Neither MEPRON nor aerosolized pentamidine was associated with a substantial change from baseline values in any measured laboratory parameter, nor were there any significant differences in any measured laboratory parameter between MEPRON and aerosolized pentamidine. Some patients had laboratory abnormalities considered serious by the investigator or that contributed to discontinuation of therapy.

PCP Treatment Studies: Table 8 summarizes all the clinical adverse experiences reported by ≥ 5% of the study population during the TMP-SMX comparative study of MEPRON (n = 408), regardless of attribution. The incidence of adverse experiences with MEPRON Suspension at the recommended dose was similar to that seen with the tablet formulation of atovaquone.

Table 8. Treatment-Emergent Adverse Experiences in the TMP-SMX Comparative PCP Treatment Study

Treatment-Emergent Adverse Experience	Percentage of Patients with Treatment-Emergent Adverse Experience	
	MEPRON (n = 203)	TMP-SMX (n = 205)
Rash (including maculopapular)	23%	34%
Nausea	21%	44%
Diarrhea	19%	7%
Headache	16%	22%
Vomiting	14%	35%
Fever	14%	25%
Insomnia	10%	9%
Asthenia	8%	8%
Pruritus	5%	9%
Monilia, oral	5%	10%
Abdominal pain	4%	7%
Constipation	3%	17%
Dizziness	3%	8%
Patients discontinuing therapy due to an adverse experience	9%	24%
Patients reporting at least 1 adverse experience	63%	65%

Although an equal percentage of patients receiving MEPRON and TMP-SMX reported at least 1 adverse experience, more patients receiving TMP-SMX required discontinuation of therapy due to an adverse event. Twenty-four percent of patients receiving TMP-SMX were prematurely discontinued from therapy due to an adverse experience versus 9% of patients receiving MEPRON. Four percent of patients receiving MEPRON had therapy discontinued due to development of rash. The majority of cases of rash among patients receiving MEPRON were mild and did not require the

discontinuation of dosing. The only other clinical adverse experience that led to premature discontinuation of dosing of MEPRON by more than 1 patient was vomiting (<1%). The most common adverse experience requiring discontinuation of dosing in the TMP-SMX group was rash (8%).

Laboratory test abnormalities reported for ≥5% of the study population during the treatment period are summarized in Table 9. Two percent of patients treated with MEPRON and 7% of patients treated with TMP-SMX had therapy prematurely discontinued due to elevations in ALT/AST. In general, patients treated with MEPRON developed fewer abnormalities in measures of hepatocellular function (ALT, AST, alkaline phosphatase) or amylase values than patients treated with TMP-SMX.

Table 9. Treatment-Emergent Laboratory Test Abnormalities in the TMP-SMX Comparative PCP Treatment Study

Laboratory Test Abnormality	Percentage of Patients Developing a Laboratory Test Abnormality	
	MEPRON	TMP-SMX
Anemia (Hgb<8.0 g/dL)	6%	7%
Neutropenia (ANC<750 cells/mm^3)	3%	9%
Elevated ALT (>5 x ULN)	6%	16%
Elevated AST (>5 x ULN)	4%	14%
Elevated alkaline phosphatase (>2.5 x ULN)	8%	6%
Elevated amylase (>1.5 x ULN)	7%	12%
Hyponatremia (<0.96 x LLN)	7%	26%

ULN = upper limit of normal range.

LLN = lower limit of normal range.

Table 10 summarizes the clinical adverse experiences reported by ≥5% of the primary therapy study population (n = 144) during the comparative trial of MEPRON and intravenous pentamidine, regardless of attribution. A slightly lower percentage of patients who received MEPRON reported occurrence of adverse events than did those who received pentamidine (63% vs 72%). However,

only 7% of patients discontinued treatment with MEPRON due to adverse events, while 41% of patients who received pentamidine discontinued treatment for this reason ($P<0.001$). Of the 5 patients who discontinued therapy with MEPRON, 3 reported rash (4%). Rash was not severe in any patient. No other reason for discontinuation of MEPRON was cited more than once. The most frequently cited reasons for discontinuation of pentamidine therapy were hypoglycemia (11%) and vomiting (9%).

Table 10. Treatment-Emergent Adverse Experiences in the Pentamidine Comparative PCP Treatment Study (Primary Therapy Group)

Treatment-Emergent Adverse Experience	Percentage of Patients with Treatment-Emergent Adverse Experience	
	MEPRON (n = 73)	Pentamidine (n = 71)
Fever	40%	25%
Nausea	22%	37%
Rash	22%	13%
Diarrhea	21%	31%
Insomnia	19%	14%
Headache	18%	28%
Vomiting	14%	17%
Cough	14%	1%
Abdominal pain	10%	11%
Pain	10%	10%
Sweat	10%	3%
Monilia, oral	10%	3%
Asthenia	8%	14%
Dizziness	8%	14%
Anxiety	7%	10%
Anorexia	7%	10%
Sinusitis	7%	6%
Dyspepsia	5%	10%
Rhinitis	5%	7%
Taste perversion	3%	13%
Hypoglycemia	1%	15%
Hypotension	1%	10%
Patients discontinuing therapy due to an	7%	41%

adverse experience		
Patients reporting at least 1 adverse experience	63%	72%

Laboratory test abnormalities reported in ≥5% of patients in the pentamidine comparative study are presented in Table 11. Laboratory abnormality was reported as the reason for discontinuation of treatment in 2 of 73 patients who received MEPRON. One patient (1%) had elevated creatinine and BUN levels and 1 patient (1%) had elevated amylase levels. Laboratory abnormalities were the sole or contributing factor in 14 patients who prematurely discontinued pentamidine therapy. In the 71 patients who received pentamidine, laboratory parameters most frequently reported as reasons for discontinuation were hypoglycemia (11%), elevated creatinine levels (6%), and leukopenia (4%).

Table 11. Treatment-Emergent Laboratory Test Abnormalities in the Pentamidine Comparative PCP Treatment Study

Laboratory Test Abnormality	Percentage of Patients Developing a Laboratory Test Abnormality	
	MEPRON	Pentamidine
Anemia (Hgb<8.0 g/dL)	4%	9%
Neutropenia (ANC<750 cells/mm^3)	5%	9%
Hyponatremia (<0.96 x LLN)	10%	10%
Hyperkalemia (>1.18 x ULN)	0%	5%
Alkaline phosphatase (>2.5 x ULN)	5%	2%
Hyperglycemia (>1.8 x ULN)	9%	13%
Elevated AST (>5 x ULN)	0%	5%
Elevated amylase (>1.5 x ULN)	8%	4%
Elevated creatinine (>1.5 x ULN)	0%	7%

ULN = upper limit of normal range.

LLN = lower limit of normal range.

Observed During Clinical Practice: In addition to adverse events reported from clinical trials, the following events have been identified during post-approval use of MEPRON. Because they are reported voluntarily from a population of unknown size, estimates of frequency cannot be made. These events have been chosen for inclusion due to a combination of their seriousness, frequency of reporting, or potential causal connection to MEPRON.

Blood and Lymphatic: Methemoglobinemia, thrombocytopenia.

Eye: Vortex keratopathy.

Hepatobiliary Tract and Pancreas: Pancreatitis.

Skin: Allergic reactions including erythema multiforme.

Urology: Acute renal impairment.

OVERDOSAGE: There is no known antidote for atovaquone, and it is currently unknown if atovaquone is dialyzable. The median lethal dose is higher than the maximum oral dose tested in mice and rats (1,825 mg/kg/day). Overdoses up to 31,500 mg of atovaquone have been reported. In 1 such patient who also took an unspecified dose of dapsone, methemoglobinemia occurred. Rash has also been reported after overdose.

DOSAGE AND ADMINISTRATION:

Dosage: ***Prevention of PCP: Adults and Adolescents (13 to 16 Years):*** The recommended oral dose is 1,500 mg (10 mL) once daily administered with a meal.

Treatment of Mild-to-Moderate PCP: Adults and Adolescents (13 to 16 Years): The recommended oral dose is 750 mg (5 mL) administered with meals twice daily for 21 days (total daily dose 1,500 mg).

Note: Failure to administer MEPRON Suspension with meals may result in lower plasma atovaquone concentrations and may limit response to therapy (see CLINICAL PHARMACOLOGY and PRECAUTIONS).

Administration: ***Foil Pouch:*** Open pouch by removing tab at perforation and tear at notch. Take entire contents by mouth. Can be discharged into a dosing spoon or cup or directly into the mouth.

Bottle: SHAKE BOTTLE GENTLY BEFORE USING.

HOW SUPPLIED: MEPRON Suspension (bright yellow, citrus flavored) containing 750 mg atovaquone in each teaspoonful (5 mL).

Bottle of 210 mL with child-resistant cap (NDC 0173-0665-18).

Store at 15° to 25°C (59° to 77°F). DO NOT FREEZE. Dispense in tight container as defined in USP.

5-mL child-resistant foil pouch - unit dose pack of 42 (NDC 0173-0547-00).

Store at 15° to 25°C (59° to 77°F). DO NOT FREEZE.

[1](A-a)DO_2 = [(713 x FiO_2) – ($PaCO_2$/0.8)] – PaO_2 (mm Hg)

GlaxoSmithKline
Research Triangle Park, NC 27709

December 2001 RL-1012

ATTENTION PHARMACIST: Detach "Patient's Instructions for Use" from package insert and dispense with product. Dispense the capsules in the unit of use container.

Aptivus®
(tipranavir)
Capsules, 250 mg

Boehringer Ingelheim

Prescribing Information

WARNING

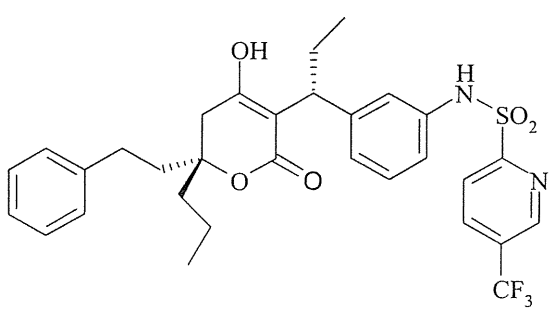
APTIVUS CO-ADMINISTERED WITH 200 MG RITONAVIR HAS BEEN ASSOCIATED WITH REPORTS OF CLINICAL HEPATITIS AND HEPATIC DECOMPENSATION INCLUDING SOME FATALITIES. EXTRA VIGILANCE IS WARRANTED IN PATIENTS WITH CHRONIC HEPATITIS B OR HEPATITIS C CO-INFECTION, AS THESE PATIENTS HAVE AN INCREASED RISK OF HEPATOTOXICITY. (SEE WARNINGS)

DESCRIPTION

APTIVUS® (tipranavir) is the brand name for tipranavir (TPV), a non-peptidic protease inhibitor (PI) of HIV belonging to the class of 4-hydroxy-5,6-dihydro-2-pyrone sulfonamides.

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

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



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

CLINICAL PHARMACOLOGY

Microbiology

Mechanism of Action

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

Antiviral Activity

Tipranavir inhibits the replication of laboratory strains of HIV-1 and clinical isolates in acute models of T-cell infection, with 50% effective concentrations (EC_{50}) ranging from 0.03 to 0.07 μM (18-42 ng/mL). Tipranavir demonstrates antiviral activity *in 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). Tipranavir 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

In vitro: HIV-1 isolates with a decreased susceptibility to tipranavir have been selected *in vitro* and obtained from patients treated with APTIVUS/ritonavir (TPV/ritonavir). HIV-1 isolates that were 87-fold resistant to tipranavir were selected *in vitro* by 9 months and contained 10 protease mutations that developed in the following order: L33F, I84V, K45I, I13V, V32I, V82L, M36I, A71V, L10F, and I54V/T. Changes in the Gag polyprotein CA/P2 cleavage site were also observed following drug selection. Experiments with site-directed mutants of HIV-1 showed that the presence of 6 mutations in the protease coding sequence (I13V, V32I, L33F, K45I, V82L, I84V) conferred > 10-fold reduced susceptibility to tipranavir. Recombinant viruses showing ≥ 3-fold reduced susceptibility to tipranavir were growth impaired.

Clinical Studies of Treatment-Experienced Patients: In Phase 3 studies 1182.12 and 1182.48, multiple protease inhibitor-resistant HIV-1 isolates from 59 highly treatment-experienced patients who received APTIVUS/ritonavir and experienced virologic rebound developed amino acid substitutions that were associated with resistance to tipranavir. The most common amino acid substitutions that developed on 500/200mg APTIVUS/ritonavir in greater than 20% of APTIVUS/ritonavir virologic failure isolates were L33V/I/F, V82T, and I84V. Other substitutions that developed in 10 to 20% of APTIVUS/ritonavir virologic failure isolates included L10V/I/S, I13V, E35D/G/N, I47V, K55R, V82L, and L89V/M. Tipranavir resistance was detected at virologic rebound after an average of

38 weeks of APTIVUS/ritonavir treatment with a median 14-fold decrease in tipranavir susceptibility. The resistance profile in treatment-naïve subjects has not been characterized.

Cross-resistance

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

Baseline Genotype and Virologic Outcome Analyses

Genotypic and/or phenotypic analysis of baseline virus may aid in determining tipranavir susceptibility before initiation of APTIVUS/ritonavir therapy. Several analyses were conducted to evaluate the impact of specific mutations and mutational patterns on virologic outcome. Both the type and number of baseline protease inhibitor mutations as well as use of additional active agents (e.g., enfuvirtide) affected APTIVUS/ritonavir response rates in Phase 3 studies 1182.12 and 1182.48 through Week 24 of treatment.

Regression analyses of baseline and/or on-treatment HIV-1 genotypes from 860 highly treatment-experienced patients in Phase 2 and 3 studies demonstrated that mutations at 16 amino acid codons in the HIV protease coding sequence were associated with reduced virologic responses at 24 weeks and/or reduced tipranavir susceptibility: L10V, I13V, K20M/R/V, L33F, E35G, M36I, K43T, M46L, I47V, I54A/M/V, Q58E, H69K, T74P, V82L/T, N83D or I84V.

Analyses were also conducted to assess virologic outcome by the number of primary protease inhibitor mutations present at baseline. Response rates were reduced if five or more protease inhibitor-associated mutations were present at baseline and subjects did not receive concomitant enfuvirtide with APTIVUS/ritonavir. See Table 1.

Table 1 Phase 3 Studies 1182.12 and 1182.48: Proportion of Responders (confirmed ≥ 1 $\log_{10}$ decrease at Week 24) by Number of Baseline Primary Protease Inhibitor (PI) Mutations

Number of Baseline Primary PI Mutations[a]	APTIVUS/ritonavir N = 513		Comparator PI/ritonavir N = 502	
	No Enfuvirtide	+ Enfuvirtide	No Enfuvirtide	+ Enfuvirtide
Overall	**40%** (147/368)	**64%** (93/145)	**19%** (75/390)	**30%** (34/112)
1 - 2	**68%** (26/38)	**75%** (3/4)	**41%** (17/41)	**100%** (2/2)
3 - 4	**44%** (78/176)	**64%** (39/61)	**23%** (39/170)	**40%** (21/52)
5+	**28%** (43/151)	**64%** (51/80)	**11%** (19/178)	**19%** (11/57)

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

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

- Approximately 1.5 $\log_{10}$ decrease in HIV-1 RNA at early time points (Week 2) regardless of the number of baseline primary protease inhibitor mutations (1-4 or 5+).
- Subjects with 5 or more primary protease inhibitor mutations in their HIV-1 at baseline who received APTIVUS/ritonavir without enfuvirtide (n=204) began to lose their antiviral response after Week 4.
- Early HIV-1 RNA decreases (1.5–2 $\log_{10}$) were sustained through Week 24 in subjects with 5 or more primary protease inhibitor mutations at baseline who received enfuvirtide with APTIVUS/ritonavir (n=88).

Conclusions regarding the relevance of particular mutations or mutational patterns are subject to change pending additional data.

Baseline Phenotype and Virologic Outcome Analyses

APTIVUS/ritonavir response rates were also assessed by baseline tipranavir phenotype. Relationships between baseline phenotypic susceptibility to tipranavir, mutations at protease amino acid codons 33, 82, 84 and 90, tipranavir resistance-associated mutations, and response to APTIVUS/ritonavir therapy at Week 24 are summarized in Table 2. These baseline phenotype groups are not meant to represent clinical susceptibility breakpoints for APTIVUS/ritonavir because the data are based on the select 1182.12 and 1182.48 patient population. The data are provided to give clinicians information on the likelihood of virologic success based on pre-treatment susceptibility to APTIVUS/ritonavir in highly protease inhibitor-experienced patients.

Table 2 Response by Baseline Tipranavir Phenotype in the 1182.12 and 1182.48 Trials

Baseline Tipranavir Phenotype (Fold Change)[a]	Proportion of Responders[b] with No Enfuvirtide Use	Proportion of Responders[b] with ENF Use	# of Baseline Protease Mutations at 33, 82, 84, 90	# of Baseline Tipranavir Resistance-Associated Mutations[c]	Tipranavir Susceptibility
0-3	45% (74/163)	77% (46/60)	0-2	0-4	Susceptible
> 3-10	21% (10/47)	43% (12/28)	3	5-7	Decreased Susceptibility
> 10	0% (0/8)	57% (4/7)	4	8+	Resistant

[a] Change in tipranavir IC_{50} value from wild-type reference

[b] Confirmed ≥1 $\log_{10}$ decrease at Week 24

[c] Number of amino acid substitutions in HIV protease among L10V, I13V, K20M/R/V, L33F, E35G, M36I, K43T, M46L, I47V, I54A/M/V, Q58E, H69K, T74P, V82L/T, N83D or I84V

Pharmacodynamics

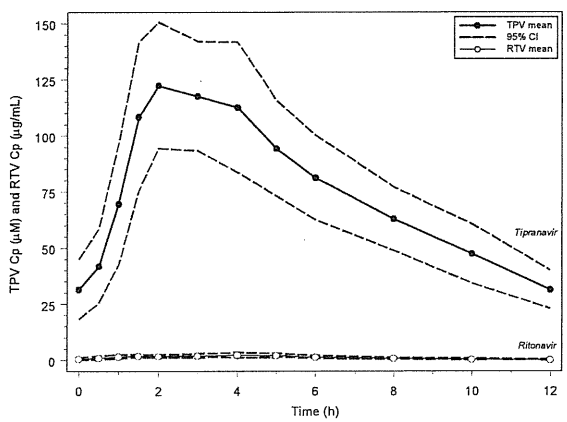
The median Inhibitory Quotient (IQ) determined from 301 highly treatment-experienced patients was about 75 (inter-quartile range: 29-189), from pivotal clinical trials 1182.12 and 1182.48. The IQ is defined as the tipranavir trough concentration divided by the viral IC_{50} value, corrected for protein binding. There was a relationship between the proportion of patients with a ≥ 1 $\log_{10}$ reduction of viral load from baseline at week 24 and their IQ value. Among the 206 patients receiving APTIVUS/ritonavir without enfuvirtide, the response rate was 23% in those with an IQ value < 75 and 55% in those with an IQ value $\geq$ 75. Among the 95 patients receiving APTIVUS/ritonavir with enfuvirtide, the response rates in patients with an IQ value < 75 versus those with an IQ value $\geq$ 75 were 43% and 84%, respectively. These IQ groups are derived from a select population and are not meant to represent clinical breakpoints.

Pharmacokinetics in Adult Patients

In order to achieve effective tipranavir plasma concentrations and a twice-daily dosing regimen, co-administration of APTIVUS with 200 mg of ritonavir is essential (see **PRECAUTIONS** and **DOSAGE AND ADMINISTRATION**). Ritonavir inhibits hepatic cytochrome P450 3A (CYP 3A), the intestinal P-glycoprotein (P-gp) efflux pump and possibly intestinal CYP 3A. In a dose-ranging evaluation in 113 HIV-negative male and female volunteers, there was a 29-fold increase in the geometric mean morning steady-state trough plasma concentrations of tipranavir following tipranavir co-administered with low-dose ritonavir (500/200 mg twice daily) compared to tipranavir 500 mg twice daily without ritonavir.

Figure 1 displays mean plasma concentrations of tipranavir and ritonavir at steady state for the 500/200 mg tipranavir/ritonavir dose.

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



Absorption and Bioavailability

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

Dosing with APTIVUS 500 mg concomitant with 200 mg ritonavir twice-daily for greater than 2 weeks and without meal restriction produced the following pharmacokinetic parameters for female and male HIV-positive patients. See Table 3.

Table 3 Pharmacokinetic Parameters[a] of tipranavir/ritonavir 500/200 mg for HIV+ Patients by Gender

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

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

Effects of Food on Oral Absorption

APTIVUS capsules co-administered with ritonavir should be taken with food. Bioavailability is increased with a high fat meal. Tipranavir capsules, administered under high fat meal conditions or with a light snack of toast and skimmed milk, were tested in a multiple dose study. High-fat meals (868 kcal, 53% derived from fat, 31% derived from carbohydrates) 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).

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

Distribution

Tipranavir is extensively bound to plasma proteins (> 99.9%). It binds to both human serum albumin and α-1-acid glycoprotein. The mean fraction of APTIVUS (dosed without ritonavir) unbound in plasma was similar in clinical samples from healthy volunteers (0.015% ± 0.006%) and HIV-positive patients (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 CYP 3A4 is the predominant CYP enzyme involved in tipranavir metabolism.

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

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

Elimination

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

Pharmacokinetics in Special Populations

Renal Impairment

APTIVUS pharmacokinetics has not been studied in patients with renal dysfunction. However, since the renal clearance of tipranavir is negligible, a decrease in total body clearance is not expected in patients with renal insufficiency.

Hepatic Impairment

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

The influence of moderate hepatic impairment (Child-Pugh B) or severe hepatic impairment (Child-Pugh C) on the multiple-dose pharmacokinetics of tipranavir administered with ritonavir has not been evaluated (see **DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS,** and **WARNINGS**).

Gender

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

Race

Evaluation of steady-state plasma tipranavir trough concentrations at 10-14 h after dosing from the 1182.12 and 1182.48 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.

Geriatric Patients

Evaluation of steady-state plasma tipranavir trough concentrations at 10-14 h after dosing from the 1182.12 and 1182.48 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.

Pediatric Patients

The pharmacokinetic profile of tipranavir in pediatric patients has not been established.

Drug Interactions

See also **CONTRAINDICATIONS, WARNINGS** and **PRECAUTIONS, Drug Interactions**.

APTIVUS co-administered with 200 mg of ritonavir can alter plasma exposure of other drugs and other drugs may alter plasma exposure of tipranavir.

Potential for tipranavir/ritonavir to Affect Other Drugs

1. APTIVUS co-administered with 200 mg of ritonavir at the recommended dose, is a net inhibitor of CYP 3A and may increase plasma concentrations of agents that are primarily metabolized by CYP 3A. Thus, co-administration of APTIVUS/ritonavir with drugs highly dependent on CYP 3A for clearance and for which elevated plasma concentrations are associated with serious and/or life-threatening events should be contraindicated. Co-administration with other CYP 3A substrates may require a dose adjustment or additional monitoring (see **CONTRAINDICATIONS** and **PRECAUTIONS**).

2. Studies in human liver microsomes indicated tipranavir is an inhibitor of CYP 1A2, CYP 2C9, CYP 2C19 and CYP 2D6. The potential net effect of tipranavir/ritonavir on CYP 2D6 is inhibition, because ritonavir is a CYP 2D6 inhibitor. The *in vivo* net effect of tipranavir administered with ritonavir on CYP 1A2, CYP 2C9 and CYP 2C19 is not known. Data are not available to indicate whether tipranavir inhibits or induces glucuronosyl transferases and whether tipranavir induces CYP 1A2, CYP 2C9 and CYP 2C19.

3. Tipranavir is a P-gp substrate, a weak P-gp inhibitor, and appears to be a potent P-gp inducer as well. Data suggest that the net effect of tipranavir co-administered with 200 mg of ritonavir is P-gp induction at steady-state, although ritonavir is a P-gp inhibitor.

4. It is difficult to predict the net effect of APTIVUS administered with ritonavir on oral bioavailability and plasma concentrations of drugs that are dual substrates of CYP 3A and P-gp. The net effect will vary depending on the relative affinity of the co-administered drugs for CYP 3A and P-gp, and the extent of intestinal first-pass metabolism/efflux.

Potential for Other Drugs to Affect tipranavir

1. Tipranavir is a CYP 3A substrate and a P-gp substrate. Co-administration of APTIVUS/ritonavir and drugs that induce CYP 3A and/or P-gp may decrease tipranavir plasma concentrations. Co-administration of APTIVUS/ritonavir and drugs that inhibit P-gp may increase tipranavir plasma concentrations.

2. Co-administration of APTIVUS/ritonavir with drugs that inhibit CYP 3A may not further increase tipranavir plasma concentrations, because the level of metabolites is low following steady-state administration of APTIVUS/ritonavir 500/200 mg twice daily.

Drug interaction studies were performed with APTIVUS, co-administered with 200 mg of ritonavir, and other drugs likely to be co-administered and some drugs commonly used as probes for pharmacokinetic interactions. The effects of co-administration of APTIVUS with 200 mg ritonavir, on the AUC, C_{max} and C_{min}, are summarized in Tables 4 and 5. For information regarding clinical recommendations (see **PRECAUTIONS, Drug Interactions, Tables 8** and **9**).

Table 4 Drug Interactions: Pharmacokinetic Parameters for Tipranavir in the Presence of Co-administered Drugs

Co-administered Drug	Co-administered Drug Dose (Schedule)	TPV/ritonavir Drug Dose (Schedule)	n	PK	Ratio (90% Confidence Interval) of Tipranavir Pharmacokinetic Parameters with/without Co-administered Drug; No Effect = 1.00		
					C_{max}	AUC	C_{min}
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 dose)	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)
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

Table 5 Drug Interactions: Pharmacokinetic Parameters for Co-administered Drug in the Presence of tipranavir/ritonavir

Co-administered Drug	Co-administered Drug Dose (Schedule)	TPV/ritonavir Drug Dose (Schedule)	n	PK	Ratio (90% Confidence Interval) of Co-administered Drug Pharmacokinetic Parameters with/without TPV/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)	- - -
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)	

[a]HIV+ patients
[b]HIV+ patients (TPV/ritonavir 250 mg/200 mg, 750 mg/200 mg and 1250 mg/100 mg) and healthy volunteers (TPV/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