PRODUCT MONOGRAPH

Pr APTIVUS®

(tipranavir)

Capsules 250 mg

Non-Peptidic Protease Inhibitor (NPPI)

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(tipranavir capsules)

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY OF PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Nonmedicinal Ingredients
Oral	Capsules 250 mg	Sorbitol, Ethanol and Cremophor® EL *For a complete listing see Dosage Forms, Composition and Packaging section.*

INDICATIONS AND CLINICAL USE

APTIVUS (tipranavir) co-administered with 200 mg ritonavir, is indicated for combination antiretroviral treatment of HIV-1 infected adults who are treatment experienced and infected with HIV-1 strains resistant to more than one protease inhibitor.

In deciding on a new regimen for patients who have failed an antiretroviral regimen, careful consideration should be given to the treatment history of the individual patient and the patterns of mutations associated with different drugs.

For a description of the clinical data in support of this indication, refer to CLINICAL TRIALS.

Geriatrics (>65 years): Clinical studies of APTIVUS did not include sufficient number of subjects aged 65 and over to determine whether they respond differently from younger subjects. In general, caution should be exercised in the administration and monitoring of APTIVUS in elderly patients reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy. See ACTION AND CLINICAL PHARMACOLOGY, WARNINGS AND PRECAUTIONS, ADVERSE REACTIONS, and DOSAGE AND ADMINISTRATION sections.

Pediatrics (2-18 years of age): The safety and efficacy of APTIVUS in this population has not yet been fully established. Treatment of children with APTIVUS is therefore not recommended. See ACTION AND CLINICAL PHARMACOLOGY, WARNINGS AND PRECAUTIONS, ADVERSE REACTIONS, and DOSAGE AND ADMINISTRATION sections.

CONTRAINDICATIONS

APTIVUS (tipranavir) is contraindicated in patients with known hypersensitivity to the active substance or to any of the ingredients of the product. For a complete listing, see DOSAGE FORMS, COMPOSITION AND PACKAGING section.

In case of rare hereditary conditions that may be incompatible with an excipient of the product (please refer to WARNINGS and PRECAUTIONS) the use of the product is contraindicated.

APTIVUS is contraindicated in patients with moderate or severe (Child-Pugh Class B or C respectively) hepatic insufficiency.

APTIVUS contains Cremophor® EL. Caution should be used when administering medicines containing Cremophor® EL (e.g. cyclosporine i.v. and paclitaxel i.v.) to patients with a prior hypersensitivity reaction to Cremophor® EL.

Co-administration of APTIVUS with 200 mg ritonavir, with drugs that are highly dependent on CYP3A for clearance and for which elevated plasma concentrations are associated with serious and/or life-threatening events is contraindicated. These drugs are listed in Table 1 below.

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
Alpha-1 adrenoreceptor antagonist	Alfuzosin
Antiarrhythmics	Amiodarone, bepridil, flecainide, propafenone, quinidine
Anti-gout	Colchicine[+]
Antihistamines	Astemizole*, terfenadine*
Antimycobacterials	Rifampin
Antipsychotics	Pimozide, quetiapine
Ergot derivatives	Dihydroergotamine, ergonovine, ergotamine, methylergonovine
GI motility agent	Cisapride*
Herbal products	St. John's wort (hypericum perforatum)
HMG-CoA reductase inhibitors	Lovastatin , simvastatin
PDE5 Inhibitors	Sildenafil, when used for the treatment of pulmonary arterial hypertension (PAH)**
Sedatives/hypnotics	Oral midazolam, oral triazolam

* Cisapride, astemizole and terfenadine are not marketed in Canada.

** See Table 8 for sildenafil when dosed for erectile dysfunction

[+] See Table 7 for contraindications and see Table 8 for dosing with patients with normal hepatic and renal function.

Due to the need for co-administration of APTIVUS with low-dose ritonavir (RTV), please refer to ritonavir product monograph for a description of ritonavir contraindications.

WARNINGS AND PRECAUTIONS

APTIVUS co-administered with 200 mg ritonavir has been associated with reports of both fatal and non-fatal intracranial hemorrhage (See WARNINGS and PRECAUTIONS).

APTIVUS co-administered with 200 mg ritonavir has been associated with reports of clinical hepatitis and hepatic decompensation including some fatalities. Extra vigilance including increased clinical and laboratory monitoring is warranted in patients with chronic hepatitis B or hepatitis C co-infection, as these patients have an increased risk of hepatotoxicity (See Hepatic Impairment).

General

APTIVUS (tipranavir) must be administered with 200 mg ritonavir to ensure its therapeutic effect (see Dosage and Administration). 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 instructed accordingly. Please refer to ritonavir product monograph for additional information on precautionary measures.

Aptivus contains up to 50.4 mg sorbitol per maximum recommended daily dose. Patients with the rare hereditary condition of fructose intolerance should not take this medicine.

APTIVUS® capsules contain ethanol 7 % (v/v). This should be taken into account in pregnant or breast-feeding women, children, and in high-risk groups such as those with liver disease or epilepsy. Ethanol could be harmful for those suffering from alcoholism.

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.

Effects on Platelet Aggregation and Coagulation

APTIVUS co-administered with 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 supplement high doses of vitamin E.

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

In rats, co-administration of a Vitamin E derivative increased the bleeding effects of tipranavir (see Toxicology section). However, analyses of stored plasma from adults treated with APTIVUS capsules plus low-dose ritonavir, and from paediatric patients treated with APTIVUS capsules or tipranavir oral solution (which contains a vitamin E derivative) plus low-dose ritonavir have demonstrated that with or without the vitamin E-containing oral solution there was no effect of tipranavir on vitamin K-dependent coagulation factors (Factor II and Factor VII), Factor V, or on prothrombin or activated partial thromboplastin times.

Carcinogenesis and Mutagenesis:

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 genetic toxicity in a battery of five *in vitro* and *in vivo* tests assessing mutagenicity and clastogenicity.

In a study conducted in rats with tipranavir at systemic exposure levels (AUC) of 1670 µM·h, equivalent to human exposure at the adult human clinical dose, no adverse effects on mating or fertility were observed. Tipranavir did not produce teratogenic effects at maternal doses producing systemic drug exposure levels of 1310 µM·h in rats or 120 µM·h in rabbits-equivalent to or below the exposure at the adult human clinical dose (APTIVUS /ritonavir 500 mg/200 mg bid), respectively.

At tipranavir exposures of 1310 µM·h in rats (0.8-fold human exposure at the clinical dose), fetal toxicity (decreased sternebrae ossification and body weights) was observed. In pre- and post-natal development studies with tipranavir in rats, no adverse effects were noted at 340 µM·h (0.2-fold human exposure), but growth inhibition of pups was observed at maternally toxic doses of 1310 µM·h (0.8-fold human exposure). Calculated exposure in animal studies were equivalent to or below human therapeutic exposure levels. For the animal studies reported above, exposures were three to five fold lower at the end of the dosing period compared to the start of the dosing period.

Cardiovascular

QT Prolongation

A specific study was conducted using the therapeutic and supratherapeutic doses of APTIVUS co-administered with RTV (TPV/r 500/200 mg and TPV/r 750/200 mg) on the QTc interval in healthy male and female volunteers using moxifloxacin (400 mg) as a positive control. There was no clinically relevant prolongation of the QT interval or other electrocardiac abnormalities compared to the baseline with either dose.

Endocrine and Metabolism

Diabetes Mellitus/Hypergylcemia

New onset diabetes mellitus, exacerbation of pre-existing diabetes mellitus and hyperglycemia have been reported during post-marketing surveillance in HIV-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 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. The causal relationship between protease inhibitor therapy and these events has not been established.

Lipid Elevation

Treatment with APTIVUS co-administered with ritonavir, and other antiretroviral agents, has resulted in increased plasma total triglycerides and cholesterol. Triglyceride and cholesterol testing should be performed prior to initiating APTIVUS therapy and during therapy. Treatment-related lipid elevations should be managed as clinically appropriate.

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.

Hematologic

Hemophilia

There have been reports of increased bleeding, including spontaneous skin haematomas and haemarthrosis in patients with haemophilia 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.

Hepatic/Biliary/Pancreatic

Hepatic Impairment

APTIVUS is contraindicated in patients with moderate or severe hepatic insufficiency (Child-Pugh Class B or C, respectively) (see CONTRAINDICATIONS). Limited data are currently available for the use of APTIVUS, co-administered with ritonavir, in patients co-infected with hepatitis B or C. Patients with chronic hepatitis B or C and treated with antiretroviral agents are

at an increased risk for severe and potentially fatal hepatic adverse events. APTIVUS should be used in this patient population only if the potential benefit outweighs the potential risk, and with increased clinical and laboratory monitoring.

Patients with mild hepatic impairment (Child-Pugh Class A) should be closely monitored.

Caution should be exercised when administering APTIVUS/ritonavir to patients with liver enzyme abnormalities or history of hepatitis. Appropriate laboratory testing should be conducted prior to initiating therapy with APTIVUS and ritonavir, and frequently during treatment. Increased monitoring should be considered when APTIVUS and ritonavir are administered to patients with elevated baseline transaminase levels, or active hepatitis B or C, as patients with underlying hepatitis B or C or marked elevations in transaminases prior to treatment may be at increased risk for developing further transaminase elevations or hepatic decompensation. APTIVUS/ritonavir should be discontinued once signs of worsening liver function occur in patients with pre-existing liver disease.

APTIVUS co-administered with ritonavir, has been associated with reports of clinical hepatitis and hepatic decompensation, including some fatalities. These have generally occurred in patients with advanced HIV disease taking multiple concomitant medications. A causal relationship to APTIVUS co-administered with 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, liver tenderness or hepatomegaly. Patients with signs or symptoms of hepatitis should discontinue APTIVUS/ritonavir treatment and seek medical evaluation.

Tipranavir is principally metabolised by the liver. Therefore caution should be exercised when administering this drug to patients with hepatic impairment because tipranavir concentrations may be increased.

For information on the multi-dose pharmacokinetics of tipranavir in hepatically impaired patients, see CLINICAL PHARMACOLOGY.

Immune

Immune Reconstitution Syndrome

During the initial phase of treatment, patients responding to antiretroviral therapy may develop an inflammatory response to indolent or residual opportunistic infections (such as MAC, CMV, PCP, and TB), which may necessitate further evaluation and treatment. Autoimmune disorders (such as Graves´ disease, polymyositis and Guillain-Barré syndrome) have also been reported to occur in the setting of immune reconstitution; however, the time to onset is more variable and can occur many months after initiation of treatment.

Renal

Renal Impairment

Since the renal clearance of tipranavir is negligible, increased plasma concentrations are not expected in patients with renal impairment.

Sensitivity/Resistance

Sulfonamide Allergy

APTIVUS (tipranavir) 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 tipranavir is unknown.

Sexual Function/Reproduction

Clinical data on fertility are not available for tipranavir. No adverse effect on fertility was observed in animal reproductive studies performed with tipranavir at an exposure equivalent to humans.

Please refer to the TOXICOLOGY section for further information on studies.

Skin

Rash

Urticarial rash, maculopapular rash, and possible photosensitivity have been reported in subjects receiving APTIVUS/ritonavir. In Phase 2 and 3 trials, rash was observed in 14% of females and in 8-10% of males receiving APTIVUS/ritonavir. Additionally, in one drug interaction trial in healthy female volunteers administered a single dose of ethinyl estradiol followed by APTIVUS/ritonavir, 33% of subjects developed a rash. Rash accompanied by joint pain or stiffness, throat tightness, or generalized pruritus has been reported in both men and women receiving APTIVUS/ritonavir. The risk of rash increases in patients with lower CD4 cell counts.

Special Populations

Pregnant Women: 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. No teratogenicity was observed in animal reproductive studies with tipranavir. See TOXICOLOGYsection.

Nursing Women: APTIVUS was shown to be excreted in breast milk in rats/mice. It is unknown if the drug is excreted in human milk. Because many drugs are excreted in human milk, precaution should be exercised. Consistent with the recommendation that HIV-infected mothers not breast-feed their infants to avoid risking postnatal transmission of HIV, mothers should discontinue breast-feeding if they are receiving APTIVUS.

Antiretroviral Pregnancy Registry: To monitor maternal-fetal outcomes of pregnant women exposed to APTIVUS, an Anti-retroviral Pregnancy Registry has been established. Physicians are encouraged to register patients by calling toll-free 1-800-258-4263.

Pediatrics (*2 - 18* years of age): Safety and efficacy of APTIVUS in this population has not yet been fully established. Treatment of children with APTIVUS is therefore not recommended.

There are no data available in children younger than 2 years of age.

Geriatrics (> *65* years of age): Clinical studies of APTIVUS did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. In general, caution should be exercised in the administration and monitoring

of APTIVUS in elderly patients reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

Monitoring and Laboratory Tests

Appropriate laboratory testing should be conducted prior to initiating therapy with APTIVUS and low-dose ritonavir, and during treatment. Increased monitoring should be considered when APTIVUS and low dose ritonavir are administered to patients with elevated AST and ALT levels, or chronic hepatitis B or C.

Triglyceride and cholesterol testing should be performed prior to initiating tipranavir therapy and during therapy.

ADVERSE REACTIONS

Clinical Trial Adverse Drug Reactions

Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

APTIVUS (tipranavir) co-administered with low-dose ritonavir has been studied in more than 6300 HIV-positive adults as combination therapy in clinical studies. More than 900 adults in formal clinical trials, including 541 in the RESIST-1 and RESIST-2 Phase III pivotal trials, have been treated with 500 mg/200 mg twice daily for at least 48 weeks. The following tables contain adverse events observed within the RESIST trials with no assigned causality.

Due to the need for co-administration of APTIVUS with low-dose ritonavir, please refer to ritonavir product monograph for ritonavir-associated adverse reactions.

Table 2: Serious Adverse Events (SAE) Occurring in ≥ 0.5% of RESIST Trial Patients

Preferred Term	TPV/r[a]		CPI/r[b]	
	No. (%) of Patients	events/100 PEY	No. (%) of Patients	events/100 PEY
Total treated	749 (100.0)	1159.6	737 (100.0)	659.3
Total of any SAE	217 (29.0)	22.4	156 (21.2)	27.0
Blood and Lymphatic System Disorders	15 (2.0)	1.3	15 (2.0)	2.3
Anemia	7 (0.9)	0.6	8 (1.1)	1.2
Gastrointestinal Disorders	49 (6.5)	4.3	25 (3.4)	3.8
Diarrhea	13 (1.7)	1.1	7 (1.0)	1.1
Pancreatitis	8 (1.1)	0.7	2 (0.3)	0.3
Abdominal pain	7 (0.9)	0.6	3 (0.4)	0.5
Vomiting	5 (0.7)	0.4	3 (0.4)	0.5
Dysphagia	4 (0.5)	0.3	2 (0.3)	0.3

Preferred Term	TPV/r[a]		CPI/r[b]	
	No. (%) of Patients	events/100 PEY	No. (%) of Patients	events/100 PEY
General Disorders and Administration Site Conditions	44 (5.9)	3.9	25 (3.4)	3.9
Pyrexia	24 (3.2)	2.1	11 (1.5)	1.7
Chills	4 (0.5)	0.3	1 (0.1)	0.2
Asthenia	4 (0.5)	0.3	3 (0.4)	0.5
Chest pain	5 (0.7)	0.4	3 (0.4)	0.5
Hepatobiliary Disorders	12 (1.6)	1.0	3 (0.4)	0.5
Hepatic failure	4 (0.5)	0.3	0 (0.0)	0.0
Infections and Infestations	104 (13.9)	9.6	72 (9.8)	11.5
Pneumonia	23 (3.1)	2.0	5 (0.7)	0.8
Gastroenteritis	5 (0.7)	0.4	4 (0.5)	0.6
Cytomegalovirus chorioretinitis	4 (0.5)	0.3	4 (0.5)	0.6
Pneumocystis *jiroveci pneumonia*	10 (1.3)	0.9	8 (1.1)	1.2
Esophageal candidiasis	8 (1.1)	0.7	7 (1.0)	1.1
Bronchitis	4 (0.5)	0.3	1 (0.1)	0.2
Condyloma acuminatum	5 (0.7)	0.4	1 (0.1)	0.2
Sepsis	5 (0.7)	0.4	0 (0.0)	0.0
Appendicitis	4 (0.5)	0.3	1 (0.1)	0.2
HIV infection	4 (0.5)	0.3	0 (0.0)	0.0
Sinusitis	4 (0.5)	0.3	2 (0.3)	0.3
Injury, poisoning and procedural complications	14 (1.9)	1.2	9 (1.2)	1.4
Hip fracture	4 (0.5)	0.3	0 (0.0)	0.0
Road traffic accident	4 (0.5)	0.3	2 (0.3)	0.3
Investigations	17 (2.3)	1.5	11 (1.5)	1.7
ALT increased	6 (0.8)	0.5	1 (0.1)	0.2
AST increased	5 (0.7)	0.4	1 (0.1)	0.2
Weight decreased	4 (0.5)	0.3	3 (0.4)	0.5
Metabolism and Nutrition Disorders	20 (2.7)	1.7	10 (1.4)	1.5
Dehydration	11 (1.5)	1.0	4 (0.5)	0.6
Neoplasms Benign, Malignant and Unspecified (including cysts and polyps)	39 (5.2)	3.4	23 (3.1)	3.6
Basal cell carcinoma	4 (0.5)	0.3	1 (0.1)	0.2
Hodgkin's disease	5 (0.7)	0.4	0 (0.0)	0.0
Nervous System Disorders	31 (4.1)	2.7	22 (3.0)	3.4
Headache	6 (0.8)	0.5	4 (0.5)	0.6
Convulsions	4 (0.5)	0.3	4 (0.5)	0.6
Psychiatric Disorders	5 (0.7)	0.4	12 (1.6)	1.8
Depression	1 (0.1)	0.1	5 (0.7)	0.8
Renal and Urinary Disorders	24 (3.2)	2.1	9 (1.2)	1.4
Acute renal failure	11 (1.5)	1.0	2 (0.3)	0.3
Renal failure	7 (0.9)	0.6	3 (0.4)	0.5
Respiratory, Thoracic and Mediastinal Disorders	23 (3.1)	2.0	11 (1.5)	1.7
Dyspnea	5 (0.7)	0.4	4 (0.5)	0.6
Respiratory failure	4 (0.5)	0.3	0 (0.0)	0.0

a Dose is TPV/r 500 mg /200 mg BID.
b Doses are BID and in mg: LPV/r 400/100, IDV/r 800/100, SQV/r 1000/100 or SQV/r 800/200, APV/r 600/100

In RESIST-1 and RESIST-2 in the APTIVUS/ritonavir arm, the most frequent adverse events were diarrhoea, nausea, headache, pyrexia, vomiting, fatigue and abdominal pain. The 48 Week Kaplan-Meier rates of adverse events leading to discontinuation were 13.3 % for APTIVUS/ritonavir-treated patients and 10.8% for the comparator arm patients.

The following clinical safety features (intracranial hemorrhage, hepatotoxicity, hyperlipidemia) were seen at higher frequency among APTIVUS/ritonavir treated patients when compared with the comparator arm treated patients in the RESIST trials.

Intracranial Hemorrhage (ICH): Five cases of ICH in 4 patients (1246 patient exposure years) were observed in patients receiving APTIVUS/ritonavir compared to no cases in the comparator arm (660 patient exposure years). Fourteen intracranial hemorrhage events (ICH), including 8 fatalities, occurred in 13 out of 6,840 HIV-1 infected individuals receiving APTIVUS (tipranavir) capsules, as part of combination antiretroviral therapy, in clinical trials. Many of these patients had other medical conditions or were receiving concomitant medications that may have caused or contributed to these events. An increased risk of ICH has previously been observed in patients with advanced HIV disease / AIDS. No pattern of abnormal coagulation parameters has been observed in patients in general, or preceding the development of ICH. The median time to onset of an ICH event was 525.5 days on treatment.

Hepatotoxicity: The frequency of Grade 3 or 4 ALT and/or AST abnormalities was higher in APTIVUS/ritonavir patients compared with comparator arm patients. Multivariate analyses showed that baseline ALT or AST above DAIDS Grade 1 and co-infection with hepatitis B or C were risk factors for these elevations.

Hyperlipidaemia: Grade 3 or 4 elevations of triglycerides and cholesterol occurred more frequently in the APTIVUS/ritonavir arm compared with the comparator arm. The clinical significance of these observations has not been fully established.

Table 3: Percentage of Patients with Treatment Emergent Adverse Events of at Least Moderate Intensity (Grades 2-4) in ≥ 2% of Patients in Either Treatment Group[a] in the RESIST Trials at the 48-Week Time Point

	Phase 3 Studies 1182.12 and 1182.48 (48-weeks)	
	Percentage of patients (rate per 100 patient-exposure years)	
	APTIVUS/ritonavir (500/200 mg BID) + OBR (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[c]	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/RTV: lopinavir/ritonavir 400/100 mg BID, indinavir/ritonavir 800/100 mg BID, saquinavir/ritonavir1000/100 mg BID, amprenavir/ritonavir 600/100 mg BID

Table 4: Adverse Events Resulting in Clinical Intervention (Discontinuation) in the RESIST Trials 1182.12 and 1182.14

System Organ Class / Preferred Term	Treatment Group			
	TPV/r		CPI/r	
	N (%)	events/100 PEY	N (%)	events/100 PEY
Total Treated	749 (100.0)	1159.6	737 (100.0)	659.3
Total With Any AE Leading to Discontinuation	117 (15.6)	10.3	69 (9.4)	10.7
Gastrointestinal Disorders	41 (5.5)	3.6	28 (3.8)	4.3
Nausea	13 (1.7)	1.1	11 (1.5)	1.7
Vomiting	12 (1.6)	1.0	9 (1.2)	1.4
Diarrhea	14 (1.9)	1.2	10 (1.4)	1.5
Abdominal Pain	2 (0.3)	0.2	6 (0.8)	0.9
Abdominal Pain Upper	2 (0.3)	0.2	1 (0.1)	0.2
Pancreatitis	3 (0.4)	0.3	0 (0.0)	0.0
Gastrointestinal disorder	2 (0.3)	0.2	1 (0.1)	0.2
General Disorders and Administration Site Conditions	15 (2.0)	1.3	10 (1.4)	1.5
Asthenia	2 (0.3)	0.2	0 (0.0)	0.0
Fatigue	4 (0.5)	0.3	4 (0.5)	0.6
Malaise	2 (0.3)	0.2	0 (0.0)	0.0
Pyrexia	4 (0.5)	0.3	2 (0.3)	0.3
Hepatobiliary Disorders	8 (1.1)	0.7	2 (0.3)	0.3
Cytolytic Hepatitis	2 (0.3)	0.2	1 (0.1)	0.2
Infections and Infestations	17 (2.3)	1.5	10 (1.4)	1.5
Retroviral infections	2 (0.3)	0.2	2 (0.3)	0.3
Pneumocystis jiroveci pneumonia	2 (0.3)	0.2	0 (0.0)	0.0
Investigations	26 (3.5)	2.3	3 (0.4)	0.5
ALT Increased	7 (0.9)	0.6	1 (0.1)	0.2
AST Increased	3 (0.4)	0.3	1 (0.1)	0.2
GGT Increased	5 (0.7)	0.4	0 (0.0)	0.0
Hepatic Enzyme Increased	4 (0.5)	0.3	1 (0.1)	0.2
Liver Function Test Abnormal	3 (0.4)	0.3	0 (0.0)	0.0
Transaminases Increased	3 (0.4)	0.3	0 (0.0)	0.0
Weight decreased	3 (0.4)	0.3	0 (0.0)	0.0
Blood Triglycerides Increased	2 (0.3)	0.2	0 (0.0)	0.0
Metabolism and Nutrition Disorders	14 (1.9)	1.2	6 (0.8)	0.9
Anorexia	4 (0.5	0.3	1 (0.1)	0.2
Cachexia	2 (0.3)	0.2	0 (0.0)	0.0
Hypertriglyceridemia	2 (0.3)	0.2	1 (0.1)	0.2
Dehydration	3 (0.4)	0.3	0 (0.0)	0.0
Hyperlipidaemia	2 (0.3)	0.2	0 (0.0)	0.0
Musculoskeletal and connective tissue disorders	5 (0.7)	0.4	3 (0.4)	0.5
Arthralgia	1 (0.1)	0.1	2 (0.3)	0.3
Back pain	0 (0.0)	0.0	2 (0.3)	0.3
Myalgia	2 (0.3)	0.2	0 (0.0)	0.0
Neoplasms Benign, Malignant and Unspecified (including cysts and polyps)	3 (0.4)	0.3	9 (1.2)	1.4
Lymphoma	0 (0.0)	0.0	3 (0.4)	0.5
Nervous System Disorders	13 (1.7)	1.1	4 (0.5)	0.6

System Organ Class / Preferred Term	Treatment Group			
	TPV/r		CPI/r	
	N (%)	events/100 PEY	N (%)	events/100 PEY
Headache	3 (0.4)	0.3	2 (0.3)	0.3
Dizziness	2 (0.3)	0.2	0 (0.0)	0.0
Psychiatric Disorders	2 (0.3)	0.2	0 (0.0)	0.0
Renal and Urinary Disorders	4 (0.5)	0.3	3 (0.4)	0.5
Renal failure acute	2 (0.3)	0.2	0 (0.0)	0.0
Nephrolithiasis	0 (0.0)	0.0	2 (0.3)	0.3
Respiratory, thoracic and mediastinal disorders	6 (0.8)	0.5	1 (0.1)	0.2
Skin and Subcutaneous Tissue Disorders	7 (0.9)	0.6	8 (1.1)	1.2
Rash	5 (0.7)	0.4	4 (0.5)	0.6
Vascular disorders	2 (0.3)	0.2	0 (0.0)	0.0

Table 5: Study-Drug-Related Adverse Events Occurring in 1% or More of Patients in Either Treatment Group in the RESIST Trials

System Organ Class/ Preferred Term	Treatment Group/Number (%) of Patients events/100 PEY			
	TPV/r[a]	**events/100 PEY**	**CPI/r[a]**	**events/100 PEY**
Total treated	749 (100.0)	1159.6	737 (100.0)	659.3
Total with any study drug-related adverse event	412 (55.0)	65.9	300 (40.7)	67.3
Gastrointestinal Disorders	268 (35.8)	33.4	226 (30.7)	45.3
Diarrhea	144 (19.2)	14.9	138 (18.7)	24.4
Nausea	105 (14.0)	10.2	87 (11.8)	14.5
Vomiting	41 (5.5)	3.7	28 (3.8)	4.4
Flatulence	26 (3.5)	2.3	25 (3.4)	3.9
Abdominal distension	22 (2.9)	2.0	19 (2.6)	2.9
Abdominal pain	22 (2.9)	1.9	29 (3.9)	4.6
Abdominal pain upper	10 (1.3)	0.9	11 (1.5)	1.7
Dyspepsia	9 (1.2)	0.8	9 (1.2)	1.4
Dry mouth	4 (0.5)	0.3	7 (1.0)	1.1
Gastritis	2 (0.3)	0.2	7 (1.0)	1.1
General Disorders and Administration Site Conditions	58 (7.7)	1094.4 (5.3)	53 (7.2)	8.5
Fatigue	39 (5.2)	1116.1 (3.5)	29 (3.9)	4.5
Asthenia	4 (0.5)	1156.5 (0.3)	13 (1.8)	2.0
Investigations	64 (8.5)	1103.6 (5.8)	19 (2.6)	2.9
ALT increased	18 (2.4)	1145.0 (1.6)	4 (0.5)	0.6
GGT increased	16 (2.1)	1147.7 (1.4)	1 (0.1)	0.2
Blood triglycerides increased	15 (2.0)	1143.7 (1.3)	6 (0.8)	0.9
AST increased	12 (1.6)	1148.8 (1.0)	3 (0.4)	0.5
Transaminases increased	8 (1.1)	1153.5 (0.7)	0 (0.0)	0.0
Metabolism and Nutrition Disorders	83 (11.1)	1065.6 (7.8)	48 (6.5)	7.7
Hypertriglyceridemia	33 (4.4)	1120.4 (2.9)	17 (2.3)	2.6
Hyperlipidemia	23 (3.1)	1127.1 (2.0)	7 (1.0)	1.1
Anorexia	10 (1.3)	1154.9 (0.9)	8 (1.1)	1.2
Nervous System Disorders	59 (7.9)	1083.2 (5.4)	56 (7.6)	9.0
Headache	29 (3.9)	1117.0 (2.6)	15 (2.0)	2.3
Dizziness	12 (1.6)	1141.1 (1.1)	11 (1.5)	1.7

Somnolence	5 (0.7)	1153.2 (0.4)	7 (1.0)	1.1
Neuropathy peripheral	3 (0.4)	1156.6 (0.3)	7 (1.0)	1.1
Psychiatric Disorders	19 (2.5)	1134.0 (1.7)	20 (2.7)	3.1
Insomnia	5 (0.7)	1151.7 (0.4)	7 (1.0)	1.1
Skin and Subcutaneous Tissue Disorders	58 (7.7)	1090.4 (5.3)	40 (5.4)	6.2
Rash	16 (2.1)	1141.2 (1.4)	12 (1.6)	1.8
Lipodystrophy acquired	9 (1.2)	1151.0 (0.8)	3 (0.4)	0.5
Pruritis	12 (1.6)	1142.6 (1.1)	3 (0.4)	0.5

[a] Doses are BID and in mg. TPV/r doses are 500/200; CPI/r doses are LPV/r 400/100, IDV/r 800/100, SQV/r 1000/100 or SQV/r 800/200, APV/r 600/100.

Less Common Clinical Trial Adverse Drug Reactions (< 1%)

Clinically meaningful adverse reactions of moderate to severe intensity occurring in less than 1% (<1/100) of adult patients in all Phase II and III trials treated with the 500 mg/200 mg APTIVUS/ritonavir dose (n=1397) are listed below by system organ class and frequency according to the following catergories:

Blood and lymphatic system disorders:
anaemia, neutropenia, thrombocytopenia

Gastrointestinal disorders:
gastrooesophageal reflux disease, pancreatitis, lipase increased

General Disorders and Administration Site Conditions:
influenza like illness, malaise, pyrexia

Hepatobiliary disorders:
hepatitis, toxic hepatitis, hepatic steatosis, hepatic failure (including fatal outcome), hyperbilirubinemia

Immune system disorders:
hypersensitivity

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

Metabolism and nutrition disorders:
decreased appetite, diabetes mellitus, hyperamylasaemia, hypercholesterolaemia, dehydration, facial wasting, hyperglycaemia

Musculoskeletal and connective tissue disorders:
muscle spasms, myalgia

Nervous system disorders:

dizziness, neuropathy peripheral, somnolence, intracranial hemorrhage

Psychiatric disorders:
insomnia, sleep disorder

Renal and urinary disorders:
renal failure

Respiratory, thoracic and mediastinal disorders:
dyspnoea

Skin and subcutaneous system disorders:
exanthem, lipoatrophy, lipodystrophy acquired, lipohypertrophy

Reactivation of herpes simplex and varicella zoster virus infections were observed in the RESIST trials.

Abnormal Hematologic and Clinical Chemistry Findings

Frequencies of marked clinical laboratory abnormalities (Grade 3 or 4) reported in at least 2 % of patients in the APTIVUS/ritonavir (TPV/r) arms in the Phase III clinical studies (RESIST -1 and RESIST-2) after 48-weeks were increased AST (6.1 %), increased ALT (9.6 %), increased ALT and/or AST (6.2 %), increased amylase (6.0 %), increased cholesterol (4.2%), increased triglycerides (24.9 %) and decreased white blood cell counts (5.7 %).

In clinical trials RESIST-1 and RESIST-2 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 29.3% at week 96 with APTIVUS/ritonavir and from 13.7% at week 48 to 14.6% at week 96 with Comparator PI/ritonavir, showing that the risk of developing transaminase elevations during the second year of therapy is lower than during the first year. Grade 3/4 ALT and/or AST elevations with APTIVUS coadministered with low dose ritonavir continued to increase from 10.0% at week 48 to 14.7% at week 96, and for comparator PI/ritonavir from 3.4% to 4.5% at weeks 48 and 96, respectively.

Marked clinical laboratory abnormalities (Grade 3 or 4) reported in phase III clinical studies (RESIST-1 and RESIST-2) in adults are summarized in Table 6 below:

Table 6: Grade 3-4 Laboratory Abnormalities Reported in ≥ 2% of Adult Patients

	RESIST-1/RESIST-2 (48-weeks) Percentage of patients (events per 100 patient-exposure years)	
	APTIVUS/RTV (500mg/200 mg bid) +-OBR (n=738)	**Comparator PI/RTV + OBR* (n=724)**
Hematology		
WBC count (decrease)	5.7 (5.8)	5.9 (9.5)
Chemistry		
ALT	9.6 (10.1)	2.1 (3.3)
AST	6.1 (6.3)	1.8 (2.8)
ALT and/or AST	10.3 (10.9)	2.9 (4.6)
Amylase	6.0 (6.2)	7.0 (11.6)
Lipase	2.8 (2.9)	2.6 (4.2)
Total Cholesterol	4.2 (4.3)	0.4 (0.7)
Triglycerides	24.9 (30.8)	13.0 (22.9)
Glucose (increase)	1.9 (1.9)	1.8 (2.8)

*OBR – optimized background regimen - Comparator PI/r: LPV/r 400/100 mg bid, IDV/r 800/100 mg bid, SQV/r 1000/100 mg bid, APV/r 600/100 mg bid

Post-Market Adverse Drug Reactions

In addition to adverse events identified in clinical trials, the following events have been reported since market introduction of APTIVUS. Because they are reported spontaneously from a population of unknown size, estimates of frequency cannot be made. The following events have been chosen for inclusion due to their seriousness, frequency of reporting, potential causal connection to APTIVUS, or a combination of these factors.

Blood and Lymphatic System Disorders: thrombocytopenia

Gastrointestinal Disorders: diarrhoea, nausea, pancreatitis, vomiting

Hepatobiliary Disorders: hepatitis, hepatotoxicity, hyperbilirubinaemia, jaundice

Immune System Disorders: hypersensitivity

Investigations: alanine aminotransferase increased, aspartate aminotransferse increased, blood bilirubin increased, blood triglycerides increased, gamma glutamyl transferase increased, hepatic enzyme increased, liver function test abnormal, transaminases increased

Metabolism and Nutrition Disorders: anorexia, hypertriglyceridaemia

Musculoskeletal, Connective Tissue and Bone Disorders: haemarthrosis, muscle haemorrhage

Nervous System Disorders: dizziness, haemorrhage intracranial, headache, somnolence

Psychiatric Disorders: insomnia

Renal and Urinary Disorders: renal failure

Skin and Subcutaneous Disorders: rash, subcutaneous haemorrhage

DRUG INTERACTIONS

Tipranavir is a substrate, an inducer and an inhibitor of cytochrome P450 CYP3A. However, when co-administered with ritonavir at the recommended dosage, there is a net inhibition of P450 CYP3A. Co-administration of APTIVUS and ritonavir with agents primarily metabolised by CYP3A may result in changed plasma concentrations of tipranavir or the other agents, which could alter their therapeutic and adverse effects. Agents that are contraindicated specifically due to the expected magnitude of interaction and potential for serious adverse events are listed in CONTRAINDICATIONS and in DRUG INTERACTIONS, Table 7: Drugs that Should Not Be Co-Administered with APTIVUS/Ritonavir.

Tipranavir is metabolised by CYP3A and is a Pgp substrate. Co-administration of tipranavir and agents that induce CYP3A and/or Pgp may decrease tipranavir concentrations and reduce its therapeutic effect. Co-administration of APTIVUS and medicinal products that inhibit Pgp may increase tipranavir plasma concentrations. Interaction with other drugs and other potentially significant drug interactions are discussed in greater detail in this Section.

Overview

APTIVUS co-administered with ritonavir at the recommended dose is a net inhibitor of CYP3A and may increase plasma concentrations of agents that are primarily metabolized by CYP3A. Thus, co-administration of APTIVUS/ritonavir with drugs highly dependent on CYP3A for clearance and for which elevated plasma concentrations are associated with serious and/or life-threatening events is contraindicated (see CONTRAINDICATIONS). Co-administration with other CYP3A substrates may require a dose adjustment or additional monitoring (see DRUG INTERACTIONS).

A phenotypic cocktail study was conducted with 16 healthy volunteers to quantify the influence of 10 days of APTIVUS/ritonavir 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.

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 slight inhibition after first dose on CYP2C19 and moderate 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 that 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 CYP3A and P-gp. The net effect will vary depending on the relative affinity of the co-administered drugs for CYP3A 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.

Drug-Drug Interaction

Drugs that are contraindicated for co-administration with APTIVUS are included in Table 7. These recommendations are based on either drug interaction studies or predicted interactions due to the expected magnitude of interaction and the potential for loss of therapeutic effect.

Table 7: Drugs That Should Not Be Co-Administered with APTIVUS/ritonavir

Drug Class: Drug Name	**Clinical Comment**
Alpha-1 adrenoreceptor antagonist: alfuzosin	CONTRAINDICATED. Potential for increased alfuzosin concentrations which can result in hypotension.
Antiarrhythmics: amiodarone bepridil flecainide propafenone quinidine	CONTRAINDICATED. Concentrations of amiodarone, bepridil, flecainide, propafenone, quinidine may be increased when co-administered with APTIVUS/ritonavir.
Anti-gout: colchicine	CONTRAINDICATED; Co-administration of colchicine with APTIVUS/ritonavir should not be given in patients with renal or hepatic impairment. See Table 8 for administration in patients with normal renal and hepatic functions.
Antihistamines: astemizole* terfenadine*	CONTRAINDICATED due to potential for serious and/or life-threatening reactions such as cardiac arrhythmias.
Antimycobacterials rifampin	CONTRAINDICATED; 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.
Antipsychotics: pimozide quetiapine	CONTRAINDICATED; due to CYP3A inhibition by APTIVUS/ritonavir, which may lead to serious and/or life-threatening reactions such as cardiac arrhythmias and coma.
Corticosteroids:	A drug interaction study in healthy subjects has shown that ritonavir significantly

Drug Class: Drug Name	Clinical Comment
fluticasone propionate	increases plasma fluticasone propionate exposures, resulting in significantly decreased serum cortisol concentrations. Concomitant use of APTIVUS, co-administered with ritonavir, and fluticasone propionate may produce the same effects. Systemic corticosteroid effects including Cushing's syndrome and adrenal suppression have been reported during post-marketing use in patients receiving ritonavir and inhaled or intranasally administered fluticasone propionate. Therefore, 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.
Ergot derivatives: dihydroergotamine ergonovine ergotamine methylergonovine	CONTRAINDICATED due to potential for serious and/or life-threatening reactions such as acute ergot toxicity characterized by peripheral vasospasm and ischemia of the extremities and other tissues.
GI motility agent: cisapride*	CONTRAINDICATED due to potential for serious and/or life-threatening reactions such as cardiac arrhythmias.
Herbal products St. John's wort	CONTRAINDICATED; 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	CONTRAINDICATED due to an increased risk of myopathy, including rhabdomyolysis.
HMG-CoA reductase inhibitors: atorvastatin	The concomitant use of APTIVUS, co-administered with low-dose ritonavir with atorvastatin is not recommended due to an increased risk of myopathy, including rhabdomyolysis.
Long-acting beta2-adrenergic receptor agonist: salmeterol	The concomitant use of salmeterol and APTIVUS, co-administered with low-dose ritonavir is not recommended. The combination may result in increased risk of cardiovascular adverse events associated with salmeterol, including QT prolongation, palpitations and sinus tachycardia.
Non-nucleoside reverse transcriptase inhibitors: etravirine	APTIVUS/ritonavir caused a 76% decrease of etravirine AUC that could significantly impair the virologic response to etravirine. Co-administration of etravirine and APTIVUS/ritonavir is not recommended.
Phosphodiesterase (PDE5) inhibitors: *Sildenafil, Pulmonary arterial hypertension (PAH)*	CONTRAINDICATED; Co-administration of APTIVUS/ritonavir with sildenafil may substantially increase the sildenafil plasma concentration and sildenafil associated adverse events such as hypotension, syncope, visual changes and priaprism. A safe and effective dose of sildenafil in combination with APTIVUS/ritonavir has not been established. See Table 8 for the use of sildenafil for erectile dysfunction.
Proton pump inhibitors / H_2 Antagonists: omeprazole esomeprazole	A drug interaction study in healthy subjects has shown that APTIVUS /ritonavir significantly decreased plasma omeprazole exposures (AUC and C_{max} by 71% and 73%, respectively). Therefore, co-administration of omeprazole or esomeprazole with APTIVUS /ritonavir is not recommended. If unavoidable, upward dose adjustments for either omeprazole or esomeprazole should be considered based on clinical response to therapy. Recommendations for maximal doses of omeprazole or esomeprazole are found in their corresponding product monographs.

Drug Class: Drug Name	Clinical Comment
Protease Inhibitors: atazanavir fosamprenavir lopinavir saquinavir	In a clinical study of dual-boosted protease inhibitor combination therapy in multiple-treatment experienced HIV-positive adults, APTIVUS, co-administered with 200 mg ritonavir, caused a 55%, 70% and 78% reduction in the C_{min} of amprenavir, lopinavir and saquinavir, respectively. An 81% reduction in the C_{min} of atazanavir was similarly observed in a healthy volunteer interaction study. Concomitant use of APTIVUS, co-administered with 200 mg ritonavir, with the protease inhibitors fosamprenavir, atazanavir, lopinavir or saquinavir (each co-administered with low-dose ritonavir) results in significant decreases in plasma concentrations of these protease inhibitors (see DRUG INTERACTIONS, Table 10). Combining a protease inhibitor with APTIVUS/ritonavir is not recommended.
Sedatives/hypnotics: oral midazolam oral triazolam	CONTRAINDICATED due to the potential for serious and/or life-threatening reactions such as prolonged or increased sedation or respiratory depression. Ritonavir is a potent inhibitor of CYP 3A, and therefore will affect drugs metabolized by this enzyme. Concentrations of intravenously administered single dose midazolam were increased 2.8-fold (AUC_{0-24h}) and concentrations of orally administered midazolam were increased 10-fold when co-administered with APTIVUS/ritonavir at steady state.

* Cisapride, astemizole and terfenadine are no longer marketed in Canada

Established and other potentially significant drug interactions with APTIVUS are included in Table 8. These recommendations are based on either drug interaction studies or predicted interactions.

Table 8: 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 APTIVUS, co-administered with ritonavir or Concomitant Drug	Clinical Comment
	HIV-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 co-administered with ritonavir dosing by at least 2 hours to avoid

Concomitant Drug Class: Drug name	Effect on Concentration of APTIVUS, co-administered with ritonavir or Concomitant Drug	Clinical Comment
		formulation incompatibility.
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.
Lamivudine and stavudine	No significant change in the AUC of lamivudine or stavudine	No dosage adjustment of lamivudine or stavudine is recommended.
Tenofovir	No significant change in the plasma concentrations of tenofovir.	No dosage adjustment of tenofovir is recommended.
Emtricitabine	Emtricitabine (not studied) Tipranavir (not studied)	No dosage adjustment of emtricitabine is recommended.
Non-nucleoside reverse transcriptase inhibitors:		
Efavirenz	No significant impact on the AUC and C_{min} of efavirenz.	Steady-state efavirenz 600 mg qd co-administered with steady-state APTIVUS and ritonavir (500/200 mg bid) had no significant impact on tipranavir AUC and C_{max} (2.9% and 8.3% decreases, respectively) and resulted in a clinically unimportant increase in Cp_{12h} (19.2%). Therefore no dose adjustment is necessary.
Nevirapine	No significant interaction with nevirapine was observed.	Therefore no dose adjustments are necessary.
Rilpivirine		The use of rilpivirine co-administered with APTIVUS/ritonavir has not been studied. Concomitant use of rilpivirine with ritonavir-boosted darunavir or lopinavir has demonstrated an increase in the plasma concentrations of rilpivirine. If APTIVUS/ritonavir is co-administered with rilpivirine, close monitoring and/or dose adjustment of either drug may be required.
Etravirine		APTIVUS/ritonavir caused a 76% decrease of etravirine AUC that could significantly impair the

Concomitant Drug Class: Drug name	Effect on Concentration of APTIVUS, co-administered with ritonavir or Concomitant Drug	Clinical Comment
		virologic response to etravirine. Co-administration of etravirine and APTIVUS/ritonavir is not recommended.
Fusion Inhibitors: Enfurvitide	No formal drug interaction data are currently available on interactions of APTIVUS, co-administered with 200 mg ritonavir, with fusion inhibitors.	The co-administration of enfurvitide with APTIVUS, co-administered with ritonavir, is associated with an increase in steady-state plasma tipranavir trough concentration for the study population by approximately 45%. Similar increases also have been observed for lopinavir (23%) and saquinavir (63%) plasma trough concentrations after combination with enfuvirtide. The mechanism for this interaction is not known. Tipranavir or ritonavir dose adjustment is not recommended.
Integrase strand transfer inhibitor: Raltegravir	Multiple doses of APTIVUS/ ritonavir decreased the raltegravir C_{12}; but AUC_{0-12} and C_{max} were not significantly affected.	Favourable efficacy data collected in phase III studies substantiate that APTIVUS/ritonavir may be co-administered with raltegravir without a dose adjustment.
	Other Agents for Opportunistic Infections	
Antifungals: Fluconazole Itraconazole Ketoconazole Voriconazole	↑ Tipranavir ↔ Fluconazole ↑ Itraconazole (not studied) ↑ Ketoconazole (not studied) ↕ Voriconazole (not studied)	Fluconazole increases TPV concentrations but dose adjustments are not needed. Fluconazole doses > 200 mg/day are not recommended. Based on theoretical considerations itraconazole and ketoconazole should be used with caution. High doses (200 mg/day) are not recommended. Due to multiple CYP isoenzymes systems involved with voriconazole metabolism, it is difficult to predict the interaction with APTIVUS, co-administered with ritonavir.
Antimycobacterials:		
Clarithromycin	↑ Tipranavir, ↑ Clarithromycin, ↓ 14-hydroxy-clarithromycin metabolite	No dose adjustment of APTIVUS or clarithromycin for patients with normal renal function is necessary. For patients with renal impairment the following dosage adjustments should be considered:

Concomitant Drug Class: Drug name	Effect on Concentration of APTIVUS, co-administered with ritonavir or Concomitant Drug	Clinical Comment
		• For patients with CL_{CR} 30 to 60 mL/min the dose of clarithromycin should be reduced by 50%. • For patients with CL_{CR} < 30 mL/min the dose of clarithromycin should be decreased by 75%.
Rifabutin	↔Tipranavir ↑Rifabutin ↑ Desacetyl-rifabutin	Single dose study. Dosage reductions of rifabutin by 75% are recommended (e.g. 150 mg every other day). Increased monitoring for adverse events in patients receiving the combination is warranted. Further dosage reduction may be necessary.
	Other Agents Commonly used	
Antacids	↓ Tipranavir	When APTIVUS/ritonavir, was co-administered with 20 mL of aluminum and magnesium-based antacid, tipranavir AUC_{12h}, C_{max} and C_{12h} were reduced by 27, 25, and 29%, respectively. Consideration should be given to separating APTIVUS/ritonavir dosing from antacid administration to prevent reduced absorption of tipranavir.
Anticonvulsants: Carbamazepine Phenobarbital Phenytoin	↓ Tipranavir ↑ Carbamazepine	Carbamazepine, phenobarbital and phenytoin should be used with caution in combination with APTIVUS/ritonavir. APTIVUS may be less effective due to decreased tipranavir plasma concentration in patients taking these agents concomitantly. Concomitant use of carbamazepine at a dose of 200 mg BID resulted in increased carbamazepine plasma concentrations (by approximately 23 % in geometric mean C_{min} for the total of carbamazepine and carbamazepine-10,11 -epoxide; both are pharmacologically active moieties), and a decrease in tipranavir C_{min} (by approximately 61% compared to historical

Concomitant Drug Class: Drug name	Effect on Concentration of APTIVUS, co-administered with ritonavir or Concomitant Drug	Clinical Comment
		controls), which may result in decreased effectiveness. Higher doses of carbamazepine may result in even larger decreases in tipranavir plasma concentrations.
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	Adverse events of nausea, dizziness, hypotension, and syncope have been observed following co-administration of trazodone and ritonavir. If trazodone is used with APTIVUS/ritonavir, the combination should be used with caution and a lower dose of trazodone should be considered.
Anti-gout: Colchicine	↑ Colchicine	Exposure of colchicine, a CYP34A substrate, may be increased when co-administered with APTIVUS/ ritonavir. In patients with normal renal and hepatic function, adjustment of the colchicine dosing regimen is advised with co-administration. with APTIVUS/ritonavir; <u>Treatment of gout-flares</u> – co-administration of colchicine in patients on APTIVUS/ritonavir: 0.6 mg (1 tablet) x 1 dose, followed by 0.3 mg (half tablet) 1 hour later. Treatment course to be repeated no earlier than 3 days. <u>Prophylaxis of gout-flares</u> – co-administration of colchicine in patients on APTIVUS/ritonavir: If the original regimen was 0.6 mg twice a day, the regimen should be adjusted to 0.3 mg (half tablet) once a day. If the original regimen was 0.6 mg once a day, the regimen should be adjusted to 0.3 mg (half tablet) once

Concomitant Drug Class: Drug name	Effect on Concentration of APTIVUS, co-administered with ritonavir or Concomitant Drug	Clinical Comment
		every other day. <u>Treatment of familial Mediterranean fever (FMF)</u> – co-administration of colchicine in patients on APTIVUS/ritonavir: maximum daily dose of 0.6 mg (may be given as 0.3 mg twice a day).
Anti-HCV: Boceprevir	↓ Boceprevir	The drug-drug interaction of boceprevir with APTIVUS/ritonavir has not been studied. In a pharmacokinetic study of healthy volunteers, boceprevir decreased the exposure of ritonavir, ritonavir-boosted lopinavir, ritonavir-boosted atazanavir and ritonavir-boosted darunavir. Boceprevir exposure was reduced by 45% and 32% when co-administered with ritonavir-boosted lopinavir and ritonavir-boosted darunavir, respectively. These drug-drug interactions may reduce the effectiveness of HIV protease inhibitors and/or boceprevir when co-administered, therefore it is not recommended to co-administer boceprevir with APTIVUS/ritonavir.
Telaprevir	Telaprevir (not studied)	Co-administration of APTIVUS and telaprevir has not been studied. Telaprevir is metabolized in the liver by CYP3A and is a P-glycoprotein (P-gp) substrate, but other enzymes may be involved in the metabolism. When coadministered with telaprevir, there is a heterogeneous effect on both telaprevir and ritonavir-boosted protease inhibitor drug plasma levels, depending on the protease inhibitors. Therefore, it is not recommended to co-administer telaprevir with APTIVUS/ritonavir.
Calcium Channel Blockers: Diltiazem Felodipine	Combination with APTIVUS/ritonavir not studied. Cannot predict effect of APTIVUS/ritonavir on calcium	Caution is warranted and clinical monitoring of patients is recommended.

Concomitant Drug Class: Drug name	Effect on Concentration of APTIVUS, co-administered with ritonavir or Concomitant Drug	Clinical Comment
Nicardipine Nisoldipine Verapamil	channel blockers that are dual substrates of CYP 3A and P-gp due to conflicting effect of APTIVUS/ritonavir on CYP 3A and P-gp. ↕ Diltiazem ↑ Felodipine (CYP 3A substrate but not P-gp substrate) ↕ Nicardipine ↕ Nisoldipine (CYP 3A substrate but not clear whether it is a P-gp substrate) ↕ Verapamil	
Despiramine	Combination with APTIVUS/ritonavir not studied ↑ Despiramine	Dosage reduction and concentration monitoring of despiramine is recommended.
Disulfiram/Metronidazole	Combination with APTIVUS/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).
Endothelin receptor antagonists: Bosentan	↑ Bosentan	Co-administration of bosentan in patients on APTIVUS/ritonavir: In patients who have been receiving APTIVUS/ritonavir for at least 10 days, start bosentan at 62.5 mg once daily or every other day based upon individual tolerability. Co-administration of APTIVUS/ritonavir in patients on bosentan: Discontinue use of bosentan at least 36 hours prior to initiation of APTIVUS/ritonavir. After at least 10 days following the initiation of APTIVUS/ritonavir, resume bosentan at 62.5 mg once daily or every other day based upon individual tolerability.
HMG-CoA reductase inhibitors:		
Rosuvastatin	↑ Rosuvastatin	Co-administration of APTIVUS/ritonavir and rosuvastatin should be initiated with the lowest

Concomitant Drug Class: Drug name	Effect on Concentration of APTIVUS, co-administered with ritonavir or Concomitant Drug	Clinical Comment
		dose (5mg/day) of rosuvastatin, titrated to treatment response, and accompanied with careful clinical monitoring for rosuvastatin associated symptoms as described in the label of rosuvastatin.
Pravastatin	↑ Pravastatin (not studied)	Based on similarities in the elimination of pravastatin and rosuvastatin it is also recommended to initiate pravastatin on the lowest possible dose (10 gm/day) with careful monitoring for pravastatin associated symptoms as described in the label of pravastatin.
Atorvastatin	↑ Atorvastatin ↓ Hydroxy-atorvastatin metabolites	In cases where co-administration is necessary, do not exceed 10 mg atorvastatin daily.
Fluvastatin	↑ Fluvastatin (not studied)	Ritonavir may theoretically induce CYP 2C9, increasing the metabolism of fluvastatin to inactive metabolites, thus potentially reducing the therapeutic effect of fluvastatin.
Hypoglycemics: Glimepiride Glyburide Pioglitazone Repaglinide Tolbutamide	Combination with APTIVUS/ritonavir not studied. ↔ Glimepiride (CYP 2C9) ↔ Glyburide (CYP 2C9) ↕ Pioglitazone (CYP 2C8 and CYP 3A4) ↕ Repaglinide (CYP 2C8 and CYP 3A4) ↔ Tolbutamide (CYP 2C9) The effect of APTIVUS/ritonavir on CYP 2C8 and CYP 2C9 substrates is not known.	Careful glucose monitoring is warranted.
Immunosuppressants: Cyclosporine	Combination with APTIVUS/ritonavir not studied. Cannot predict effect of	More frequent concentration monitoring of these medicinal products is recommended until

Concomitant Drug Class: Drug name	Effect on Concentration of APTIVUS, co-administered with ritonavir or Concomitant Drug	Clinical Comment
Sirolimus Tacrolimus	TPV/ritonavir on immunosuppressants due to conflicting effect of TPV/ritonavir on CYP 3A and P-gp. ↕ Cyclosporine ↕ Sirolimus ↕ Tacrolimus The effect of co-administration of APTIVUS with ritonavir on a substrate for CYP3A4/5 showed potent inhibition at both first-dose and steady-state APTIVUS/ritonavir. When APTIVUS with ritonavir was co-administered with a substrate for P-gp moderate inhibition of P-gp occurred with first-dose APTIVUS/ritonavir, however no effect on P-gp occurred with steady-state APTIVUS/ritonavir. It is anticipated that similar effects will be seen with these immunosuppressants.	blood levels have been stabilized.
Loperamide	A pharmacodynamic interaction study in healthy volunteers demonstrated that administration of loperamide and APTIVUS, co-administered with low-dose ritonavir, does not cause any clinically relevant change in the respiratory response to carbon dioxide. The pharmacokinetic analysis showed that the AUC and C_{max} of loperamide are reduced by 51% and 61%, respectively, and the C_{min} of tipranavir by 26%.	The clinical relevance of these changes is unknown.
Long-acting beta2-adrenergic receptor agonist: Salmeterol		The concomitant use of salmeterol and APTIVUS, co-administered with low-dose ritonavir is not recommended. The combination may result in increased risk of cardiovascular adverse events associated with salmeterol, including QT prolongation, palpitations and sinus tachycardia.
Narcotic analgesics:		

Concomitant Drug Class: Drug name	Effect on Concentration of APTIVUS, co-administered with ritonavir or Concomitant Drug	Clinical Comment
Meperidine	Combinations with APTIVUS/ritonavir not studied ↓ Meperidine, ↑ Normeperidine	Dosage increase and long-term use of meperidine are not recommended due to increased concentrations of the metabolite normeperidine which has both analgesic activity and CNS stimulant activity (e.g. seizures).
Methadone	↓ Methadone AUC and C_{max} by 50%	Because APTIVUS/ritonavir decreases methadone AUC and C_{max} patients should be monitored for opiate withdrawal syndrome. Dosage of methadone may need to be increased when co-administered with tipranavir and 200 mg of ritonavir.
Nucleoside analogue DNA polymerase inhibitor: Valaciclovir	Co-administration of valaciclovir, APTIVUS® and ritonavir was not associated with clinically relevant pharmacokinetic effects.	Therefore, these agents can be co-administered without dose adjustment.
Oral contraceptives/Estrogens:		
Ethinyl estradiol	↓ Ethinyl estradiol concentrations by 50%	Alternative methods of non-hormonal contraception should be used when estrogen based oral contraceptives are co-administered with APTIVUS and 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 rash.
PDE5 inhibitors: Sildenafil Tadalafil Vardenafil	↑ PDE-5 Inhibitors ↑ Sildenafil (not studied) ↑ Tadalafil ↑ Vardenafil (not studied)	Co-administration with APTIVUS/rtv may result in an increase in PDE-5 Inhibitor adverse events, including hypotension, syncope, visual disturbances and priaprism. <u>For treatment of erectile dysfunction</u> Concomitant use of PDE-5 Inhibitors with APTIVUS/ritonavir should be used with caution and in no case should the starting of: • sildenafil exceed 25 mg within 48 hours, • tadalafil exceed 10 mg every 72 hours, or • vardenafil exceed 2.5 mg every 72

Concomitant Drug Class: Drug name	Effect on Concentration of APTIVUS, co-administered with ritonavir or Concomitant Drug	Clinical Comment
		hours* * the dosage of 2.5 mg of vardenafil is not approved in Canada
	↑ Sildenafil (not studied)	<u>For treatment of pulmonary arterial hypertension (PAH)</u> • Use of sildenafil is contraindicated with APTIVUS/ritonavir when used for treatment of pulmonary arterial hypertension (Table 7).
	↑ Tadalafil ↑ Vardenafil (not studied)	• Co-administration of APTIVUS/ritonavir and tadalafil or vadenafil for the treatment of pulmonary arterial hypertension (PAH) is not recommended.
Selective Serotonin-Reuptake Inhibitors: Fluoxetine Paroxetine Sertraline	Combination with APTIVUS/ritonavir not studied ↑ Fluoxetine ↑ Paroxetine ↑ Sertraline	Antidepressants have a wide therapeutic index, but doses may need to be adjusted upon initiation of APTIVUS/ritonavir therapy.
Theophylline	APTIVUS, co-administered with low-dose ritonavir, is expected to decrease theophylline concentrations.	Increased dosage of theophylline may be required and therapeutic monitoring should be considered.
Warfarin and other oral anticoagulants	↔ S-Warfarin	Clinical and biological (INR measurement) monitoring is recommended when these medicinal products are combined.
Buprenorphine/naloxone	↔ Buprenorphine/naloxone ↓ Tipranavir	A pharmacokinetic study (n=10) indicated that buprenorphine AUC and Cp24h were not significantly affected by co-administered TPV/rtv. Compared to historical controls the Cmin of tipranavir was decreased by 39% with this combination.
Bupropion	↓ Bupropion	APTIVUS, co-administered with ritonavir at steady-state resulted in approximately a 50% decrease in bupropion Cmax and AUC. Careful clinical monitoring should be recommended when combining these three drugs.

Drug-Food Interactions

APTIVUS capsules, administered under high fat meal conditions or with a light snack of toast and skimmed milk, were tested in a multiple dose study. Food enhanced the extent of bioavailability (AUC point estimate 1.31, confidence interval 1.23-1.39), but had minimal effect on peak tipranavir concentrations (C_{max} point estimate 1.16, confidence interval 1.09-1.24).

APTIVUS may be safely taken with standard or high-fat meals. APTIVUS capsules, co-administered with ritonavir, should be taken with food.

Drug-Herb Interactions

Herbal preparations containing St. John's wort should not be combined with APTIVUS, co-administered with low dose ritonavir. Co-administration of protease inhibitors, including APTIVUS, with St. John's wort is expected to substantially decrease protease inhibitor concentrations and may result in sub-optimal levels of tipranavir and lead to loss of virologic response and possible resistance to APTIVUS or to the class of protease inhibitors (See Tables 1 and 7).

Drug-Laboratory Test Interactions

Interactions with laboratory tests have not been established.

Drug-Lifestyle Interactions

Driving and Using Machines: No studies on the effects on the ability to drive and use machines have been performed for APTIVUS/ritonavir. However, dizziness, somnolence, and fatigue have been reported in some patients; therefore, caution should be recommended when driving a car or operating machinery. If patients experience fatigue, dizziness, or somnolence they should avoid potentially hazardous tasks such as driving or operating machinery.

Other Medications

The following medications were discouraged in the pivotal trials: amitriptyline, benazepril, buspirone, carbamazepine, cimetidine, clonazepam, desiryl, encainide erythromycin, fentanyl, loratadine, milk thistle (Silybum marianum), mirtazapine, nortriptyline, phenobarbital, phenytoin, quetiapine fumarate, risperidone, sublimaze, sulfinpyrazone, systemic cytotoxic chemotherapy, temazepam, troleandomycin, venlafaxine, verapamil, zaleplon, and zolpidem tartrate. Clinicians should monitor patients taking any of these medications concomitantly with APTIVUS/r.

Table 9: Drug Interactions: Pharmacokinetic Parameters for Tipranavir in the Presence of Co-administered Drugs

Coadministered Drug	Co-administered Drug Dose (Schedule)	APTIVUS/ritonavir Drug Dose (Schedule)	n	PK	Ratio (90% Confidence Interval) of Tipranavir Pharmacokinetic Parameters with/without Co-administered Drug;		
					C_{max}	AUC	C_{min}
Atazanavir	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)
Rosuvastatin	10 mg (1 dose)	500/200 mg BID (24 doses)	16	↔	1.08 (1.00, 1.17)	1.06 (0.97, 1.15)	0.99 (0.88, 1.11)
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)

Table 10: Drug Interactions: Pharmacokinetic Parameters for Co-administered Drug in the Presence of APTIVUS/ritonavir

Co-administered Drug	Co-administered Drug Dose (Schedule)	APTIVUS/ritonavir Drug Dose (Schedule)	n	PK	Ratio (90% Confidence Interval) of Co-administered Drug Pharmacokinetic Parameters with/without APTIVUS/ritonavir; No Effect = 1.00		
					C_{max}	AUC	C_{min}
Amprenavir/RTV [a]	600/100 mg BID (27 doses)	500/200 mg BID (28 doses)	16 74	↓ ↓	0.61 (0.51, 0.73)[d] -	0.56 (0.49, 0.64)[d] -	0.45 (0.38, 0.53)[d] 0.44 (0.39, 0.49)[e]
Abacavir [a]	300 mg BID (43 doses)	250/200 mg BID 750/100 mg BID 1250/100 mg BID (42 doses)	28 14 11	↓ ↓ ↓	0.56 (0.48, 0.66) 0.54 (0.47, 0.63) 0.48 (0.42, 0.53)	0.56 (0.49, 0.63) 0.64 (0.55, 0.74) 0.65 (0.55, 0.76)	- - -
Atazanavir	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)
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 750/100 mg BID 1250/100 mg BID (42 doses)	10 8 9	↓ ↔ ↔	0.57 (0.42, 0.79) 0.76 (0.49, 1.17) 0.77 (0.47, 1.26)	0.67 (0.51, 0.88) 0.97 (0.64, 1.47) 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 750/200 mg BID (15 doses)	24 22	↔ ↔	1.09 (0.99, 1.19) 1.12 (0.98, 1.28)	1.04 (0.97, 1.12) 1.00 (0.93, 1.09)	1.02 (0.92, 1.12) 0.94 (0.84, 1.04)
Ethinyl estradiol	0.035 mg (1 dose)	500/100 mg BID 750/200 mg BID (21 doses)	21 13	↓ ↓	0.52 (0.47, 0.57) 0.48 (0.42, 0.57)	0.52 (0.48, 0.56) 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 19	↔ ↔	0.97 (0.94, 1.01) 0.94 (0.91, 0.98)	0.99 (0.97, 1.02) 0.92 (0.88, 0.95)	0.98 (0.94, 1.02) 0.89 (0.85, 0.92)
Lopinavir/RTV[a]	400/100 mg BID (27 doses)	500/200 mg BID (28 doses)	21 69	↓ ↓	0.53 (0.40, 0.69)[d] -	0.45 (0.32, 0.63)[d] -	0.30 (0.17, 0.51)[d] 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)	
Lamivudine[a]	150 mg BID (43 doses)	250/200 mg BID 750/100 mg BID 1250/100 mg BID (42 doses)	64 46 35	↔ ↔ ↔	0.96 (0.89, 1.03) 0.86 (0.78, 0.94) 0.71 (0.62, 0.81)	0.95 (0.89, 1.02) 0.96 (0.90, 1.03) 0.82 (0.66, 1.00)	- - -
Nevirapine[a]	200 mg BID (43 doses)	250/200 mg BID 750/100 mg BID 1250/100 mg BID (42 doses)	26 22 17	↔ ↔ ↔	0.97 (0.90, 1.04) 0.86 (0.76, 0.97) 0.71 (0.62, 0.82)	0.97 (0.91, 1.04) 0.89 (0.78, 1.01)	0.96 (0.87, 1.05) 0.93 (0.80, 1.08) 0.77 (0.64, 0.92)

Co-administered Drug	Co-administered Drug Dose (Schedule)	APTIVUS/ritonavir Drug Dose (Schedule)	n	PK	Ratio (90% Confidence Interval) of Co-administered Drug Pharmacokinetic Parameters with/without APTIVUS/ritonavir; No Effect = 1.00		
					C_{max}	AUC	C_{min}
						0.76 (0.63, 0.91)	
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)
Rosuvastatin	10 mg (1 dose)	500/200 mg BID (24 doses)	16	↑	2.23 (1.83, 2.72)	1.26 (1.08, 1.46)	1.06 (0.93, 1.20)
Saquinavir/RTV[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	250/200 mg BID	26	↔	0.90 (0.81, 1.02)	1.00 (0.91, 1.11)	-
	30 mg BID, < 60 kg (43 doses)	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	↑	-	2.33 (2.02, 2.69)	0.78 (0.72, 0.84)
	10 mg (1 dose)	500/200 mg BID (17 doses)	17	↔	-	1.01 (0.83, 1.21)	0.70 (0.63, 0.78)
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+ patients
[b]HIV+ patients (APTIVUS/ritonavir 250 mg/200 mg, 750 mg/200 mg and 1250 mg/100 mg) and healthy volunteers (APTIVUS/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

DOSAGE AND ADMINISTRATION

Dosing Considerations

APTIVUS must be administered with 200 mg ritonavir to ensure its therapeutic effect. Patients should be instructed accordingly.

Please also refer to the ritonavir product monograph for contraindications, warnings, precautions, side effects and potential drug interactions.

Triglyceride and cholesterol testing should be performed prior to initiating tipranavir therapy and during therapy.

Dosage for Elderly Patients

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. See ACTION AND CLINICAL PHARMACOLOGY, WARNINGS AND PRECAUTIONS, ADVERSE REACTIONS sections.

Dosage for Pediatric Patients

The safety and efficacy of APTIVUS in this population has not been established. Treatment of children with APTIVUS is therefore not recommended. See ACTION AND CLINICAL PHARMACOLOGY, WARNINGS AND PRECAUTIONS, Special Populations, ADVERSE REACTIONS sections.

Dosage for Hepatically Impaired Patients

APTIVUS is contraindicated in patients with moderate or severe hepatic insufficiency (Child-Pugh Class B or C, respectively) (See CONTRAINDICATIONS). APTIVUS co-administered with 200-mg ritonavir should be used with caution in patients with mild hepatic insufficiency (Child-Pugh Class A); these patients should be monitored closely.

Recommended Dose and Dosage Adjustment

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

APTIVUS, co-administered with 200 mg ritonavir, should be administered with food.

APTIVUS, co-administered with 200 mg ritonavir, should be taken with at least two additional antiretroviral agents. The manufacturers' product monograph of the antiretroviral agents should be followed.

APTIVUS, co-administered with 200 mg ritonavir, causes a reduction in the AUC of didanosine. Dosing of enteric-coated didanosine and tipranavir, co-administered with 200 mg ritonavir, should be separated by at least 2 hours to avoid formulation incompatibility.

Missed Dose:
Patients should be advised of the need to take APTIVUS every day as prescribed. If a dose is missed the patient should not double the next dose but should take the next dose as soon as possible.

OVERDOSAGE

For management of a suspected drug overdose, please contact your regional Poison Control Centre.

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. Administration of activated charcoal may also be used to aid in removal of unabsorbed drug. Since tipranavir is highly protein bound, dialysis is unlikely to be beneficial in significant removal of this medicine.

ACTION AND CLINICAL PHARMACOLOGY

Microbiology
Mechanism of action: The human immunodeficiency virus (HIV-1) encodes an aspartyl protease that is essential for the cleavage and maturation of viral protein precursors. Tipranavir is a non-peptidic inhibitor of the HIV-1 protease that inhibits viral replication by preventing the maturation of viral particles.

Pharmacokinetics:
In order to achieve effective tipranavir plasma concentrations and a bid dosing regimen, co-administration of APTIVUS with 200 mg ritonavir twice daily is essential (see DOSAGE AND ADMINISTRATION). Ritonavir acts by inhibiting hepatic cytochrome P450 CYP3A, the intestinal P-glycoprotein (Pgp) efflux pump and possibly intestinal cytochrome P450 CYP3A as well. As demonstrated in a dose-ranging evaluation in 113 HIV-negative healthy male and female volunteers, ritonavir increases $AUC_{0\text{-}12h}$, C_{max} and C_{min} and decreases the clearance of tipranavir. APTIVUS co-administered with ritonavir (500 mg/200 mg twice daily) was associated with a 29-fold increase in the geometric mean morning steady-state trough plasma concentrations compared to APTIVUS 500 mg twice daily without ritonavir.

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-positive patients presented in Table 11.

Table 11: Pharmacokinetic Parameters[a] of tipranavir/ritonavir 500/200 mg for HIV+ 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
$AUC_{0\text{-}12h}$(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

A trial of HIV infected patients assessed the pharmacokinetics and safety of APTIVUS/ritonavir 500/200 mg administered with and without lopinavir, amprenavir, or saquinavir compared to ritonavir 100 mg administered with lopinavir, amprenavir, or saquinavir. The mean systemic ritonavir concentration when 200 mg of ritonavir was given with APTIVUS was similar to the concentrations observed when 100 mg was given with the other protease inhibitors.

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.

Peak plasma concentrations are reached within 1 to 5 hours after dose administration depending upon the dosage used. With repeated dosing, tipranavir plasma concentrations are lower than predicted from single dose data, presumably due to hepatic and transporter enzyme induction. Steady state is attained in most subjects after 7 days of dosing. APTIVUS, co-administered with 200 mg ritonavir, exhibits linear pharmacokinetics at steady-state.

Dosing with APTIVUS 500 mg concomitant with 200 mg ritonavir twice daily for 2 to 4 weeks and without meal restriction produced a mean tipranavir peak plasma concentration (C_{max}) of 94.8 ± 22.8 μM for female patients (n=14) and 77.6 ± 16.6 μM for male patients (n=106), occurring approximately 3 hours after administration.

The mean steady-state trough concentration prior to the morning dose was 41.6 ± 24.3 μM for female patients and 35.6 ± 16.7 μM for male patients. Tipranavir AUC over a 12 hour dosing interval averaged 851 ± 309 μM•h (CL=1.15 l/h) for female patients and 710 ± 207 μM•h (CL=1.27 l/h) for male patients. The mean half-life was 5.5 (females) or 6.0 hours (males).

Effects of food on oral absorption: For APTIVUS capsules co-administered with ritonavir at steady-state, no clinically significant changes in C_{max}, Cp_{12h}, and AUC were observed under fed conditions (500-682 Kcal, 23-25% calories from fat) compared to fasted conditions. In view of the better tolerability of ritonavir when taken with food and the importance of taking APTIVUS

and ritonavir together, APTIVUS/ritonavir should be taken with food (see DOSAGE AND ADMINISTRATION).

When APTIVUS, co-administered with 200 mg ritonavir, was co-administered with 20 ml of aluminium and magnesium-based antacid, tipranavir AUC_{12h}, C_{max} and C_{12h} were reduced by 25-29 %. Consideration should be given to separating APTIVUS/ritonavir dosing from anatacid administration to prevent reduced absorption of tipranavir.

Distribution: Tipranavir is extensively bound to plasma proteins (>99.9%). From clinical samples of healthy volunteers and HIV-positive subjects who received APTIVUS without ritonavir the mean fraction of tipranavir unbound in plasma was similar in both populations (healthy volunteers 0.015% ± 0.006%; HIV positive subjects 0.019% ± 0.076%). 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 CYP3A4 is the predominant CYP isoform 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 low-dose ritonavir is minimal. In a ^{14}C-tipranavir human study (^{14}C-tipranavir/ritonavir, 500 mg/200 mg bid), unchanged tipranavir was predominant and 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.

Excretion: Administration of ^{14}C-tipranavir to subjects (n = 8) that received APTIVUS/ritonavir 500 mg/200 mg bid dosed to steady-state demonstrated that most radioactivity (median 82.3%) was excreted in faeces, while only a median of 4.4% of the radioactive dose administered was recovered in urine. In addition, most radioactivity (56.3 %) 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-infected adult patients (n = 120) was 4.8 and 6.0 hours, respectively, at steady state following a dose of 500/200 mg bid daily with a light meal.

Special Populations and Conditions

Geriatric Patients: Evaluation of steady-state plasma tipranavir trough concentrations at 10-14 h after dosing from the RESIST-1 and RESIST-2 studies 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, but the trend of consistent trough tipranavir concentrations with increasing age through 80 years for men was supported.

Gender: Evaluation of steady-state plasma tipranavir trough concentrations at 10-14 h after dosing from the RESIST-1 and RESIST-2 studies demonstrated that females generally had higher tipranavir concentrations than males. After 4 weeks of APTIVUS /ritonavir 500 mg/200 mg bid, the median plasma trough concentration of tipranavir was 43.9 μM for females and 31.1 μM for males. This 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 RESIST-1 and RESIST-2 studies 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. Females of either race generally had higher trough tipranavir concentrations than males.

Renal Insufficiency: Tipranavir 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 Insufficiency: In a study comparing 9 patients with mild (Child-Pugh A) hepatic impairment to 9 controls, the single and multiple dose pharmacokinetic profiles of tipranavir and ritonavir were increased in patients with hepatic impairment but still within the range observed in the clinical studies. No dosing adjustment is required in patients with mild hepatic impairment; however, patients should be closely monitored.

The influence of moderate hepatic impairment (Child Pugh B) on the multiple-dose pharmacokinetics of either tipranavir or ritonavir has not been evaluated. APTIVUS is contraindicated in patients with moderate or severe hepatic impairment.

STORAGE AND STABILITY

APTIVUS capsules should be stored under refrigeration (2°C to 8°C). Once opened, the bottle can be stored at 25ºC, excursions permitted to 15 to 30°C for up to 60 days.

DOSAGE FORMS, COMPOSITION AND PACKAGING

Availability of Dosage Forms

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

Composition:
Each APTIVUS (tipranavir) capsule contains 250 mg of tipranavir. Inactive ingredients include Cremophor® EL, ethanol, mono/diglycerides of caprylic/capric acid, propyl gallate, propylene glycol, purified water, and trometamol.

Capsule shell: gelatin, iron oxide red, propylene glycol, purified water, 'sorbitol special glycerin blend' (d-sorbitol, 1,4-sorbitan, mannitol and glycerin) and titanium dioxide.

Black printing ink: ammonium hydroxide, ethylacetate, iron oxide black, isopropyl alcohol, Macrogol, polyvinyl acetate phthalate, propylene glycol, purified water and SDA 35 alcohol.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

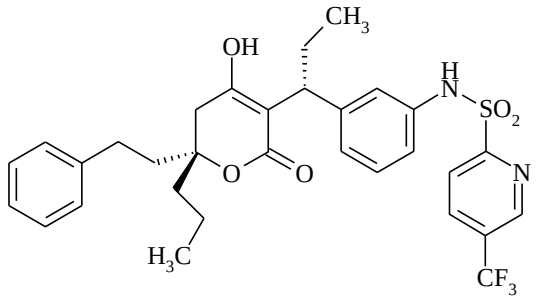
Drug Substance

Proper name: Tipranavir

Chemical name: 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)

Molecular formula and molecular mass: $C_{31}H_{33}F_3N_2O_5S$; 602.7

Structural formula:



Single Stereoisomer 1R, 6R
Tipranavir (free acid form)

Physicochemical properties:

Description: Tipranavir is a white to off-white to slightly yellow solid.

Melting point: Tipranavir melts at approximately 90ºC. The DSC data show an onset of melt at 88ºC and a peak temperature of 97ºC when heated at 10ºC per minute.

Crystallinity/Polymorphism: Tipranavir is partially crystalline substance. No polymorphs have been observed in the drug substance manufactured by the A1, B, B1, and B2 synthesis routes.

Solubility: 0.11 μg/mL at pH 2 aqueous buffer, 13 μg/mL at pH 7.4 aqueous buffer, and 385 μg/mL at pH 8.6 aqueous buffer. Soluble in organic solvents such as ethanol (>1 g/mL), propylene glycol (>500 mg/mL), and PEG 400 (>600 mg/mL).

CLINICAL TRIALS
Description of clinical studies:

Treatment Experienced Patients

Studies RESIST-1 and RESIST-2: APTIVUS/Ritonavir 500/200 mg bid + optimized background regimen (OBR) vs. Comparator PI/Ritonavir bid + OBR

The following clinical data is derived from analyses of 48-week data from ongoing studies (RESIST-1 and RESIST-2) measuring effects on plasma HIV-1 RNA levels and CD4 cell counts. At present there are no results from controlled trials evaluating the effect of APTIVUS on clinical progression of HIV.

Table 12: Study Demographic and Trial Design

Study #	Trial Design	Dosage, route of administration and planned duration	Study subjects (N=number)	Mean age (Range)	Gender
1182.12 RESIST 1	Randomised, open-label	APTIVUS/r 500mg/200mg Oral, 240 weeks Comparator PIs (CPI/r):LPV, indinavir (IDV), SQV, and APV	620	44 (24-80)	91.1% Male 8.9% Female
1182.48 RESIST2	Randomised, open-label	APTIVUS/r 500mg/200mg Oral, 240 weeks Comparator PIs (CPI/r):LPV, indinavir (IDV), SQV, and APV	863	42 (17-76)	82.9% Male 17.1% Female

RESIST-1 and RESIST-2 are ongoing, randomized, open-label, multicenter studies in HIV-positive, triple-class experienced patients, evaluating treatment with APTIVUS, co-administered with 200 mg ritonavir (APTIVUS/ritonavir), plus an OBR individually defined for each patient based on genotypic resistance testing and patient history. The comparator regimen included a ritonavir-boosted PI (CPI/r; also individually defined) plus an OBR. The ritonavir-boosted PI was chosen from among saquinavir, amprenavir, indinavir or lopinavir/ritonavir. All patients had received at least two PI-based antiretroviral regimens and were failing a PI-based regimen at the time of study entry. 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 on codons 33, 82, 84 or 90. After week 8, patients in the comparator arm who met the protocol defined criteria of initial lack of virologic response had the option of discontinuing treatment and switching over to APTIVUS/ritonavir in a separate roll-over study.

There were 1483 patients (APTIVUS/ritonavir: n=746, CPI/ritonavir: n=737) included in the primary analysis of the combined RESIST trials. The patient groups had median ages of 43 years (range 17-80 years) and 42 years (range 21-72) for APTIVUS/ritonavir and CPI/ritonavir, respectively. Patients were 84% and 88 % male, 77% and 74 % white, 12.6% and 13.3 % black and 0.7% and 1.2 % Asian for the APTIVUS/ritonavir and CPI/ritonavir groups, respectively. In the APTIVUS/ritonavir and CPI/ritonavir groups median baseline CD4 cell counts were 158 and 166 cells/mm^3, respectively, (interquartile ranges (IQRs) 66-285 and 53-280 cells/mm^3); median baseline plasma HIV-1 RNA was 4.79 and 4.80 log_{10} copies/ml, respectively (IQRs: 4.32-5.24 and 4.25-5.27 log_{10} copies/ml).

Study Results

Treatment response and outcomes of randomised treatment at week 48 and 96 are presented for the two RESIST studies as well as combined studies as shown in the table 13 below.

Table 13: Outcomes of Randomised Treatment at Week 48 and 96 (Pooled Studies RESIST-1 and RESIST-2 in Treatment Experienced Patients)

	APTIVUS/RTV (500/200 mg bid) + OBR *N=746*		**Comparator PI/RTV*** + OBR** *N=737*		**p value**
	48 weeks	96 weeks	48 weeks	96 weeks	
Treatment Response*	34.2 %	26.4%	15.5 %	10.7%	p<0.0001
with new enfuvirtide	60.5 % (N=75/124)	45.2% (N=56/124)	22.7 % (N=22/97)	16.5% (N=16/97)	p<0.0001
without enfuvirtide	29.5 % (N=170/576)	23.1% (N=133/576)	14.3 % (N=86/602)	9.5% (N=57/602)	p<0.0001
Median HIV VL log change from baseline (log_{10} copies/ml)	-0.64	-0.58	-0.22	-0.22	--
HIV VL <400 copies/ml	30.3 %	26.9 %	13.6 %	10. 9 %	--
HIV VL <50 copies/ml	22.7 %	20.4 %	10.2 %	9.1 %	--
Median increase in CD4+ cell count (cells/mm^3)	23	19	4	3	--
Treatment Failure	65.8 %	73.6%	84.5 %	89.3%	--
Reasons for treatment failure					
Death	1.6 %	2.4 %	0.7 %	0.9 %	--
Discontinued study drug or OBR change due to lack of efficacy	12.5 %	19.2 %	45.9 %	49.5 %	--
Virologic rebound	23.1 %	26.7 %	18.3 %	20.6 %	--
No confirmed virologic response	49.5 %	51.6 %	69.9 %	72.0 %	--
Discontinued due to any adverse event	8.7 %	10.2%	4.7 %	5.2%	--
Discontinued due to other reasons**	6.0 %	9.4%	9.2 %	11.1%	--

* Composite endpoint defined as patients with a confirmed 1 log RNA drop from baseline and without evidence of treatment failure

** Lost to follow-up, nonadherence to protocol, consent withdrawn, or other reasons

*** Comparator PI/RTV: LPV/r 400/100 mg bid, IDV/r 800/100 mg bid, SQV/r 1000/100 mg bid or 800/200 mg bid, APV/r 600/100 mg bid (n=149)

RESIST data also demonstrate that APTIVUS co-administered with low dose ritonavir exhibited a better treatment response at 48 weeks when the OBR contained genotypically available antiretroviral agents (eg enfuvirtide).

Through 96 weeks of treatment, the median time to treatment failure was 115 days among APTIVUS/ritonavir treated patients and 0 days among CPI/ritonavir treated patients. In patients who received new enfuvirtide (defined as initiation of enfuvirtide for the first time), the median time to treatment failure was 587 days among APTIVUS/ritonavir treated patients and 60 days among CPI/ritonavir treated patients.

Analyses of tipranavir resistance in treatment experienced patients
APTIVUS/ritonavir response rates were assessed by baseline tipranavir genotype and phenotype. Relationships between baseline phenotypic susceptibility to tipranavir, tipranavir resistance-associated mutations and response to APTIVUS/ritonavir therapy have been assessed.

Tipranavir resistance-associated mutations:
Virological and treatment response to APTIVUS/ritonavir therapy has been evaluated using a tipranavir-associated mutation score based on baseline genotype in RESIST-1 and RESIST-2 patients. This score (counting the 16 amino acids that have been associated with reduced tipranavir susceptibility and/or reduced viral load response: 10V, 13V, 20M/R/V, 33F, 35G, 36I, 43T, 46L, 47V, 54A/M/V, 58E, 69K, 74P, 82L/T, 83D and 84V) was applied to baseline viral protease sequences. A correlation between the tipranavir mutation score and response to APTIVUS/ritonavir therapy at weeks 2 and 48 has been established.

At week 48, a higher proportion of patients receiving APTIVUS, co-administered with low-dose ritonavir, achieved a treatment response in comparison to the comparator protease inhibitor/ritonavir for nearly all of the possible combinations of genotypic resistance mutations (see Table 14).

Table 14: Proportion of patients achieving treatment response at Week 48 (confirmed ≥ 1 log_{10} copies/mL decrease in viral load compared to baseline), according to tipranavir baseline mutation score and ENF use in RESIST patients.

	New ENF		No New ENF[1]	
Number of Tipranavir Score Mutations	TPV/r	CPI/r	TPV/r	CPI/r
0,1	73%	21%	53%	25%
2	61%	43%	33%	17%
3	75%	23%	27%	14%
4	59%	19%	23%	8%
≥ 5	47%	15%	13%	13%
All patients	61%	23%	29%	14%

[1] Includes patients who did not receive ENF and those who were previously treated with and continued ENF

Sustained HIV-1 RNA decreases through Week 48 (Table 15) were mainly observed in patients who received APTIVUS/ritonavir and new ENF. If patients did not receive APTIVUS/r with new ENF, diminished treatment responses at week 48 were observed, relative to new ENF use.

Table 15: Mean decrease in viral load from baseline to Week 48, according to tipranavir baseline mutation score and ENF use in RESIST patients.

	New ENF		No New ENF[1]	
Number of Tipranavir Score Mutations	TPV/r	CPI/r	TPV/r	CPI/r
0, 1	-2.3	-1.5	-1.6	-0.6
2	-2.1	-1.4	-1.1	-0.6
3	-2.4	-1.0	-0.9	-0.5
4	-1.7	-0.7	-0.8	-0.3
≥ 5	-1.9	-0.6	-0.6	-0.4
All patients	-2.0	-1.0	-1.0	-0.5

[1] Includes patients who did not receive ENF and those who were previously treated with and continued ENF

Protease mutations at positions 33, 82, 84 and 90*:* Mutations at two, three or more of these positions resulted in reduced susceptibility to APTIVUS/ritonavir and four mutations resulted in resistance.

Tipranavir phenotypic resistance:
Increasing baseline phenotypic fold change to tipranavir in isolates is correlated to decreasing virologic response. Isolates with baseline fold change of 0 to 3 are considered susceptible; isolates with >3 to 10 fold changes have decreased susceptibility; isolates with >10 fold changes are resistant.

Conclusions regarding the relevance of particular mutations or mutational patterns are subject to change with additional data, and it is recommended to always consult current interpretation systems for analysing resistance test results

Table 16: Outcomes of Randomised Treatment at Week 48 (Individual Studies RESIST-1 and RESIST-2 in Treatment Experienced Patients)

RESIST Efficacy Data				
48-week Data	**RESIST 1**		**RESIST 2**	
	tipranavir + ritonavir	**chosen PI + ritonavir**	**tipranavir + ritonavir**	**chosen PI + ritonavir**
N	311	309	435	428
% 1 log drop, FAS NCF	36.7	16.2	36.8	16.8
Treatment Failure*				
% DC due to virologic failure[a]	10.6	45.3	13.8	46.3
% DC due to AE	9.6	4.5	8.0	4.9
Median viral load change (log copies/mL)	-0.61	-0.24	-0.65	-0.21
% BLQ 400	30.9	13.9	30.1	13.8
% BLQ 50	22.5	9.7	23.0	10.5
CD4 count change (cells/mm^3)	+19	+6	+26	+1

FAS = full analysis set; NCF = non completers considered failures; PPS = per protocol set; DC = discontinuation; AE = adverse event; BLQ = below the level of quantification

* Statistical testing not performed due to the relatively small number of patients involved

[a] Includes premature discontinuation of the study PI due to virologic failure and the addition of a drug to the background regimen, if not introduced to replace a background drug discontinued due to AEs attributable to the discontinued background drug.

Data from the RESIST trials were combined to analyze treatment response within each pre-selected PI stratum (Table 17). The APTIVUS/r group had significantly higher treatment responses than LPV/r, SQV/r, or APV/r groups. The IDV stratum had too few patients to make definitive statements. After adjustment for PI and ENF stratum, being randomized to the APTIVUS group increased the odds of a treatment response at Week 24 by nearly three fold ($p<0.0001$).

Table 17: Sensitivity analyses of response at Week 24, 48 and 96 by PI strata - RESIST trials (FAS)

Treatment Group									Treatment Difference [a]			
PI Strata	Analysis	Week	TPV/r			CPI/r			Weighted Diff. %	95% CI		p-value
			n	%	N	n	%	N		LL %	UL %	
LPV	FAS (NCF)	24	116	39.6	293	62	21.4	290	17.7	10.5	25.0	--
		48	122	33.5	364	60	16.8	358	16.4	10.2	22.6	<0.0001
		96	94	25.8	364	40	11.2	358	14.4	8.9	20.0	<0.0001
SQV	FAS (NCF)	24	51	43.6	117	18	15.3	118	27.4	16.5	38.3	--
		48	57	35.4	161	20	12.3	162	22.3	13.5	31.1	<0.0001
		96	43	26.7	161	12	7.4	162	18.7	10.9	26.4	<0.0001
APV	FAS (NCF)	24	63	41.7	151	28	18.8	149	22.0	12.1	31.9	--
		48	68	34.3	198	33	17.0	194	16.7	8.4	25.0	<0.0001
		96	53	26.8	198	26	13.4	194	12.8	5.1	20.6	<0.0001

n = Number of responders; N = Number of evaluable patients

[a] Treatment difference and confidence interval weighted for the size of ENF strata and PI strata.

Genotypic analyses of tipranavir resistance in treatment-experienced patients

The virologic response to APTIVUS co-administered with low-dose ritonavir has been evaluated with respect to baseline viral genotype in treatment-experienced patients participating in studies RESIST-1 and RESIST-2. In these studies, the patients had baseline HIV-1 isolates with an average of 16 HIV-1 protease gene mutations, including a median of 3 primary protease gene mutations D30N, L33F/I, V46I/L, G48V, I50V, V82A/F/T/L, I84V, and L90M. In addition the majority of participants evaluated had mutations associated with both NRTI and NNRTI resistance.

The use of genotypic resistance testing and the clinical interpretation of genotypic mutations is a complex and evolving field. Conclusions regarding the relevance of particular mutations or mutational patterns are subject to change pending additional data.

Several analyses were conducted to evaluate the impact of specific mutations and mutational patterns on virology outcome. The HIV-1 RNA response at Week 48 in studies RESIST-1 and RESIST-2 by number of protease gene mutations is shown in Table 18 below.

Table 18: Change in Viral load at Week 48 by baseline IAS protease gene mutations – RESIST trials integrated (FAS-LOCF)

	Change in viral load from baseline at 48 weeks (APTIVUS/ritonavir)*	Change in viral load from baseline at 48 weeks (Comparator PI/r)*
PI resistance related mutations, IAS 2005[ab]	**Median (N)**	**Median (N)**
≤ 7	-1.61 (114)	-0.35 (105)
8 - 9	-1.00 (156)	-0.40 (167)
10 - 11	-0.53 (239)	-0.16 (244)
≥ 12	-0.37 (236)	-0.11 (221)

a Individual codons counted, mixture of wild type and mutant counted as mutant.

b Number of protease mutations out of (10FIRV, 13V, 16E, 20IMR, 24I, 30N, 32I, 33FIV, 35G, 36ILV, 43T, 46IL, 47AV, 48V, 50LV, 53L, 54ALMSTV, 58E, 60E, 62V, 63P, 69K, 71ILTV, 73ACST, 74P, 77I, 82AFLST, 83D, 84V, 85V, 88DS,90M, 93L)

Virologic response to APTIVUS/ritonavir therapy has been evaluated with respect to baseline genotype and phenotype in treatment experienced patients participating in four studies (RESIST-1, RESIST-2, 1182.52, 1182.51), which provided the greatest spectrum of patients with highly mutated virus. A correlation between key protease mutations (at amino acids 33, 82, 84 and 90), baseline phenotypic susceptibility to tipranavir and response to APTIVUS/ritonavir therapy at weeks 2 and 24 has been established and is summarized in Table 19. Data on comparator protease inhibitor/ritonavir arm is not shown in Table 19 because the 1182.51 and 1182.52 trials did not include a comparator arm.

Table 19: HIV RNA Response at Weeks 2 and 24 by Baseline Key Mutations and Tipranavir Phenotypic Susceptibility in RESIST-1 and RESIST-2 and Studies 1182.52 and 1182.51*

No. of key mutations at amino acids 33, 82, 84, 90	Baseline Fold Change in Tipranavir Phenotypic Susceptibility**	Change in viral load at 2 weeks	Change in viral load at 24 weeks
≤ 1	1.0	-1.35	-1.27
2	1.7	-1.39	-0.78
3	3.4	-1.25	-0.24
4	12.0	-1.08	-0.33

* All trials tipranavir/ritonavir 500 mg/200 mg bid dose; Trials 1182.52 and 1182.51 had patient population infected with highly mutated virus. All patients included from 1182.51 received APTIVUS/ritonavir 500 mg/200 mg bid, without additional PI therapy

** Fold change in susceptibility from wild-type determined by recombinant phenotypic Antivirogram™ assay.

Phenotypic analyses of tipranavir resistance in treatment-experienced patients

Virologic response to APTIVUS/ritonavir therapy has been evaluated with respect to baseline genotype in treatment experienced patients participating in trials RESIST-1 and RESIST-2. A score (counting the 16 amino acids that have been associated with reduced tipranavir susceptibility and/or reduced 24-week viral load response: 10V, 13V, 20M/R/V, 33F, 35G, 36I, 43T, 46L, 47V, 54A/M/V, 58E, 69K, 74P, 82L/T, 83D and 84V) was applied to baseline viral protease sequences. A correlation between the tipranavir susceptibility score and response to APTIVUS/ritonavir therapy at weeks 2 and 24 has been established and is summarized in Table 20.

Table 20: HIV Response: Change in Viral load at Weeks 2 and 24 by Baseline Tipranavir Susceptibility Score in Studies RESIST-1, and RESIST-2**

Tipranavir Susceptibility Score**	Change in viral load from baseline at 2 weeks (APTIVUS/ritonavir)* Median (N)	Change in viral load from baseline at 24 weeks (APTIVUS/ritonavir)* Median (N)
0-1	-1.25 (125)	-1.87 (134)
2-3	-1.41 (250)	-0.92 (266)
4-5	-1.43 (262)	-0.44 (285)
$\geq$ 6	-1.35 (58)	-0.45 (60)

* Change in Viral load was the change in HIV RNA from baseline through weeks 2 and 24 in $\log_{10}$ copies/mL (LOCF).

** Count of altered bases at 10V, 13V, 20M/R/V, 33F, 35G, 36I, 43T, 46L, 47V, 54A/M/V, 58E, 69K, 74P, 82L/T, 83D and 84V in baseline HIV-1 sequence

The virologic response to APTIVUS, co-administered with low-dose ritonavir, therapy has been evaluated with respect to baseline tipranavir phenotypic susceptibility (N=454) in treatment-experienced patients participating in trials RESIST-1 and RESIST-2. In these studies, the patients had baseline HIV isolates with an average decrease in susceptibility of 12-fold wild-type (WT) for amprenavir, 55-fold WT for atazanavir, 41-fold WT for indinavir, 87-fold WT for lopinavir, 41-fold WT for nelfinavir, 195-fold WT for ritonavir, 20-fold WT for saquinavir, and 2-fold WT for tipranavir. Phenotypic analysis of baseline isolates from these studies demonstrated a correlation between baseline susceptibility to tipranavir and response to tipranavir, co-administered with low-dose ritonavir, therapy. Table 21 below summarizes the HIV RNA response by tipranavir susceptibility.

Table 21: HIV Response at Weeks 2 and 24 by Baseline Tipranavir Susceptibility in Studies RESIST-1, RESIST-2

	Change in Viral Load from Baseline at 2 weeks (APTIVUS/RTV)*		Change in Viral Load from Baseline at 24 weeks (APTIVUS/RTV)*	
Fold-change at baseline in tipranavir IC_{50}	**N**	**Median**	**N**	**Median**
< 1	115	-1.53	122	-1.82
1 to < 4	190	-1.44	199	-0.64
≥ 4	89	-0.66	91	-0.32

* Change in Viral load was the change in HIV RNA from baseline through week 2 (OT) or week 24 (LOCF) in $\log_{10}$ copies/mL.

DETAILED PHARMACOLOGY

Microbiology

Mechanism of action: The human immunodeficiency virus (HIV-1) encodes an aspartyl protease that is essential for the cleavage and maturation of viral protein precursors. Tipranavir is a non-peptidic inhibitor of the HIV-1 protease that inhibits viral replication by preventing the maturation of viral particles.

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 vitro* 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 vitro* to tipranavir with EC_{50} values ranging from 0.164-1 µM and 0.233-0.522 µM, respectively. Protein binding studies have shown that the antiviral activity of tipranavir decreases on average 3.75-fold in conditions where human serum is present. When used with other antiretroviral agents *in vitro*, 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). APTIVUS was synergistic with the HIV fusion inhibitor enfuvirtide. There was no antagonism of the *in vitro* combinations of tipranavir with either adefovir or ribavirin, used in the treatment of viral hepatitis.

***Resistance*:** The development of resistance to tipranavir *in vitro* is slow and complex. In one particular *in vitro* resistance experiment, an HIV-1 isolate that was 87-fold resistant to tipranavir was selected after 9 months, and contained 10 mutations in the protease: L10F, I13V, V32I, L33F, M36I, K45I, I54V/T, A71V, V82L, I84V as well as a mutation in the gag polyprotein CA/P2 cleavage site. Reverse genetic experiments showed that the presence of 6 mutations in the protease (I13V, V32I, L33F, K45I, V82L, I84V) was required to confer > 10-fold resistance to tipranavir while the full 10-mutation genotype conferred 69-fold resistance to tipranavir. *In vitro*, there is an inverse correlation between the degree of resistance to tipranavir and the

capacity of viruses to replicate. Recombinant viruses showing ≥ 3-fold resistance to tipranavir grow at less than 1 % of the rate detected for wild type HIV-1 in the same conditions.

Through a series of multiple stepwise regression analyses of baseline and on-treatment genotypes from all clinical studies, 16 amino acids have been associated with reduced tipranavir susceptibility and/or reduced 24-week viral load response: 10V, 13V, 20M/R/V, 33F, 35G, 36I, 43T, 46L, 47V, 54A/M/V, 58E, 69K, 74P, 82L/T, 83D and 84V. Clinical isolates that exhibited a ≥10-fold decrease in tipranavir susceptibility harboured eight or more tipranavir-associated mutations. In Phase II and III clinical trials, 276 patients with on-treatment genotypes have demonstrated that the predominant emerging mutations with APTIVUS treatment are L33F/I/V, V82T/L and I84V. Combination of all three of these is usually required for reduced susceptibility. Mutations at position 82 occur via two pathways: one from pre-existing mutation 82A selecting to 82T, the other from wild type 82V selecting to 82L.

Cross resistance: Tipranavir maintains significant antiviral activity (< 4-fold resistance) against the majority of HIV-1 clinical isolates showing post-treatment decreased susceptibility to the currently approved protease inhibitors: amprenavir, atazanavir, indinavir, lopinavir, ritonavir, nelfinavir and saquinavir.

Greater than 10-fold resistance to tipranavir is uncommon (< 2.5 % of tested isolates) in viruses obtained from treatment experienced patients who have received multiple peptidic protease inhibitors.

Tipranavir resistant viruses which emerge *in vitro* from wild-type HIV-1 show decreased susceptibility to the protease inhibitors amprenavir, atazanavir, indinavir, lopinavir, nelfinavir and ritonavir but remain sensitive to saquinavir.

TOXICOLOGY

Animal toxicology studies have been conducted with tipranavir alone and co-administered with ritonavir (3.75:1 w/w ratio) in various species. Studies with co-administration of tipranavir and ritonavir did not reveal any additional toxicological effects when compared to those seen in the tipranavir single agent toxicological studies.

Acute and Chronic Toxicity

The predominant effects of repeated administration of tipranavir across all species toxicologically tested were on the gastrointestinal tract (emesis, soft stool, diarrhoea) and the liver (hypertrophy). In animals, this effect was observed at exposure levels of 290 - 450 µM·h, dependent on duration of treatment. The effects were reversible with termination of treatment.

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 majority of the effects in repeat-dose toxicity studies appeared at systemic exposure levels which are equivalent to or below the human exposure levels at the recommended clinical dose. Bleeding in rats was observed at exposure levels of 300 - 1100 µM·h (rodent specific). The co-administration of tipranavir with vitamin E in the form of TPGS (d-alpha-tocopherol polyethylene glycol 1000 succinate) resulted in a significant increase in

effects on coagulation parameters, bleeding events and death. The mechanism for these effects is unknown.

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.

Carcinogenicity and Genotoxicity

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 genetic toxicity in a battery of five *in vitro* and *in vivo* tests assessing mutagenicity and clastogenicity.

Reproductive and Developmental Toxicity

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 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 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_{0-24} levels of 30.4 µM / 340 µM·h/mL and 8.4 µM / 120 µM·h/mL. These exposure levels (AUC) are ~~0.4~~ 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, but caused growth inhibition in pups and maternal toxicity at dose levels of 400 mg/kg/day and above. No post-weaning functions were affected at any dose level. Calculated exposure in animal studies were equivalent to or below human therapeutic exposure levels. For the animal studies reported above, exposures were three to five fold lower at the end of the dosing period compared to the start of the dosing period.

In a study conducted in rats with tipranavir at systemic exposure levels (AUC) of 1670 µM·h, equivalent to human exposure at the adult human clinical dose, no adverse effects on mating or fertility were observed. Tipranavir did not produce teratogenic effects at maternal doses producing systemic drug exposure levels of 1310 µM·h in rats or 120 µM·h in rabbits-equivalent to or below the exposure at the adult human clinical dose (APTIVUS /ritonavir 500 mg/200 mg bid), respectively.

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PART III: CONSUMER INFORMATION

[Pr]Aptivus®
(Tipranavir) Capsules

This leaflet is part III of a three-part "Product Monograph" published when APTIVUS was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about APTIVUS. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

Read this information carefully before you start taking APTIVUS. Read it again each time you refill your prescription. There may be new information. You and your doctor should discuss APTIVUS when you start taking your medicine and at regular checkups. You should stay under a doctor's care when using APTIVUS. Do not change treatment or stop treatment without first talking to your doctor.

Before taking your medicine, make sure you have received the correct medicine. Compare the name of the product stated above with the name of the product on your bottle and the appearance of your medicine with the description provided below. Contact your pharmacist immediately if you believe you have been given the wrong medication.

In addition, since APTIVUS must be taken together with Norvir® (ritonavir), please read the Patient Information for Norvir® (ritonavir).

What the medication is used for:
APTIVUS is a medicine to treat adults with Human Immunodeficiency Virus (HIV), the virus that causes AIDS (Acquired Immune Deficiency Syndrome). APTIVUS must always be taken with Norvir® (ritonavir) and with other anti-HIV medicines to treat people with HIV infection.

What it does:
HIV infection destroys CD4 (T) cells, which are important to the immune system. After a large number of T cells are destroyed, acquired immune deficiency syndrome (AIDS) develops.

APTIVUS blocks HIV protease, an enzyme which is needed for HIV to multiply (make more virus). APTIVUS reduces the amount of HIV in your blood and increases the number of T cells. Reducing the amount of HIV in the blood reduces the risk of death or infections that happen when your immune system is weak (opportunistic infections).

When it should not be used:
Do not take APTIVUS:

- If you are hypersensitive (allergic) to tipranavir, ritonavir, or any of the other ingredients of APTIVUS or ritonavir (Norvir®) (**see What the important non-medicinal ingredients are and ritonavir product monograph)**;
- If you have moderate to severe liver problems;
- If you are currently taking any of the following medications:
  - alfuzosin
  - amiodarone
  - astemizole*
  - bepridil
  - cisapride*
  - colchicine if you have kidney or liver problems
  - dihydroergotamine, ergonovine, ergotamine and methylergonovine
  - flecainide
  - lovastatin
  - oral midazolam
  - pimozide
  - propafenone
  - quetiapine
  - quinidine
  - rifampin
  - sildenafil when used for pulmonary arterial hypertension (PAH)
  - simvastatin
  - St. John's wort (*Hypericum perforatum*)
  - terfenadine*
  - oral triazolam
  - vardenafil

* These drugs are currently not marketed in Canada.

Do not take APTIVUS if you have a rare hereditary condition of fructose intolerance as this product contains 50.4 mg sorbitol per maximum recommended daily dose.

What the medicinal ingredient is:
APTIVUS capsules contain the active ingredient called tipranavir.

What the important non-medicinal ingredients are:
Inactive ingredients include Cremophor® EL, ethanol, mono/diglycerides of caprylic/capric acid, propyl gallate, propylene glycol, purified water, and trometamol.

Capsule shell: gelatin, iron oxide red, propylene glycol, purified water, 'sorbitol special glycerin blend' (d-sorbitol, 1,4-sorbitan, mannitol and glycerin) and titanium dioxide.

Black printing ink: ammonium hydroxide, ethylacetate, iron oxide black, isopropyl alcohol, Macrogol, polyvinyl acetate phthalate, propylene glycol, purified water and SDA 35 alcohol.

What dosage forms it comes in:
APTIVUS capsules are available in 250 mg strength.

WARNINGS AND PRECAUTIONS

Patients taking APTIVUS, together with 200 mg of Norvir® (ritonavir) may develop bleeding in the brain that can cause death. You should report any unusual or unexplained bleeding to your doctor.

Patients taking APTIVUS, together with 200 mg Norvir® (ritonavir), may develop severe liver disease that can cause death. If you have chronic hepatitis B or C infection you have an increased chance of developing liver problems (See SIDE EFFECTS AND WHAT TO DO ABOUT THEM, below).

APTIVUS does not cure HIV infection or AIDS. People taking APTIVUS may still get infections or other conditions common in people with HIV (opportunistic infections). Some of these conditions are pneumonia, herpes virus infections, and *Mycobacterium avium* complex (MAC) infection, which may necessitate further evaluation and treatment. Therefore, it is very important that you stay under the care of your doctor.

APTIVUS does not reduce the risk of passing HIV to others through sexual contact or blood contamination. Continue to practice safe sex and 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.

APTIVUS capsules contain ethanol 7 % (v/v). This should be taken into account in pregnant or breast-feeding women, children, and in high-risk groups such as those with liver disease or epilepsy. Ethanol could be harmful for those suffering from alcoholism.

APTIVUS can cause dangerous and life-threatening interactions if taken with certain other medicines. Tell your doctor about all the medicines you take including those available without a prescription, vitamins, and herbal supplements (see INTERACTIONS WITH THIS MEDICATION).

Do not take the following medicines with APTIVUS/ritonavir:

- rifampin, as this may lower APTIVUS in your blood and make it less effective.
- fluticasone proprionate (e.g. Flonase®, Flovent®, Advair®) unless your doctor believes the benefit outweighs the risk.
- trazodone (e.g. Desyrel®) as APTIVUS may increase the level of trazodone in the blood. The doctor may lower the trazodone dosage.
- St. John's wort (*Hypericum perforatum*) as this may reduce APTIVUS levels and lead to increased HIV levels or the development of resistance to APTIVUS or other HIV medications.
- omeprazole or esomeprazole, unless your doctor believes the benefits outweigh the risks.
- APTIVUS makes birth control pills work less well. Talk to your doctor about other methods of birth control.
- Tell your doctor if you are allergic to sulfa drugs.

BEFORE you use APTIVUS talk to your doctor or pharmacist:

- *If you are pregnant or planning to become pregnant:* The effects of APTIVUS on pregnant women or their unborn babies are not known. If you are pregnant, APTIVUS should only be taken after careful discussion with your doctor. Tell your doctor immediately if you become pregnant.
- *If you are breast-feeding:* Do not breast-feed if you are taking APTIVUS. You should not breast-feed if you have HIV. If you are a woman who has or will have a baby, talk with your doctor about the best way to feed your baby. You should be aware that if your baby does not already have HIV infection, there is a chance that HIV can be transmitted through breast-feeding.
- *If you are using estrogens for birth control or hormone replacement:* Women who use estrogens for birth control or hormone replacement have an increased chance of developing a skin rash while taking APTIVUS. If a rash occurs, it is usually mild to moderate, but you should talk to your doctor as you may need to temporarily stop taking either APTIVUS or the other medicine that contains estrogen or female hormones.
- *If you have liver problems:* If you have liver problems or are infected with Hepatitis B or Hepatitis C, you should tell your doctor before taking APTIVUS.
- *If you have diabetes:* Some people taking protease inhibitors develop new or more serious diabetes or high blood sugar. Tell your doctor if you have diabetes or an increase in thirst or frequent urination while taking APTIVUS.
- *If you have hemophilia, have had or will have surgery, or other medical conditions that increase your chance of bleeding, or are taking medicines which increase your chance of bleeding (e.g, anticoagulants, antiplatement medication, or vitamin E supplements):* you may have an increased chance of bleeding.

INTERACTIONS WITH THIS MEDICATION

APTIVUS may interact with other medicines. Tell your doctor about all the medicines you take including those available without a prescription, herbal supplements and natural health products. You should keep a list of all the medicines that you take.

The following medicines may require your healthcare provider to either monitor your therapy or to change the dose of either APTIVUS or the other medicine:

- bupropion (antidepressant)
- bosentan
- boceprevir
- telaprevir
- etravirine
- salmeterol
- rilpivirine

- colchicine if you have kidney or liver problems.
- fluconazole increases the blood levels of APTIVUS; fluconazole doses greater than 200 mg/day are not recommended.
- ketoconazole and itraconazole, use with caution. Ketoconazole doses greater than 200 mg/day are not recommended.
- clarithromycin, your doctor should reduce the dose of clarithromycin based on the extent of your kidney disease.
- selective serotonin reuptake inhibitors (SSRIs – medications for depression).
- methadone, the dose of methadone may need to be increased.
- meperidine, a dose increase and long-term use of meperidine are not recommended.
- oral contraceptive ("the pill") levels may be reduced. The combination may cause a rash. You should use an additional or different type of contraceptive (e.g. condoms). You should be clinically monitored for estrogen deficiency if you are using estrogen for hormone replacement therapy.
- desipiramine may have to be decreased.
- theophylline may have to be increased.
- atorvastatin is not recommended unless at the lowest dose. Your doctor may switch you to another cholesterol-lowering medication.
- rosuvastatin, your doctor may decrease the dosage of rosuvastatin or may switch you to another cholesterol-lowering medication.
- rifabutin will be reduced.
- didanosine should be taken at least two hours after APTIVUS.
- antacids should be given as a separate does after two hours.
- warfarin and other blood thinners should be monitored.
- metronidazole or disulfiram contain alcohol and can lead to severe side effects.
- tadalafil. The use of APTIVUS/ritonavir with tadalafil, for the treatment of pulmonary arterial hypertension (PAH) is not recommended.
- carbamazepine, phenobarbital or phenytoin may make APTIVUS less effective.
- immunosuppressants (cyclosporin, tacrolimus, sirolimus) need to be monitored.
- Levels are decreased for HIV protease inhibitors such as saquinavir, amprenavir, atazanavir and lopinavir. Fosamprenavir is expected to act the same way. The use of these inhibitors in combination with APTIVUS is not recommended. Your doctor needs to carefully consider whether to treat you with combinations of APTIVUS and these protease inhibitors.

PROPER USE OF THIS MEDICATION

Usual adult dose:
Always take APTIVUS exactly as your doctor has instructed you. The dose of APTIVUS may be different for you than for other patients. You should check with your doctor or pharmacist if you are unsure. **It is essential that you take APTIVUS together with Norvir® (ritonavir),** and it is necessary to refer to the Norvir® Patient Information.

If you are taking APTIVUS capsules, the usual dose is 500 mg (two 250 mg capsules) of APTIVUS, together with 200 mg (two 100 mg capsules) of ritonavir (Norvir®), twice per day. The capsules should always be taken by mouth, and swallowed whole with plenty of liquid and not chewed. APTIVUS must also always be taken in combination with other antiretroviral medicines, for which you should be sure to follow the directions from your doctor or pharmacist.

Always take APTIVUS with food at all times to improve tolerability.

Do not change your dose or stop taking APTIVUS without first talking with your doctor.

It has been shown that taking all doses at the appropriate times may greatly increase the effectiveness of your combination antiretroviral medicines and reduce the chances of developing antiretroviral resistance. Therefore, unless your doctor instructs you to stop treatment, it is important to keep taking APTIVUS correctly, as described.

When your APTIVUS supply starts to run low, get more from your doctor or pharmacy. This is very important because the amount of virus in your blood may increase if the medicine is stopped for even a short period of time. The virus may develop resistance to APTIVUS and become harder to treat.

Only take medicine that has been prescribed specifically for you. Do not give APTIVUS to others or take medicine prescribed for someone else.

You should stay under a doctor's care when taking APTIVUS. Do not change your treatment or stop treatment without first talking with your doctor.

Overdose:

In case of drug overdose, contact a healthcare practitioner, hospital emergency department or regional poison control centre, even if there are no symptoms. Always take the labelled medicine container with you.

Missed Dose:
If you forget to take APTIVUS, do not double the next dose, but take the next dose as soon as possible.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

APTIVUS can have side effects. It may be difficult to tell the difference between side effects caused by APTIVUS, by the other medicines you are also taking, or by the complications of HIV infection. For this reason it is very important that you tell your doctor about any changes in your health. The following list of side effects is **not** complete. You should report any new or continuing symptoms to your doctor right away. Your doctor may be able to help you manage these side effects.

The most commonly reported side effects of moderate severity that are thought to be drug-related are mostly associated with the gastrointestinal tract and include diarrhea, nausea, vomiting and abdominal pain. Other commonly reported side effects are tiredness and headache. Women taking oral contraceptives may get a mild skin rash.

Blood tests in patients taking APTIVUS may show possible liver problems. Patients with liver disease such as Hepatitis B and Hepatitis C who take APTIVUS may have worsening liver disease. Liver problems including liver failure and death have occurred in patients taking APTIVUS. In studies, it is unclear if APTIVUS caused these liver problems because some patients had other illnesses or were taking other medicines at the time. Patients with signs or symptoms of hepatitis should discontinue APTIVUS/ritonavir treatment and seek medical evaluation**.** If you notice the signs or symptoms of hepatitis (fever, malaise, nausea, vomiting, abdominal pain, fatigue, jaundice) you should inform your doctor as soon as possible. Your doctor should use caution when administering APTIVUS/ritonavir to patients with liver enzyme abnormalities or history of hepatitis. Your doctor may consider increased liver monitoring.

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

Some patients taking APTIVUS have large increases in triglycerides and cholesterol (fat in the blood). The long-term chance of getting complications such as heart attacks or stroke due to increases in triglycerides and cholesterol caused by protease inhibitors is not known at this time.

Diabetes and high blood sugar (hyperglycemia) can occur in patients taking protease inhibitors such as APTIVUS. Some patients had diabetes before starting protease inhibitors, others did not. Some patients need changes in their diabetes medicine while others need new diabetes medicine.

In some individuals, combination antiretroviral therapy and treatment with protease inhibitors may cause changes in body shape due to changes in fat distribution. These may include loss of fat from legs, arms and face, increased fat in the abdomen (belly) and other internal organs, breast enlargement and fatty lumps on the back of the neck (‘buffalo hump’). The cause and long-term health effects of these conditions are not known at this time. Combination antiretroviral therapy may also cause raised lactic acid and sugar in the blood, hyperlipidemia (increased fats in the blood) and resistance to insulin.

In patients with hemophilia type A and B, there have been reports of increased bleeding while taking this treatment or another protease inhibitor. People taking anticoagulant or antiplatelet medications, or those undergoing surgery may have an increased risk of bleeding while taking this treatment. Bleeding in the brain has occurred in patients treated with APTIVUS, together with Norvir® (ritonavir), 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 contributed to it. Should any unusual or unexplained bleeding happen while you are taking this treatment, seek immediate advice from your doctor.

Changes in your immune system (Immune Reconstitution Syndrome) can happen when you start taking HIV medicines. Your immune system may get stronger and begin to fight infections that have been hidden in your body for a long time, or you could develop an autoimmune disease in which your immune system reacts against your own body (e.g. Grave's disease (which affects the thyroid gland), Guillain-Barre syndrome (which affects the nervous system) or polymyositis (which affects the muscles) and it may develop at any time, sometimes months later after the start of HIV therapy). Sometimes symptoms can be severe, so if you develop high temperature (fever), joint or muscle pain, redness, rash, swelling, or fatigue or any new symptoms contact your doctor straight away.

Other side effects may occur with APTIVUS. Ask your doctor or pharmacist for more information about this or any other symptoms that may develop or if symptoms persist or worsen.

There have been other side effects in patients taking APTIVUS. However, these side effects may have been due to other medicines that patients were taking or to the illness itself. Some of these side effects can be serious.

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

(For more details see text)

Symptom / effect		**Talk with your doctor or pharmacist**	
		Only if severe	**In all cases**
Common	**Hyperlipidemia (increased fats in the blood)**		**T**
	Rash		**T**
Uncommon	**Diabetes, high blood sugar, resistance to insulin and symptoms**		**T**
	Increased bleeding		**T**
	Liver problems		**T**

This is not a complete list of side effects. For any unexpected effects while taking APTIVUS contact your doctor or pharmacist.

Ability to drive and operate machinery:
No studies on the effects on the ability to drive and use machines have been performed for APTIVUS/ritonavir. However, dizziness, sleepiness, and fatigue have been reported in some patients. If you experience fatigue, dizziness, or sleepiness, do not drive or operate machinery until these symptoms go away.

HOW TO STORE IT

APTIVUS capsules are pink, oblong with a black print imprint of "TPV 250". Each APTIVUS capsule contains 250 mg of the active substance tipranavir. APTIVUS is supplied in unit-of-use bottles, with a child-resistant closure, containing 120 capsules.

APTIVUS capsules should be stored at 2-8°C (refrigerated). Once the bottle is opened, refrigeration of the capsules by the patient is not required if used within 60 days and stored **at controlled room temperature 15-30°C.** You can write the date of opening the bottle on the label. Do not use after the expiration date stated on the bottle.

REPORTING SUSPECTED SIDE EFFECTS

You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways:

- **Report online at www.healthcanada.gc.ca/medeffect**
- **Call toll-free at 1-866-234-2345**
- **Complete a Canada Vigilance Reporting Form and:**
  - **Fax toll-free to 1-866-678-6789, or**
  - **Mail to: Canada Vigilance Program**
    Health Canada
    Postal Locator 0701E
    Ottawa, ON K1A 0K9

Postage paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available on the MedEffect™ Canada Web site at www.healthcanada.gc.ca/medeffect

NOTE: Should you require information related to the management of side effects, contact your health professional. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

This document plus the full product monograph, prepared for health professionals can be found at: http://www.boehringer-ingelheim.ca or by contacting the sponsor, Boehringer Ingelheim (Canada) Ltd., at: 1-800-263-5103 Ext. 84633 (Medical Information). Please visit our website to see if more up-to-date information has been posted.

This leaflet was prepared by Boehringer Ingelheim (Canada) Ltd.

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