
| **PDE-5 inhibitors:**<br>Sildenafil<br>Tadalafil<br>Vardenafil | Only the combination of tadalafil with APTIVUS/ritonavir has been studied.<br>↑ Sildenafil (not studied)<br>↑ Tadalafil with first dose APTIVUS/ritonavir<br>↔ Tadalafil at APTIVUS/ritonavir steady-state<br>↑ Vardenafil (not studied) | Concomitant use of PDE-5 inhibitors with APTIVUS and ritonavir should be used with caution and in no case should the starting dose of:<br>• sildenafil exceed 25 mg within 48 hours<br>• tadalafil exceed 10 mg every 72 hours<br>• vardenafil exceed 2.5 mg every 72 hours |
| Warfarin | ↔ S-Warfarin | Frequent INR (international normalized ratio) monitoring upon initiation of APTIVUS/ritonavir therapy. |

↑ increase, ↓ decrease, ↔ no change, ↕ unable to predict

## 8 USE IN SPECIFIC POPULATIONS

### 8.1 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.

**8.3 Nursing Mothers**
The Centers for Disease Control and Prevention recommend that HIV-1 infected mothers not breastfeed their infants to avoid risking postnatal transmission of HIV-1. Because of both the potential for HIV-1 transmission and any possible adverse effects of APTIVUS, mothers should be instructed not to breastfeed if they are receiving APTIVUS.

**8.4 Pediatric Use**
The safety, pharmacokinetic profile, and virologic and immunologic responses of APTIVUS oral solution and capsules were evaluated in HIV-1 infected pediatric patients age 2 to 18 years. [*see Adverse Reactions (6.2), Clinical Studies (14.2)*].

The most frequent adverse reactions (grades 2-4) were similar to those described in adults. However, rash was reported more frequently in pediatric patients than in adults [*see Warning and Precautions (5.6) and Adverse Reactions (6.2)*].

The risk-benefit has not been established in pediatric patients <2 years of age.

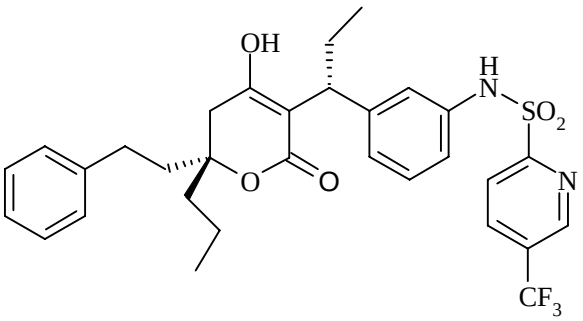
**8.5 Geriatric Use**
Clinical studies of APTIVUS/ritonavir did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently than younger subjects. In general, caution should be exercised in the administration and monitoring of APTIVUS in elderly patients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

**8.6 Hepatic Impairment**
Tipranavir is principally metabolized by the liver. Caution should be exercised when administering APTIVUS/ritonavir to patients with mild (Child-Pugh Class A) hepatic impairment because tipranavir concentrations may be increased [*see Clinical Pharmacology (12.3)*]. APTIVUS/ritonavir is contraindicated in patients with moderate or severe (Child-Pugh Class B or Child-Pugh Class C) hepatic impairment [*see Contraindications (4.1)*].

## 10 OVERDOSAGE
There is no known antidote for APTIVUS 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 provide significant removal of the drug.

## 11 DESCRIPTION
APTIVUS is a protease inhibitor of HIV-1 belonging to the class of 4-hydroxy-5,6-dihydro-2-pyrone sulfonamides.

The chemical name of tipranavir is 2-Pyridinesulfonamide, N-[3-[(1R)-1-[(6R)-5,6-dihydro-4-hydroxy-2-oxo-6-(2-phenylethyl)-6-propyl-2H-pyran-3-yl]propyl]phenyl]-5-(trifluoromethyl). It has a molecular formula of $C_{31}H_{33}F_3N_2O_5S$ and a molecular weight of 602.7. Tipranavir has the following structural formula and is a single stereoisomer with the 1R, 6R configuration.




Tipranavir is a white to off-white to slightly yellow solid. It is freely soluble in dehydrated alcohol and propylene glycol, and insoluble in aqueous buffer at pH 7.5.

APTIVUS soft gelatin capsules are for oral administration. Each capsule contains 250 mg tipranavir. The major inactive ingredients in the capsule are dehydrated alcohol (7% w/w or 0.1 g per capsule), polyoxyl 35 castor oil, propylene glycol, mono/diglycerides of caprylic/capric acid and gelatin.

APTIVUS oral solution is available in a strength of 100 mg/mL of tipranavir. APTIVUS oral solution is a yellow, viscous clear liquid with a buttermint-butter toffee flavor. The major inactive ingredients in the oral solution are polyethylene glycol 400, vitamin E polyethylene glycol succinate (TPGS), purified water, and propylene glycol. Each milliliter of APTIVUS oral solution contains 116 IU of vitamin E, and when taken at the recommended maximum dose of 500 mg/200 mg tipranavir/ritonavir BID results in a daily dose of 1160 IU.

## 12 CLINICAL PHARMACOLOGY

### 12.1 Mechanism of Action

Tipranavir is an antiviral drug [*see Clinical Pharmacology (12.4)*].

### 12.2 Pharmacodynamics

*Antiviral Activity in vivo*

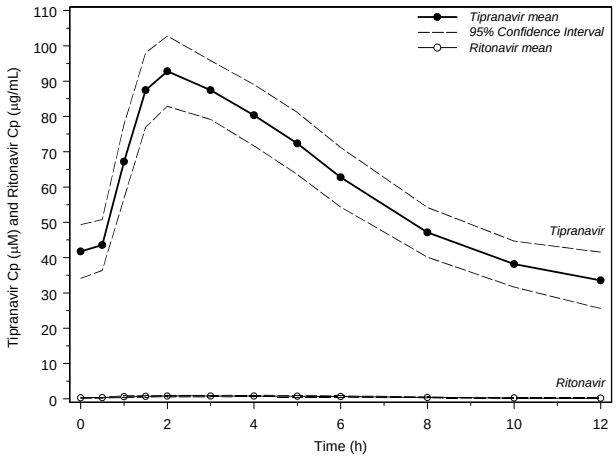
The median Inhibitory Quotient (IQ) determined from 264 treatment-experienced adult patients was about 80 (inter-quartile range: 31-226), from the controlled clinical trials 1182.12 and 1182.48. The IQ is defined as the tipranavir trough concentration divided by the viral $EC_{50}$ value, corrected for protein binding. There was a relationship between the proportion of patients with a $\geq 1$ $\log_{10}$ reduction of viral load from baseline at week 48 and their IQ value. Among the 198 patients receiving APTIVUS/ritonavir with no new enfuvirtide use (e.g., new enfuvirtide, defined as initiation of enfuvirtide for the first time), the response rate was 23% in those with an IQ value < 80 and 59% in those with an IQ value ≥ 80. Among the 66 patients receiving APTIVUS/ritonavir with new enfuvirtide, the response rates in patients with an IQ value < 80 versus those with an IQ value ≥ 80 were 55% and 71%, respectively. These IQ groups are derived from a select population and are not meant to represent clinical breakpoints.

### 12.3 Pharmacokinetics

In order to achieve effective tipranavir plasma concentrations and a twice-daily dosing regimen, co-administration of APTIVUS with ritonavir is essential [*see Dosage and Administration (2)*]. Ritonavir inhibits hepatic cytochrome P450 3A (CYP 3A), the intestinal P-gp efflux pump and possibly intestinal CYP 3A. In a dose-ranging evaluation in 113 HIV-1 negative male and female volunteers, there was a 29-fold increase in the geometric mean morning steady-state trough plasma concentrations of tipranavir following APTIVUS co-administered with low-dose ritonavir (500/200 mg twice daily) compared to APTIVUS 500 mg twice daily without ritonavir. In adults the mean systemic ritonavir concentration when 200 mg of ritonavir was given with 500 mg of APTIVUS was similar to the concentrations observed when 100 mg was given with the other protease inhibitors.

Figure 1 displays mean plasma concentrations of tipranavir and ritonavir at steady state for 30 HIV-1 infected adult patients dosed with 500/200 mg tipranavir/ritonavir for 14 days.

**Figure 1 Mean Steady State Tipranavir Plasma Concentrations (95% CI) with Ritonavir Co-administration (tipranavir/ritonavir 500/200 mg BID)**




*Absorption and Bioavailability*

Absorption of tipranavir in humans is limited, although no absolute quantification of absorption is available. Tipranavir is a P-gp substrate, a weak P-gp inhibitor, and appears to be a potent P-gp inducer as well. *In vivo* data suggest that tipranavir/ritonavir, at the dose of 500/200 mg, is a P-gp inhibitor after the first dose and induction of P-gp occurs over time. Tipranavir trough concentrations at steady-state are about 70% lower than those on Day 1, presumably due to intestinal P-gp induction. Steady state is attained in most subjects after 7-10 days of dosing.

Dosing APTIVUS 500 mg with 200 mg ritonavir twice-daily for greater than 2 weeks and without meal restriction produced the pharmacokinetic parameters for male and female HIV-1 positive patients presented in Table 5.

**Table 5 Pharmacokinetic Parameters[a] of tipranavir/ritonavir 500/200 mg for HIV-1 Positive Patients by Gender**

| | **Females (n=14)** | **Males (n=106)** |
|---|---|---|
| **$Cp_{trough}$ (μM)** | 41.6 ± 24.3 | 35.6 ± 16.7 |
| **$C_{max}$ (μM)** | 94.8 ± 22.8 | 77.6 ± 16.6 |
| **$T_{max}$ (h)** | 2.9 | 3.0 |
| **$AUC_{0-12h}$ (μM•h)** | 851 ± 309 | 710 ± 207 |
| **CL (L/h)** | 1.15 | 1.27 |
| **V (L)** | 7.7 | 10.2 |
| **$t_{1/2}$ (h)** | 5.5 | 6.0 |

[a] Population pharmacokinetic parameters reported as mean ± standard deviation

*Effects of Food on Oral Absorption*

For APTIVUS capsules or oral solution co-administered with ritonavir at steady-state, no clinically significant changes in $C_{max}$, Cp12h, and AUC were observed under fed conditions (500-682 Kcal, 23-25% calories from fat) compared to fasted conditions. APTIVUS co-administered with ritonavir may be taken with or without food, [*see Dosage and Administration (2)*].

*Distribution*
Tipranavir is extensively bound to plasma proteins (> 99.9%). It binds to both human serum albumin and α-1-acid glycoprotein. The mean fraction of tipranavir (dosed without ritonavir) unbound in plasma was similar in clinical samples from healthy volunteers and HIV-1 positive patients. Total plasma tipranavir concentrations for these samples ranged from 9 to 82 μM. The unbound fraction of tipranavir appeared to be independent of total drug concentration over this concentration range.

No studies have been conducted to determine the distribution of tipranavir into human cerebrospinal fluid or semen.

*Metabolism*
*In vitro* metabolism studies with human liver microsomes indicated that CYP 3A4 is the predominant CYP enzyme involved in tipranavir metabolism.

The oral clearance of tipranavir decreased after the addition of ritonavir, which may represent diminished first-pass clearance of the drug at the gastrointestinal tract as well as the liver.

The metabolism of tipranavir in the presence of 200 mg ritonavir is minimal. Administration of $^{14}$C-tipranavir to subjects that received APTIVUS/ritonavir 500/200 mg dosed to steady-state demonstrated that unchanged tipranavir accounted for 98.4% or greater of the total plasma radioactivity circulating at 3, 8, or 12 hours after dosing. Only a few metabolites were found in plasma, and all were at trace levels (0.2% or less of the plasma radioactivity). In feces, unchanged tipranavir represented the majority of fecal radioactivity (79.9% of fecal radioactivity). The most abundant fecal metabolite, at 4.9% of fecal radioactivity (3.2% of dose), was a hydroxyl metabolite of tipranavir. In urine, unchanged tipranavir was found in trace amounts (0.5% of urine radioactivity). The most abundant urinary metabolite, at 11.0% of urine radioactivity (0.5% of dose) was a glucuronide conjugate of tipranavir.

*Elimination*
Administration of $^{14}$C-tipranavir to subjects (n=8) that received APTIVUS/ritonavir 500/200 mg dosed to steady-state demonstrated that most radioactivity (median 82.3%) was excreted in feces, while only a median of 4.4% of the radioactive dose administered was recovered in urine. In addition, most radioactivity (56%) was excreted between 24 and 96 hours after dosing. The effective mean elimination half-life of tipranavir/ritonavir in healthy volunteers (n=67) and HIV-1 infected adult patients (n=120) was approximately 4.8 and 6.0 hours, respectively, at steady state following a dose of 500/200 mg twice daily with a light meal.

*Special Populations*
Renal Impairment
APTIVUS pharmacokinetics have not been studied in patients with renal dysfunction. However, since the renal clearance of tipranavir is negligible, a decrease in total body clearance is not expected in patients with renal insufficiency.

Hepatic Impairment
In a study comparing 9 HIV-1 negative patients with mild (Child-Pugh Class A) hepatic impairment to 9 HIV-1 negative controls, the single and multiple dose plasma concentrations of tipranavir and ritonavir were increased in patients with hepatic impairment, but were within the range observed in clinical trials. No dosing adjustment is required in patients with mild hepatic impairment.

The influence of moderate hepatic impairment (Child-Pugh Class B) or severe hepatic impairment (Child-Pugh Class C) on the multiple-dose pharmacokinetics of tipranavir administered with ritonavir has not been evaluated [*see Dosage and Administration (2), Contraindications (4.1), and Warnings and Precautions (5.1)*].

Gender

Evaluation of steady-state plasma tipranavir trough concentrations at 10-14 h after dosing from the controlled clinical trials 1182.12 and 1182.48 demonstrated that females generally had higher tipranavir concentrations than males. After 4 weeks of APTIVUS/ritonavir 500/200 mg BID, the median plasma trough concentration of tipranavir was 43.9 μM for females and 31.1 μM for males. The difference in concentrations does not warrant a dose adjustment.

Race

Evaluation of steady-state plasma tipranavir trough concentrations at 10-14 h after dosing from the controlled clinical trials 1182.12 and 1182.48 demonstrated that white males generally had more variability in tipranavir concentrations than black males, but the median concentration and the range making up the majority of the data are comparable between the races.

Geriatric Patients

Evaluation of steady-state plasma tipranavir trough concentrations at 10-14 h after dosing from the controlled clinical trials 1182.12 and 1182.48 demonstrated that there was no change in median trough tipranavir concentrations as age increased for either gender through 65 years of age. There were an insufficient number of women greater than age 65 years in the two trials to evaluate the elderly.

Pediatric Patients

Among pediatric patients in clinical trial 1182.14, steady-state plasma tipranavir trough concentrations were obtained 10 to 14 hours following study drug administration. Pharmacokinetic parameters by age group are presented in Table 6.

**Table 6 Pharmacokinetic Parameters[a] of tipranavir/ritonavir 375 mg/m$^2$/150 mg/m$^2$ for HIV-1 Positive Pediatric Patients by Age**

| Parameter | 2 to <6 years (n=12) | 6 to <12 years (n=8) | 12 to 18 years (n=6) |
|---|---|---|---|
| $Cp_{trough}$ (µM) | 59.6 ± 23.6 | 66.3 ± 12.5 | 53.3 ± 32.4 |
| $C_{max}$ (µM) | 135 ± 44 | 151 ± 32 | 138 ± 52 |
| $T_{max}$ (h) | 2.5 | 2.6 | 2.7 |
| $AUC_{0\text{-}12h}$ (µM•h) | 1190 ± 332 | 1354 ± 256 | 1194 ± 517 |
| CL/F (L/h) | 0.34 | 0.45 | 0.99 |
| V (L) | 4.0 | 4.7 | 5.3 |
| $t_{1/2}$ (h) | 8.1 | 7.1 | 5.2 |

[a] Population pharmacokinetic parameters reported as mean ± standard deviation

*Drug Interactions*
Drug interaction studies were performed with APTIVUS capsules co-administered with ritonavir, and other drugs likely to be co-administered and some drugs commonly used as probes for pharmacokinetic interactions. The effects of co-administration of APTIVUS with 200 mg ritonavir on the AUC, $C_{max}$, and $C_{min}$ of tipranavir or the co-administered drug, are summarized in Tables 7 and 8, respectively. For information regarding clinical recommendations see *Drug Interactions (7.2)*.

**Table 7 Drug Interactions: Pharmacokinetic Parameters for Tipranavir in the Presence of Co-administered Drugs**

| Co-administered Drug | Co-administered Drug Dose (Schedule) | tipranavir/ ritonavir Drug Dose (Schedule) | n | PK | Ratio (90% Confidence Interval) of Tipranavir Pharmacokinetic Parameters with/without Co-administered Drug; No Effect = 1.00 | | |
|---|---|---|---|---|---|---|---|
| | | | | | $C_{max}$ | AUC | $C_{min}$ |
| Antacids (Maalox®) | 20 mL (1 dose) | 500/200 mg (1 dose) | 23 | ↓ | 0.75 (0.63, 0.88) | 0.73 (0.64, 0.84) | - |
| Atazanavir/ritonavir | 300/100 mg QD (9 doses) | 500/100 mg BID (34 doses) | 13 | ↑ | 1.08 (0.98, 1.20) | 1.20 (1.09, 1.32) | 1.75 (1.39, 2.20) |
| Atorvastatin | 10 mg (1 dose) | 500/200 mg BID (14 doses) | 22 | ↔ | 0.96 (0.86, 1.07) | 1.08 (1.00, 1.15) | 1.04 (0.89, 1.22) |
| Clarithromycin | 500 mg BID (25 doses) | 500/200 mg BID* | 24 (68) | ↑ | 1.40 (1.24, 1.47) | 1.66 (1.43, 1.73) | 2.00 (1.58, 2.47) |
| Didanosine | 400 mg (1 dose) | 500/100 mg BID (27 doses) | 5 | ↓ | 1.32 (1.09, 1.60) | 1.08 (0.82, 1.42) | 0.66 (0.31, 1.43) |
| Efavirenz | 600 mg QD (8 doses) | 500/100 mg BID* | 21 (89) | ↓ | 0.79 (0.69, 0.89) | 0.69 (0.57, 0.83) | 0.58 (0.36, 0.86) |
| | | 750/200 mg BID* | 25 (100) | ↔ | 0.97 (0.85, 1.09) | 1.01 (0.85, 1.18) | 0.97 (0.69, 1.28) |
| Ethinyl estradiol /Norethindrone | 0.035/1.0 mg (1 dose) | 500/100 mg BID (21 doses) | 21 | ↓ | 1.10 (0.98, 1.24) | 0.98 (0.88, 1.11) | 0.73 (0.59, 0.90) |
| | | 750/200 mg BID (21 doses) | 13 | ↔ | 1.01 (0.96, 1.06) | 0.98 (0.90, 1.07) | 0.91 (0.69, 1.20) |
| Fluconazole | 100 mg QD (12 doses) | 500/200 mg BID* | 20 (68) | ↑ | 1.32 (1.18, 1.47) | 1.50 (1.29, 1.73) | 1.69 (1.33, 2.09) |
| Loperamide | 16 mg (1 dose) | 750/200 mg BID (21 doses) | 24 | ↓ | 1.03 (0.92, 1.17) | 0.98 (0.86, 1.12) | 0.74 (0.62, 0.88) |
| Rifabutin | 150 mg (1 dose) | 500/200 mg BID (15 doses) | 21 | ↔ | 0.99 (0.93, 1.07) | 1.00 (0.96, 1.04) | 1.16 (1.07, 1.27) |
| Tadalafil | 10 mg (1 dose) | 500/200 mg BID (17 doses) | 17 | ↔ | 0.90 (0.80, 1.01) | 0.85 (0.74, 0.97) | 0.81 (0.70, 0.94) |
| Tenofovir | 300 mg (1 dose) | 500/100 mg BID | 22 | ↓ | 0.83 (0.74, 0.94) | 0.82 (0.75, 0.91) | 0.79 (0.70, 0.90) |
| | | 750/200 mg BID (23 doses) | 20 | ↔ | 0.89 (0.84, 0.96) | 0.91 (0.85, 0.97) | 0.88 (0.78, 1.00) |
| Zidovudine | 300 mg (1 dose) | 500/100 mg BID | 29 | ↓ | 0.87 (0.80, 0.94) | 0.82 (0.76, 0.89) | 0.77 (0.68, 0.87) |
| | | 750/200 mg BID (23 doses) | 25 | ↔ | 1.02 (0.94, 1.10) | 1.02 (0.92, 1.13) | 1.07 (0.86, 1.34) |

*steady state comparison to historical data (n)
↑ increase, ↓ decrease, ↔ no change, ↕ unable to predict

**Table 8 Drug Interactions: Pharmacokinetic Parameters for Co-administered Drug in the Presence of APTIVUS/ritonavir**

| Co-administered Drug | Co-administered Drug Dose (Schedule) | tipranavir/ritonavir Drug Dose (Schedule) | n | PK | Ratio (90% Confidence Interval) of Co-administered Drug Pharmacokinetic Parameters with/without tipranavir/ritonavir; No Effect = 1.00 | | |
|---|---|---|---|---|---|---|---|
| | | | | | $C_{max}$ | AUC | $C_{min}$ |
| Amprenavir/ritonavir [a] | 600/100 mg BID (27 doses) | 500/200 mg BID (28 doses) | 16 | ↓ | 0.61 (0.51, 0.73)[d] | 0.56 (0.49, 0.64)[d] | 0.45 (0.38, 0.53)[d] |
| | | | 74 | ↓ | - | - | 0.44 (0.39, 0.49)[e] |
| Abacavir [a] | 300 mg BID (43 doses) | 250/200 mg BID | 28 | ↓ | 0.56 (0.48, 0.66) | 0.56 (0.49, 0.63) | - |
| | | 750/100 mg BID | 14 | ↓ | 0.54 (0.47, 0.63) | 0.64 (0.55, 0.74) | - |
| | | 1250/100 mg BID (42 doses) | 11 | ↓ | 0.48 (0.42, 0.53) | 0.65 (0.55, 0.76) | - |
| Atazanavir/ritonavir | 300/100 mg QD (9 doses) | 500/100 mg BID (34 doses) | 13 | ↓ | 0.43 (0.38, 0.50) | 0.32 (0.29, 0.36) | 0.19 (0.15, 0.24) |
| Atorvastatin | 10 mg (1 dose) | 500/200 mg BID (17 doses) | 22 | ↑ | 8.61 (7.25, 10.21) | 9.36 (8.02, 10.94) | 5.19 (4.21, 6.40) |
| Orthohydroxy-atorvastatin | | | 21, 12, 17 | ↓ | 0.02 (0.02, 0.03) | 0.11 (0.08, 0.17) | 0.07 (0.06, 0.08) |
| Parahydroxy-atorvastatin | | | 13, 22, 1 | ↓ | 1.04 (0.87, 1.25) | 0.18 (0.14, 0.24) | 0.33 (NA) |
| Carbamazepine | 100 mg BID (29 doses) | 500/200 mg (1 dose) | 7 | ↔ | 1.04 (1.00, 1.07) | 1.05 (1.02, 1.09) | 1.17 (1.11, 1.24) |
| | (43 doses) | (15 doses) | 7 | ↔ | 1.10 (0.85, 1.42) | 1.08 (0.91, 1.27) | 1.07 (0.90, 1.27) |
| | 200 mg BID (29 doses) | 500/200 mg (1 dose) | 17 | ↔ | 1.00 (0.96, 1.04) | 1.04 (1.00, 1.08) | 1.16 (1.11, 1.22) |
| | (43 doses) | (15 doses) | 17 | ↑ | 1.22 (1.11, 1.34) | 1.26 (1.15, 1.38) | 1.35 (1.22, 1.50) |
| Clarithromycin | 500 mg BID (25 doses) | 500/200 mg BID (15 doses) | 21 | ↑ | 0.95 (0.83, 1.09) | 1.19 (1.04, 1.37) | 1.68 (1.42, 1.98) |
| 14-OH-clarithromycin | | | 21 | ↓ | 0.03 (0.02, 0.04) | 0.03 (0.02, 0.04) | 0.05 (0.04, 0.07) |
| Didanosine[b] | 200 mg BID, ≥ 60 kg 125 mg BID, < 60 kg (43 doses) | 250/200 mg BID | 10 | ↓ | 0.57 (0.42, 0.79) | 0.67 (0.51, 0.88) | - |
| | | 750/100 mg BID | 8 | ↔ | 0.76 (0.49, 1.17) | 0.97 (0.64, 1.47) | - |
| | | 1250/100 mg BID (42 doses) | 9 | ↔ | 0.77 (0.47, 1.26) | 0.87 (0.47, 1.65) | - |
| | 400 mg (1 dose) | 500/100 mg BID (27 doses) | 5 | ↔ | 0.80 (0.63, 1.02) | 0.90 (0.72, 1.11) | 1.17 (0.62, 2.20) |
| Efavirenz[b] | 600 mg QD (15 doses) | 500/100 mg BID | 24 | ↔ | 1.09 (0.99, 1.19) | 1.04 (0.97, 1.12) | 1.02 (0.92, 1.12) |
| | | 750/200 mg BID (15 doses) | 22 | ↔ | 1.12 (0.98, 1.28) | 1.00 (0.93, 1.09) | 0.94 (0.84, 1.04) |
| Ethinyl estradiol | 0.035 mg (1 dose) | 500/100 mg BID | 21 | ↓ | 0.52 (0.47, 0.57) | 0.52 (0.48, 0.56) | - |
| | | 750/200 mg BID (21 doses) | 13 | ↓ | 0.48 (0.42, 0.57) | 0.57 (0.54, 0.60) | - |
| Fluconazole | 200 mg (Day 1) then 100 mg QD (6 or 12 doses) | 500/200 mg BID (2 or 14 doses) | 19 | ↔ | 0.97 (0.94, 1.01) | 0.99 (0.97, 1.02) | 0.98 (0.94, 1.02) |
| | | | 19 | ↔ | 0.94 (0.91, 0.98) | 0.92 (0.88, 0.95) | 0.89 (0.85, 0.92) |
| Lopinavir/ritonavir[a] | 400/100 mg BID (27 doses) | 500/200 mg BID (28 doses) | 21 | ↓ | 0.53 (0.40, 0.69)[d] | 0.45 (0.32, 0.63)[d] | 0.30 (0.17, 0.51)[d] |
| | | | 69 | ↓ | - | - | 0.48 (0.40, 0.58)[e] |
| Loperamide | 16 mg (1 dose) | 750/200 mg BID (21 doses) | 24 | ↓ | 0.39 (0.31, 0.48) | 0.49 (0.40, 0.61) | - |
| N-Demethyl-Loperamide | | | 24 | ↓ | 0.21 (0.17, 0.25) | 0.23 (0.19, 0.27) | - |

**Table 8 Drug Interactions: Pharmacokinetic Parameters for Co-administered Drug in the Presence of APTIVUS/ritonavir**

| Co-administered Drug | Co-administered Drug Dose (Schedule) | tipranavir/ritonavir Drug Dose (Schedule) | n | PK | Ratio (90% Confidence Interval) of Co-administered Drug Pharmacokinetic Parameters with/without tipranavir/ritonavir; No Effect = 1.00 | | |
|---|---|---|---|---|---|---|---|
| | | | | | $C_{max}$ | AUC | $C_{min}$ |
| Lamivudine[a] | 150 mg BID (43 doses) | 250/200 mg BID | 64 | ↔ | 0.96 (0.89, 1.03) | 0.95 (0.89, 1.02) | - |
| | | 750/100 mg BID | 46 | ↔ | 0.86 (0.78, 0.94) | 0.96 (0.90, 1.03) | - |
| | | 1250/100 mg BID (42 doses) | 35 | ↔ | 0.71 (0.62, 0.81) | 0.82 (0.66, 1.00) | - |
| Methadone | 5 mg (1 dose) | 500/200 mg BID (16 doses) | 14 | ↓ | 0.45 (0.41, 0.49) | 0.47 (0.44, 0.51) | 0.50 (0.46, 0.54) |
| R-methadone | | | | | 0.54 (0.50, 0.58) | 0.52 (0.49, 0.56) | - |
| S-methadone | | | | | 0.38 (0.35, 0.43) | 0.37 (0.34, 0.41) | - |
| Nevirapine[a] | 200 mg BID (43 doses) | 250/200 mg BID | 26 | ↔ | 0.97 (0.90, 1.04) | 0.97 (0.91, 1.04) | 0.96 (0.87, 1.05) |
| | | 750/100 mg BID | 22 | ↔ | 0.86 (0.76, 0.97) | 0.89 (0.78, 1.01) | 0.93 (0.80, 1.08) |
| | | 1250/100 mg BID (42 doses) | 17 | ↔ | 0.71 (0.62, 0.82) | 0.76 (0.63, 0.91) | 0.77 (0.64, 0.92) |
| Norethindrone | 1.0 mg (1 dose) | 500/100 mg BID | 21 | ↔ | 1.03 (0.94, 1.13) | 1.14 (1.06, 1.22) | - |
| | | 750/200 mg BID (21 doses) | 13 | ↔ | 1.08 (0.97, 1.20) | 1.27 (1.13, 1.43) | - |
| Rifabutin | 150 mg (1 dose) | 500/200 mg BID (15 doses) | 20 | ↑ | 1.70 (1.49, 1.94) | 2.90 (2.59, 3.26) | 2.14 (1.90, 2.41) |
| 25-O-desacetyl-rifabutin | | | 20 | ↑ | 3.20 (2.78, 3.68) | 20.71 (17.66, 24.28) | 7.83 (6.70, 9.14) |
| Rifabutin + 25-O-desacetyl- rifabutin[c] | | | 20 | ↑ | 1.86 (1.63, 2.12) | 4.33 (3.86, 4.86) | 2.76 (2.44, 3.12) |
| Saquinavir/ritonavir[a] | 600/100 mg BID (27 doses) | 500/200 mg BID (28 doses) | 20 | ↓ | 0.30 (0.23, 0.40)[d] | 0.24 (0.19, 0.32)[d] | 0.18 (0.13, 0.26)[d] |
| | | | 68 | ↓ | - | - | 0.20 (0.16, 0.25)[e] |
| Stavudine[a] | 40 mg BID ≥ 60 kg 30 mg BID < 60 kg (43 doses) | 250/200 mg BID | 26 | ↔ | 0.90 (0.81, 1.02) | 1.00 (0.91, 1.11) | - |
| | | 750/100 mg BID | 22 | ↔ | 0.76 (0.66, 0.89) | 0.84 (0.74, 0.96) | - |
| | | 1250/100 mg BID (42 doses) | 19 | ↔ | 0.74 (0.69, 0.80) | 0.93 (0.83, 1.05) | - |
| Tadalafil | 10 mg (1 dose) | 500/200 mg (1 dose) | 17 | ↑ | 0.78 (0.72, 0.84) | 2.33 (2.02, 2.69) | - |
| | 10 mg (1 dose) | 500/200 mg BID (17 doses) | 17 | ↔ | 0.70 (0.63, 0.78) | 1.01 (0.83, 1.21) | - |
| Tenofovir | 300 mg (1 dose) | 500/100 mg BID | 22 | ↓ | 0.77 (0.68, 0.87) | 0.98 (0.91, 1.05) | 1.07 (0.98, 1.17) |
| | | 750/200 mg BID (23 doses) | 20 | ↓ | 0.62 (0.54, 0.71) | 1.02 (0.94, 1.10) | 1.14 (1.01, 1.27) |
| Zidovudine[b] | 300 mg BID | 250/200 mg BID | 48 | ↓ | 0.54 (0.47, 0.62) | 0.58 (0.51, 0.66) | - |
| | 300 mg BID | 750/100 mg BID | 31 | ↓ | 0.51 (0.44, 0.60) | 0.64 (0.55, 0.75) | - |
| | 300 mg BID (43 doses) | 1250/100 mg BID (42 doses) | 23 | ↓ | 0.49 (0.40, 0.59) | 0.69 (0.49, 0.97) | - |
| | 300 mg (1 dose) | 500/100 mg BID | 29 | ↓ | 0.39 (0.33, 0.45) | 0.57 (0.52, 0.63) | 0.89 (0.81, 0.99) |
| | | 750/200 mg BID (23 doses) | 25 | ↔ | 0.44 (0.36, 0.54) | 0.67 (0.62, 0.73) | 1.25 (1.08, 1.44) |
| Zidovudine glucuronide | | 500/100 mg BID | 29 | ↑ | 0.82 (0.74, 0.90) | 1.02 (0.97, 1.06) | 1.52 (1.34, 1.71) |
| | | 750/200 mg BID (23 doses) | 25 | ↑ | 0.82 (0.73, 0.92) | 1.09 (1.05, 1.14) | 1.94 (1.62, 2.31) |

[a] HIV-1 positive patients
[b] HIV-1 positive patients (tipranavir/ritonavir 250 mg/200 mg, 750 mg/200 mg and 1250 mg/100 mg) and healthy volunteers (tipranavir/ritonavir 500 mg/100 mg and 750 mg/200 mg)
[c] Normalized sum of parent drug (rifabutin) and active metabolite (25-O-desacetyl-rifabutin)
[d] Intensive PK analysis
[e] Drug levels obtained at 8-16 hrs post-dose
↑ increase, ↓ decrease, ↔ no change, ↕ unable to predict

### 12.4 Microbiology

*Mechanism of Action*

Tipranavir (TPV) is an HIV-1 protease inhibitor that inhibits the virus-specific processing of the viral Gag and Gag-Pol polyproteins in HIV-1 infected cells, thus preventing formation of mature virions.

*Antiviral Activity*

Tipranavir inhibits the replication of laboratory strains of HIV-1 and clinical isolates in acute models of T-cell infection, with 50% effective concentrations ($EC_{50}$) ranging from 0.03 to 0.07 µM (18-42 ng/mL). Tipranavir demonstrates antiviral activity in cell culture against a broad panel of HIV-1 group M non-clade B isolates (A, C, D, F, G, H, CRF01 AE, CRF02 AG, CRF12 BF). Group O and HIV-2 isolates have reduced susceptibility in cell culture to tipranavir with $EC_{50}$ values ranging from 0.164 -1 µM and 0.233-0.522 µM, respectively. When used with other antiretroviral agents in cell culture, the combination of tipranavir was additive to antagonistic with other protease inhibitors (amprenavir, atazanavir, indinavir, lopinavir, nelfinavir, ritonavir, and saquinavir) and generally additive with the NNRTIs (delavirdine, efavirenz, and nevirapine) and the NRTIs (abacavir, didanosine, emtricitabine, lamivudine, stavudine, tenofovir, and zidovudine). Tipranavir was synergistic with the HIV-1 fusion inhibitor enfuvirtide. There was no antagonism of the cell culture combinations of tipranavir with either adefovir or ribavirin, used in the treatment of viral hepatitis.

*Resistance*

In cell culture:

HIV-1 isolates with a decreased susceptibility to tipranavir have been selected in cell culture and obtained from patients treated with APTIVUS/ritonavir (TPV/ritonavir). After 9 months of culture in TPV-containing media, HIV-1 isolates with 87-fold reduced susceptibility to tipranavir were selected in cell culture; these contained 10 protease substitutions that developed in the following order: L33F, I84V, K45I, I13V, V32I, V82L, M36I, A71V, L10F, and I54V/T. Changes in the Gag polyprotein CA/P2 cleavage site were also observed following drug selection. Experiments with site-directed mutants of HIV-1 showed that the presence of 6 substitutions in the protease coding sequence (I13V, V32I, L33F, K45I, V82L, I84V) conferred > 10-fold reduced susceptibility to tipranavir.

Clinical Studies of Treatment-Experienced Patients:

In controlled clinical trials 1182.12 and 1182.48, multiple protease inhibitor-resistant HIV-1 isolates from 59 treatment-experienced adult patients who received APTIVUS/ritonavir and experienced virologic rebound developed amino acid substitutions that were associated with resistance to tipranavir. The most common amino acid substitutions that developed on 500/200 mg APTIVUS/ritonavir in greater than 20% of APTIVUS/ritonavir virologic failure isolates were L33V/I/F, V82T, and I84V. Other substitutions that developed in 10 to 20% of APTIVUS/ritonavir virologic failure isolates included L10V/I/S, I13V, E35D/G/N, I47V, I54V/A/M, K55R, V82L, and L89V/M. Evolution at protease gag polyprotein cleavage sites was also observed. Among 28 pediatric patients in clinical trial 1182.14 who experienced virologic failure or non-response, the emergent protease amino acid codon substitutions were similar to those observed in adult virologic failure isolates.

In clinical trials 1182.12 and 1182.48 tipranavir resistance was detected at virologic rebound after an average of 38 weeks of APTIVUS/ritonavir treatment with a median 14-fold decrease in tipranavir susceptibility. Similarly, reduced tipranavir susceptibility was associated with emergent mutations in pediatric patient isolates.

*Cross-resistance*

Cross-resistance among protease inhibitors has been observed. Tipranavir had < 4-fold decreased susceptibility against 90% (94/105) of HIV-1 clinical isolates resistant to amprenavir, atazanavir, indinavir, lopinavir, nelfinavir, ritonavir, or saquinavir. Tipranavir-resistant viruses which emerged in cell culture from wild-type HIV-1 had decreased susceptibility to the protease inhibitors amprenavir, atazanavir, indinavir, lopinavir, nelfinavir and ritonavir but remained sensitive to saquinavir.

*Baseline Genotype and Virologic Outcome Analyses*

Genotypic and/or phenotypic analysis of baseline virus may aid in determining tipranavir susceptibility before initiation of APTIVUS/ritonavir therapy. Several analyses were conducted to evaluate the impact of specific substitutions and combination of substitutions on virologic outcome. Both the type and number of baseline protease inhibitor substitutions as well as use of additional active agents (e.g., enfuvirtide) affected APTIVUS/ritonavir response rates in controlled clinical trials 1182.12 and 1182.48 through Week 48 of treatment.

Regression analyses of baseline and/or on-treatment HIV-1 genotypes from 860 treatment-experienced patients in Phase 2 and 3 trials demonstrated that amino acid substitutions at 16 codons in the HIV-1 protease coding sequence were associated with reduced virologic responses and/or reduced tipranavir susceptibility: L10V, I13V, K20M/R/V, L33F, E35G, M36I, K43T, M46L, I47V, I54A/M/V, Q58E, H69K, T74P, V82L/T, N83D or I84V.

As-treated analyses were also conducted to assess virologic outcome by the number of primary protease inhibitor substitutions present at baseline. Response rates were reduced if five or more protease inhibitor-associated substitutions were present at baseline and subjects did not receive concomitant new enfuvirtide with APTIVUS/ritonavir. See Table 9.

**Table 9 Controlled Clinical Trials 1182.12 and 1182.48: Proportion of Responders (confirmed ≥ 1 $log_{10}$ decrease at Week 48) by Number of Baseline Primary Protease Inhibitor (PI) Resistance Associated Substitutions**

| Number of Baseline Primary PI Mutations[a] | APTIVUS/ritonavir N=578 | | Comparator PI/ritonavir N=610 | |
|---|---|---|---|---|
| | No New Enfuvirtide[b] | + New Enfuvirtide[c] | No New Enfuvirtide[b] | + New Enfuvirtide[c] |
| **Overall** | **38%** (180/470) | **69%** (75/108) | **18%** (92/524) | **26%** (22/86) |
| **1 - 2** | **62%** (24/39) | **60%** (3/5) | **33%** (14/43) | **0%** (0/1) |
| **3 - 4** | **48%** (96/202) | **71%** (27/38) | **23%** (45/193) | **38%** (13/34) |
| **5+** | **26%** (60/229) | **69%** (45/65) | **11%** (33/288) | **18%** (9/51) |

[a] Primary PI mutations include any amino acid substitution at positions 30, 32, 36, 46, 47, 48, 50, 53, 54, 82, 84, 88 and 90

[b] No new enfuvirtide is defined as recycled or continued use of enfuvirtide or no use of enfuvirtide

[c] New enfuvirtide is defined as initiation of enfuvirtide for the first time

The median change from baseline in plasma HIV-1 RNA at weeks 2, 4, 8, 16, 24 and 48 was evaluated by the number of baseline primary protease inhibitor resistance associated substitutions (1-4 or ≥ 5) in subjects who received APTIVUS/ritonavir with or without new enfuvirtide. The following observations were made:

- Approximately 1.5 $\log_{10}$ decrease in HIV-1 RNA at early time points (Week 2) regardless of the number of baseline primary protease inhibitor resistance associated substitutions (1-4 or 5+).
- Subjects with 5 or more primary protease inhibitor resistance associated substitutions in their HIV-1 at baseline who received APTIVUS/ritonavir without new enfuvirtide (n=303) began to lose their antiviral response after Week 4.
- Early HIV-1 RNA decreases (1.5–2 $\log_{10}$) were sustained through Week 48 in subjects with 5 or more primary protease inhibitor resistance associated substitutions at baseline who received new enfuvirtide with APTIVUS/ritonavir (n=74).

*Baseline Phenotype and Virologic Outcome Analyses*
APTIVUS/ritonavir response rates were also assessed by baseline tipranavir phenotype. Relationships between baseline phenotypic susceptibility to tipranavir, mutations at protease amino acid codons 33, 82, 84 and 90, tipranavir resistance-associated mutations, and response to APTIVUS/ritonavir therapy at Week 48 are summarized in Tables 10 and 11. These baseline phenotype groups are not meant to represent clinical susceptibility breakpoints for APTIVUS/ritonavir because the data are based on the select 1182.12 and 1182.48 patient population. The data are provided to give clinicians information on the likelihood of virologic success based on pre-treatment susceptibility to APTIVUS/ritonavir in protease inhibitor-experienced patients.

**Table 10 Response by Baseline Tipranavir Phenotype at 48 weeks in the Controlled Clinical Trials 1182.12 and 1182.48**

| Baseline Tipranavir Phenotype (Fold Change)[a] | Proportion of Responders[b] with No New Enfuvirtide[c] Use N=211 | Proportion of Responders[b] with New Enfuvirtide[d] Use N=68 | Tipranavir Susceptibility |
|---|---|---|---|
| 0-3 | 48% (73/153) | 70% (33/47) | Susceptible |
| > 3-10 | 21% (10/48) | 53% (8/15) | Decreased Susceptibility |
| > 10 | 10% (1/10) | 50% (3/6) | Resistant |

[a] Change in tipranavir $EC_{50}$ value from wild-type reference
[b] Confirmed ≥ 1 $\log_{10}$ decrease at Week 48
[c] No new enfuvirtide is defined as recycled or continued use of enfuvirtide or no use of enfuvirtide
[d] New enfuvirtide is defined as initiation of enfuvirtide for the first time

**Table 11 Correlation of Baseline Tipranavir Phenotype to Genotype using HIV-1 isolates from Phase 2 and Phase 3 Clinical Trials**

| Baseline Tipranavir Phenotype (Fold Change)[a] | # of Baseline Protease Mutations at 33, 82, 84, 90 | # of Baseline Tipranavir Resistance-Associated Mutations[b] | Tipranavir Susceptibility[c] |
|---|---|---|---|
| 0-3 | 0-2 | 0-4 | Susceptible |
| > 3-10 | 3 | 5-7 | Decreased Susceptibility |
| > 10 | 4 | 8+ | Resistant |

[a] Change in tipranavir $EC_{50}$ value from wild-type reference
[b] Number of amino acid substitutions in HIV-1 protease among L10V, I13V, K20M/R/V, L33F, E35G, M36I, K43T, M46L, I47V, I54A/M/V, Q58E, H69K, T74P, V82L/T, N83D or I84V
c defined by week 48 response

Analyses of pediatric clinical trial 1182.14 also demonstrated that response to therapy was influenced by the number of baseline protease inhibitor mutations present.

## 13 NONCLINICAL TOXICOLOGY

### 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term carcinogenicity studies in mice and rats have been conducted with tipranavir. Mice were administered 30, 150 or 300 mg/kg/day tipranavir, 150/40 mg/kg/day tipranavir/ritonavir in combination, or 40 mg/kg/day ritonavir. The incidences of benign hepatocellular adenomas and combined adenomas/carcinomas were increased in females of all groups except the low dose of tipranavir. These tumors were also increased in male mice at the high-dose of tipranavir and the tipranavir/ritonavir combination group. Hepatocellular carcinoma incidence was increased in female mice given the high dose of tipranavir and both sexes receiving tipranavir/ritonavir. The combination of tipranavir and ritonavir caused an exposure-related increase in this same tumor type in both sexes. The clinical relevance of the carcinogenic findings in mice is unknown. Systemic exposures in mice (based on AUC or $C_{max}$) at all dose levels tested were below those in humans receiving the

recommended dose level. Rats were administered 30, 100 or 300 mg/kg/day tipranavir, 100/26.7 mg/kg/day tipranavir/ritonavir in combination, or 10 mg/kg/day ritonavir. No drug-related findings in male rats were observed. At the highest dose of tipranavir, an increased incidence of benign follicular cell adenomas of the thyroid gland was observed in female rats. Based on AUC measurements, exposure to tipranavir at this dose level in rats is approximately equivalent to exposure in humans at the recommended therapeutic dose. This finding is probably not relevant to humans, because thyroid follicular cell adenomas are considered a rodent-specific effect secondary to enzyme induction.

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 APTIVUS/ritonavir BID.

### 13.2 Animal Toxicology and/or Pharmacology

In preclinical studies in rats, tipranavir treatment induced dose-dependent changes in coagulation parameters (increased prothrombin time, increased activated partial thromboplastin time, and a decrease in some vitamin K dependent factors). In some rats, these changes led to bleeding in multiple organs and death. The co-administration of vitamin E in the form of TPGS (d-alpha-tocopherol polyethylene glycol 1000 succinate) with tipranavir resulted in a significant increase in effects on coagulation parameters, bleeding events, and death.

In preclinical studies of tipranavir in dogs, an effect on coagulation parameters was not seen. Co-administration of tipranavir and vitamin E has not been studied in dogs. Clinical evaluation of coagulation effects on HIV-1-infected patients demonstrated no tipranavir plus ritonavir effect and no effect of the vitamin E-containing oral solution on coagulation parameters [*see Effects on Platelet Aggregation and Coagulation (5.4)*]**.**

## 14 CLINICAL STUDIES

### 14.1 Adult Patients

The following clinical data is derived from analyses of 48-week data from ongoing studies measuring effects on plasma HIV-1 RNA levels and CD4+ cell counts. At present there are no results from controlled studies evaluating the effect of APTIVUS/ritonavir on clinical progression of HIV-1.

*APTIVUS/ritonavir 500/200 mg BID + optimized background regimen (OBR) vs. Comparator Protease Inhibitor/ritonavir BID + OBR*

The two clinical trials 1182.12 and 1182.48 (RESIST 1 and RESIST 2) are ongoing, randomized, controlled, open-label, multicenter studies in HIV-1 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 48 weeks in a total of 1483 patients receiving either APTIVUS co-administered with 200 mg of ritonavir plus OBR versus a control group receiving a ritonavir-boosted protease inhibitor (lopinavir, amprenavir, saquinavir or indinavir) plus OBR. Prior to randomization, OBR was individually defined for each patient based on genotypic resistance testing and patient history. The investigator had to declare OBR, comparator protease inhibitor, and use of new enfuvirtide prior to randomization. Randomization was stratified by choice of comparator protease inhibitor and use of new enfuvirtide.

After Week 8, patients in the control group who met the protocol defined criteria of initial lack of virologic response or confirmed virologic failure had the option of discontinuing treatment and switching to APTIVUS/ritonavir in a separate roll-over study.

Demographics and baseline characteristics were balanced between the APTIVUS/ritonavir arm and control arm. In both studies combined, the 1483 patients had a median age of 43 years (range 17-80), and were 86.3% male, 75.6% white, 12.9% black, and 0.9% Asian. The median baseline plasma HIV-1 RNA for both treatment groups was 4.8 (range 2.0 to 6.8) $\log_{10}$ copies/mL and median baseline CD4+ cell count was 162 (range 1 to 1894) cells/$mm^3$. Overall, 38.4% of patients had a baseline HIV-1 RNA of >100,000 copies/mL, 58.6% had a baseline CD4+ cell count ≤ 200 cells/$mm^3$, and 57.8% had experienced an AIDS defining Class C event at baseline.

Patients had prior exposure to a median of 6 NRTIs, 1 NNRTI, and 4 PIs. A total of 10.1% of patients had previously used enfuvirtide. In baseline patient samples (n=454), 97% of the HIV-1 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.

The individually pre-selected protease inhibitor based on genotypic testing and the patient's medical history was lopinavir in 48.7%, amprenavir in 26.4%, saquinavir in 21.8% and indinavir in 3.1% of patients. A total of 85.1% were possibly resistant or resistant to the pre-selected comparator protease inhibitors. Approximately 21% of patients used enfuvirtide during the study of which 16.6% in the APTIVUS/ritonavir arm and 13.2% in the comparator/ritonavir arm represented first time use of enfuvirtide (new enfuvirtide).

Treatment response and efficacy outcomes of randomized treatment through Week 48 of studies 1182.12 and 1182.48 are shown in Table 12.

**Table 12 Outcomes of Randomized Treatment Through Week 48 (Pooled Studies 1182.12 and 1182.48)**

| Outcome | APTIVUS/ritonavir (500/200 mg BID) + OBR (N=746) | Comparator Protease Inhibitor*/ritonavir + OBR (N=737) |
|---|---|---|
| Virologic Responders[a] (confirmed at least 1 $\log_{10}$ HIV-1 RNA below baseline) | 33.8% | 14.9% |
| Virologic failures | 55.1% | 77.3% |
| Initial lack of virologic response by Week 8[b] | 33.0% | 57.9% |
| Rebound | 18.9% | 16.4% |
| Never suppressed | 3.2% | 3.0% |
| Death[c] or discontinued due to adverse events | 5.9% | 1.9% |
| Death | 0.5% | 0.3% |
| Discontinued due to adverse events | 5.4% | 1.6% |
| Discontinued due to other reasons[d] | 5.2% | 5.8% |

* Comparator protease inhibitors were lopinavir, amprenavir, saquinavir or indinavir and 85.1% of patients were possibly resistant or resistant to the chosen protease inhibitors.

[a] Patients achieved and maintained a confirmed ≥ 1 $\log_{10}$ HIV-1 RNA drop from baseline through Week 48 without prior evidence of treatment failure.

[b] Patients did not achieve a 0.5 $\log_{10}$ HIV-1 RNA drop from baseline and did not have viral load < 100,000 copies/mL by Week 8.

[c] Death only counted if it was the reason for treatment failure.

[d] Includes patients who were lost to-follow-up, withdrawn consent, non-adherent, protocol violations, added/changed background antiretroviral drugs for reasons other than tolerability or toxicity, or discontinued while suppressed.

Through 48 weeks of treatment, the proportion of patients in the APTIVUS/ritonavir arm compared to the comparator PI/ritonavir arm with HIV-1 RNA < 400 copies/mL was 30.3% and 13.6% respectively, and with HIV-1 RNA < 50 copies/mL was 22.7% and 10.2% respectively. Among all randomized and treated patients, the median change from baseline in HIV-1 RNA at the last measurement up to Week 48 was -0.64 $\log_{10}$ copies/mL in patients receiving APTIVUS/ritonavir versus -0.22 $\log_{10}$ copies/mL in the comparator PI/ritonavir arm.

Among all randomized and treated patients, the median change from baseline in CD4+ cell count at the last measurement up to Week 48 was +23 cells/$mm^3$ in patients receiving APTIVUS/ritonavir (N=740) versus +4 cells/$mm^3$ in the comparator PI/ritonavir (N=727) arm.

Patients in the APTIVUS/ritonavir arm achieved a significantly better virologic outcome when APTIVUS/ritonavir was combined with enfuvirtide. Among patients with new enfuvirtide use, the proportion of patients in the APTIVUS/ritonavir arm compared to the comparator PI/ritonavir arm with HIV-1 RNA < 400 copies/mL was 52.4 % and 19.6% respectively, and with HIV-1 RNA < 50 copies/mL was 37.3% and 14.4% respectively [*see Clinical Pharmacology (12.2, 12.4)*]. The median change from baseline in CD4+ cell count at the last measurement up to Week 48 was +89 cells/$mm^3$ in patients receiving APTIVUS/ritonavir in combination with newly introduced enfuvirtide (N=124) and +18 cells/$mm^3$ in the comparator PI/ritonavir (N=96) arm.

### 14.2 Pediatric Patients

The pharmacokinetic profile, safety and activity of APTIVUS/ritonavir was evaluated in a randomized, open-label, multicenter study. This study enrolled HIV-1 infected, treatment-experienced pediatric patients (with the exception of 3 treatment naïve patients), with baseline HIV-1 RNA of at least 1500 copies/mL. The age ranged from 2 through 18 years and patients were stratified by age (2 to < 6 years, 6 to < 12 years and 12 to 18 years). One hundred and ten (110) patients were randomized to receive one of two APTIVUS/ritonavir dose regimens: 375 mg/$m^2$/150 mg/$m^2$ dose (N=55) or 290 mg/$m^2$/115 mg/$m^2$ dose (N=55), plus background therapy of at least two non-protease inhibitor antiretroviral drugs, optimized using baseline genotypic resistance testing. All patients initially received APTIVUS oral solution. Pediatric patients who were 12 years or older and received the maximum dose of 500/200 mg BID could subsequently change to APTIVUS capsules at day 28 [*see Adverse Reactions (6.2), Use in Specific Populations (8.4) , Clinical Pharmacology (12.3) and Microbiology (12.4)*].

Demographics and baseline characteristics were balanced between the APTIVUS/ritonavir dose groups. The 110 randomized pediatric patients had a median age of 11.7 years (range 2 to18), and were 57.2% male, 68.1% white, 30% black, and 1.8% Asian. The median baseline plasma HIV-1 RNA was 4.7 (range 3.0 to 6.8) $\log_{10}$ copies/mL and median baseline CD4+ cell count was 379 (range 2 to 2578) cells/$mm^3$. Overall, 37.4% of patients had a baseline HIV-1 RNA of >100,000 copies/mL; 28.7% had a baseline CD4+ cell count ≤ 200 cells/$mm^3$, and 48% had experienced a prior AIDS defining Class C event at baseline. Patients had prior exposure to a median of 4 NRTIs, 1 NNRTI, and 2 PIs.

Eighty three (75%) completed the 48 week period while 25% discontinued prematurely. Of the patients who discontinued prematurely, 9 (8%) discontinued due to virologic failure, and 9 (8%) discontinued due to adverse reactions.

At 48 weeks, 40% of patients had viral load <400 copies/mL. The proportion of patients with viral load <400 copies/mL tended to be greater (70%) in the youngest group of patients, who had less baseline viral resistance, compared to the older groups (37% and 31%). The HIV-1 RNA results are presented in Table 13.

**Table 13 Proportion of Patients with HIV-1 RNA < 400 copies/mL (<50 copies/mL) by age and dose***

| APTIVUS/ritonavir Dose Regimen | 2 to <6 years (N=20) | 6 to < 12 years (N=38) | 12 to 18 years (N=52) |
|---|---|---|---|
| 375 mg/m²/150 mg/m² | n=10<br>70% (42%) | n=19<br>50% (39%) | n=26<br>33% (30%) |
| 290 mg/m²/115 mg/m² | n=10<br>70% (54%) | n=19<br>37% (32%) | n=26<br>31% (23%) |

* The number of baseline tipranavir resistance-associated substitutions were fewer in the 2 to <6 year old patients than the 6 to 18 year old patients enrolled in study 1182.14

The dose selection for all age groups was based on the following:

- A greater proportion of patients receiving APTIVUS/ritonavir 375 mg/m$^2$/150 mg/m$^2$ compared to 290 mg/m$^2$/115 mg/m$^2$ achieved HIV-1 RNA < 400 and < 50 copies/mL.
- A greater proportion of patients 6 to18 years of age with multiple baseline protease inhibitor resistance-associated substitutions receiving APTIVUS/ritonavir 375 mg/m$^2$/150 mg/m$^2$ achieved HIV-1 RNA <400 copies/mL at 48 weeks compared to patients receiving APTIVUS/ritonavir 290 mg/m$^2$/115 mg/m$^2$.
- No clinically significant increase in adverse event rates observed with 375 mg/m$^2$/150 mg/m$^2$ compared to 290 mg/m$^2$/115 mg/m$^2$
- Overall, 6 (5%) patients ages 6 to18 had AIDS defining illness during the treatment period and all received the 290 mg/m$^2$/115 mg/m$^2$ dose.

The guidance for possible dose reduction for patients who develop intolerance or toxicity and cannot continue with APTIVUS/ritonavir 14 mg/kg/6 mg/kg (or 375 mg/m$^2$/150 mg/m$^2$ ) is based on the following:

- The 290 mg/m$^2$/115 mg/m$^2$ twice daily regimen provided tipranavir plasma concentrations similar to those obtained in adults receiving 500/200 mg twice-daily. The 375 mg/m$^2$/150 mg/m$^2$ twice daily regimen provided tipranavir plasma concentrations 37% higher than those obtained in adults receiving 500/200 mg twice-daily.
- The observed response rates for APTIVUS/ritonavir dose of 290 mg/m$^2$/115 mg/m$^2$ as shown in Table 13.

Dose reduction is not appropriate for patients whose virus is resistant to more than one protease inhibitor.

When body surface area (BSA) dosing is converted to mg/kg dosing, the APTIVUS/ritonavir 375 mg/m$^2$/150 mg/m$^2$ twice daily regimen is similar to 14 mg/kg/6 mg/kg and APTIVUS/ritonavir 290 mg/m$^2$/115 mg/m$^2$ twice daily regimen is similar to 12 mg/kg/5 mg/kg twice daily . [*See Dosage and Administration, (2.2)*].

## 16 HOW SUPPLIED/STORAGE AND HANDLING

APTIVUS 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 oral solution is a clear yellow viscous buttermint-butter toffee flavored liquid containing 100 mg tipranavir in each mL. The solution is supplied in a unit-of-use amber glass bottle providing 95 mL of solution with a child resistant closure. A 5 mL plastic oral dispensing syringe is also provided. (NDC 0597-0002-01)

*Storage*

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 after first opening the bottle.

APTIVUS oral solution should be **stored at 25°C (77°F); excursions permitted to 15°-30°C (59°-86°F). Do not refrigerate or freeze.** The solution must be used within 60 days after first opening the bottle.

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

## 17 PATIENT COUNSELING INFORMATION

*See FDA-Approved Patient Labeling (17.10)*

### 17.1 Hepatic Impairment and Toxicity

Patients should be informed that APTIVUS co-administered with 200 mg of ritonavir, has been associated with severe liver disease, including some deaths. Patients with signs or symptoms of clinical hepatitis should discontinue APTIVUS/ritonavir treatment and seek medical evaluation. Symptoms of hepatitis include fatigue, malaise, anorexia, nausea, jaundice, bilirubinuria, acholic stools, liver tenderness or hepatomegaly. Extra vigilance is needed for patients with chronic hepatitis B or C co-infection, as these patients have an increased risk of developing hepatotoxicity.

Liver function tests should be performed prior to initiating therapy with APTIVUS and 200 mg of ritonavir, and frequently throughout the duration of treatment. Patients with chronic hepatitis B or C co-infection or elevations in liver enzymes prior to treatment are at increased risk (approximately 2-fold) for developing further liver enzyme elevations or severe liver disease. Caution should be exercised when administering APTIVUS/ritonavir to patients with liver enzyme abnormalities or history of chronic liver disease. Increased liver function testing is warranted in these patients. APTIVUS should not be given to patients with moderate to severe hepatic impairment.

### 17.2 Intracranial Hemorrhage

Patients should be informed that APTIVUS co-administered with 200 mg of ritonavir has been associated with reports of both fatal and non-fatal intracranial hemorrhage. Patients should report any unusual or unexplained bleeding to their physician.

### 17.3 Drug Interactions

APTIVUS may interact with some drugs; therefore, patients should be advised to report to their healthcare provider the use of any other prescription or non-prescription medications or herbal products, particularly St. John’s wort.

**17.4 Use 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 and when taken at the recommended maximum dose of 500 mg/200 mg tipranavir/ritonavir BID, results in a daily dose of 1160 IU. This intake is higher than the Reference Daily Intake (adults 30 IU, pediatrics approximately 10 IU).

**17.5 Rash**

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 one or more of the following symptoms: joint pain or stiffness, throat tightness, generalized itching, muscle aches, fever, redness, blisters, or peeling of the skin. Women taking birth control pills may get a skin rash. Patients should be told to discontinue use of APTIVUS and call their physician right away if any of these symptoms develop.

**17.6 Sulfa Allergy**

Patients should be told to report any history of sulfonamide allergy to the physician.

**17.7 Contraceptives**

Women receiving estrogen-based hormonal contraceptives should be instructed that additional or alternative contraceptive measures should be used during therapy with APTIVUS/ritonavir. There may be an increased risk of rash when APTIVUS is given with hormonal contraceptives.

**17.8 Fat Redistribution**

Patients should be informed that redistribution or accumulation of body fat may occur in patients receiving antiretroviral therapy and that the cause and long-term health effects of these conditions are not known at this time.

**17.9 Administration**

Patients should be informed that APTIVUS must be co-administered with ritonavir to ensure its therapeutic effect. Failure to correctly co-administer APTIVUS with ritonavir will result in reduced plasma levels of tipranavir that may be insufficient to achieve the desired antiviral effect.

Patients should be told that sustained decreases in plasma HIV-1 RNA have been associated with a reduced risk of progression to AIDS and death. Patients should remain under the care of a physician while using APTIVUS. Patients should be advised to take APTIVUS and other concomitant antiretroviral therapy every day as prescribed. APTIVUS, co-administered with ritonavir, must be given in combination with other antiretroviral drugs. Patients should not alter the dose or discontinue therapy without consulting with their healthcare professional. If a dose of APTIVUS is missed, patients should take the dose as soon as possible and then return to their normal schedule. However, if a dose is skipped the patient should not double the next dose.

Patients should be informed that APTIVUS is not a cure for HIV-1 infection and that they may continue to develop opportunistic infections and other complications associated with HIV-1 disease. The long-term effects of APTIVUS are unknown at this time. Patients should be told that there are currently no data demonstrating that therapy with APTIVUS can reduce the risk of transmitting HIV-1 to others through sexual contact.

APTIVUS can be taken with or without food.

**17.10 FDA-Approved Patient Labeling**

Patient information is supplied as a tear-off following the full prescribing information.

Distributed by:

Boehringer Ingelheim Pharmaceuticals, Inc.

Ridgefield, CT 06877 USA

**Address medical inquiries to: (800) 542-6257 or (800) 459-9906 TTY.**



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

OT2000HF1808 10003515/06

**Patient Information**

**APTIVUS®**
**(tipranavir) capsules 250 mg**

**APTIVUS®**
**(tipranavir) oral solution 100 mg/mL**

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 healthcare professional about your medical condition or treatment. You should stay under a healthcare professional'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 and NORVIR® (ritonavir) and call your healthcare professional 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 healthcare professional should check your blood tests more often because you have an increased chance of developing liver problems.**

**Patients taking APTIVUS together with 200 mg NORVIR® (ritonavir) may develop bleeding in the brain that can cause death.**

**You should report any unusual or unexplained bleeding to your healthcare professional if you are taking APTIVUS together with NORVIR® (ritonavir).**

**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 infections.

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 healthcare professional 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 NORVIR® (ritonavir)

- 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 your healthcare professional or pharmacist if any of them are "ergot alkaloids".
    - Halcion® (triazolam)
    - Orap® (pimozide)
    - Propulsid® (cisapride)
    - Versed® (midazolam) taken orally
    - Pacenone® (amiodarone)
    - Vascor® (bepridil)
    - Tambocor® (flecainide)
    - Rythmol® (propafenone)
    - Quinaglute dura® (quinidine)
    - Zocor® (simvastatin)
    - Mevacor® (lovastatin)

- take St. John's wort or Rifampin. It may result in reduced virologic activity and possible resistance to tipranavir or to the class of protease inhibitors.

**What should I tell my healthcare professional before I take APTIVUS?**

**Tell your healthcare professional about all of your medical conditions, including if you:**

- **have hemophilia or another medical condition that increases your chance of bleeding, or are taking medicines which increase your chance of bleeding.** These patients may have an increased chance of bleeding.

- **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 diabetes.** APTIVUS may worsen 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 healthcare professional will need to decide if APTIVUS is right for you. If you take APTIVUS while you are pregnant, talk to your healthcare professional 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 healthcare professional 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 healthcare professional as you may need to temporarily stop taking either APTIVUS or the other medicine that contains estrogen or female hormones.

**Tell your healthcare professional 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.

Do not take Flonase®, Viagra®, Cialis®, or Levitra® with APTIVUS/ritonavir without first speaking with your healthcare professional.

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

If you are taking APTIVUS oral solution, which contains vitamin E, you should not take additional vitamin E other than that contained in a standard multivitamin.

**Know all the medicines you take and keep a list of them with you**. Show this list to all your healthcare professionals 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 healthcare professional or pharmacist.** You can ask your healthcare professional or pharmacist for a list of medicines that can interact with APTIVUS.

**How should I take APTIVUS?**

- Take APTIVUS exactly as your healthcare professional has prescribed. You should check with your healthcare professional or pharmacist if you are not sure. **You must take APTIVUS at the same time as NORVIR® (ritonavir).** The adult 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.

- Children 2 years of age or older can also take APTIVUS with ritonavir. The child's healthcare professional will decide the right dose based on the child's weight or size. The dose should not exceed the recommended adult dose.

- APTIVUS should not be used in children under 2 years of age.

APTIVUS comes in capsule and oral solution forms. You should **swallow APTIVUS capsules whole. Do not chew the capsules.**

- You can take APTIVUS and ritonavir with or without food.

- Do not change your dose or stop taking APTIVUS without talking with your healthcare professional.

- If you take too much APTIVUS, call your healthcare professional 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 healthcare professional 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 healthcare professional.

**What are the possible side effects of APTIVUS?**

**APTIVUS may cause serious side effects, including:**

- **liver problems, including liver failure and death.** Your healthcare professional 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 of blood tests.
- **bleeding in the brain.** This has occurred in patients treated with APTIVUS in clinical trials and can lead to permanent disability or death. Many of the patients experiencing bleeding in the brain had other medical conditions or were receiving other medications that may have caused or added to bleeding in the brain. Patients with hemophilia or another medical condition that increases the chance of bleeding, or patients taking medicines that may cause bleeding may have an increased chance of bleeding in the brain.
- **rash.** 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 one or more of the following symptoms: joint pain or stiffness, throat tightness, generalized itching, muscle aches, fever, redness, blisters, or peeling of the skin. Women taking birth control pills may get a skin rash. If you develop any of these symptoms, stop using APTIVUS and call your healthcare professional right away.
- **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 healthcare professional 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 of APTIVUS include diarrhea, nausea, fever, vomiting, tiredness, headache, and stomach pain. Rash was seen more frequently in children.

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

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

**How should I store APTIVUS?**

- Store APTIVUS capsules in a refrigerator at approximately **36ºF to 46ºF (2ºC to 8ºC).** 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 **59ºF to 86ºF (15ºC to 30ºC).** You can write the date of opening the bottle on the label. Do not use after the expiration date written on the bottle.

- Store APTIVUS oral solution at approximately **59°F to 86°F (15°C to 30°C)**. **Do not refrigerate or freeze**. The solution must be used within 60 days after first opening of 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 healthcare professional. You can ask your pharmacist or healthcare professional 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 1-800-459-9906 TTY.**

**What are the ingredients in APTIVUS?**

**Capsules:**

**Active Ingredient:** tipranavir

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

**Oral Solution:**

**Active Ingredient:** tipranavir

**Major Inactive Ingredients:** polyethylene glycol 400, vitamin E polyethylene glycol succinate, purified water, and propylene glycol.

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

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

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