# APTIVUS® Soft Capsules
# APTIVUS® Oral Solution
# (tipranavir)

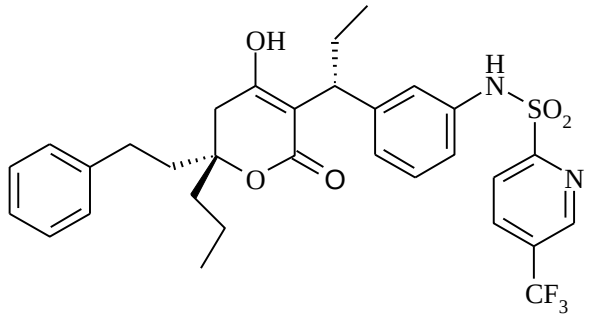
## NAME OF THE MEDICINE

APTIVUS contains the active ingredient tipranavir.

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).

Tipranavir is a white to off-white to slightly yellow solid with a molecular weight of 602.7 and the molecular formula is $C_{31}H_{33}F_3N_2O_5S$.

Tipranavir has the following structural formula:




CAS registration number: 174484-41-4

## DESCRIPTION

Tipranavir is a non-peptidic protease inhibitor (NPPI) with activity against the Human Immunodeficiency Virus Type 1 (HIV-1).

APTIVUS is available as soft capsules and as an oral solution for oral administration.

Each soft capsule contains 250 mg tipranavir. 1 mL oral solution contains 100 mg tipranavir.

Excipients in the capsule are PEG-35 castor oil, ethanol absolute, glyceryl caprylate/caprate, propylene glycol, purified water, trometamol, nitrogen and propyl gallate.

The capsule shell consists of gelatin, iron oxide red CI77491, propylene glycol, purified water, Sorbitol Special Glycerin Blend (sorbitol, 1, 4-sorbitan, mannitol and glycerin), titanium dioxide CI77891 and black printing ink (Black Opacode NSP-78-17827: SDA 35 alcohol, propylene glycol, iron oxide black CI77499, polyvinyl acetate phthalate, purified water, isopropyl alcohol, macrogol 400 and ammonia solution concentrated 28%).

The oral solution contains the following excipients: Macrogol 400, tocofersolan, purified water, propylene glycol, glyceryl caprylate/caprate, sucralose, buttermint flavour, butter-toffee flavour and ascorbic acid.

## PHARMACOLOGY

**Pharmacotherapeutic group:** Antivirals for systemic use, protease inhibitors, ATC code: J05AE09

**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.

**Microbiology**

**Antiviral activity *in vitro:*** 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 have ranged from additive to antagonistic with other protease inhibitors (amprenavir, atazanavir, indinavir, lopinavir, nelfinavir, and saquinavir). The combination of tipranavir with ritonavir showed synergy to additivity. The combination of tipranavir with NNRTIs (delavirdine, efavirenz, and nevirapine) and NRTIs (abacavir, didanosine, emtricitabine, lamivudine, stavudine, tenofovir, and zidovudine) was generally additive.

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:*

The development of resistance to tipranavir *in vitro* is slow and complex. HIV-1 isolates with a decreased susceptibility to tipranavir have been selected *in vitro* and obtained from patients treated with APTIVUS/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. Reverse genetic experiments with site-directed mutants of HIV-1 showed that the presence of 6 mutations in the protease (I13V, V32I, L33F, K45I, V82L, I84V) conferred >10-fold resistance 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.

*In vivo:*

*Treatment-Experienced Adult Patients:* 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,

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.

*Treatment-Naïve Adult Patients:* In a study of treatment-naïve patients, the development of protease resistance was investigated in patients experiencing virologic rebound after administration of an APTIVUS/ritonavir-containing regimen. Of the seventeen patients evaluated with baseline virus without pre-existing PI mutations, none of the viruses developed protease inhibitor resistance.

*Paediatric Patients:* Among 28 paediatric patients in clinical trial 1182.14 who experienced virologic failure or non-response, the emergent amino acid codon substitutions were similar to those observed in adults. As with adults, reduced TPV susceptibility was associated with emergent mutations in paediatrics.

**Cross resistance:** Tipranavir maintains significant *in vitro* antiviral activity (<4-fold resistance) against the majority (90%) of HIV-1 clinical isolates showing 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 highly 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.

ECG evaluation: QT prolongation: The effect of APTIVUS/ritonavir on the QTcI interval was measured in a study in which 80 healthy subjects (33 female and 47 male healthy subjects) received the APTIVUS/ritonavir treatments twice daily for 2.5 days. The studied dosing regimens were: APTIVUS/ritonavir (500/200 mg), APTIVUS/ritonavir 750/200 mg, and placebo/ritonavir (-/200 mg). After baseline and placebo adjustment, the maximum mean QTcI change was 3.1 ms (1-sided 95% Upper CI: 5.6 ms) for the 500/200 mg dose and 8.1 ms (1-sided 95% Upper CI: 10.8 ms) for the supra-therapeutic 750/200 mg dose.

APTIVUS/ritonavir at therapeutic doses [APTIVUS/ritonavir (500/200 mg)] did not prolong the QTc interval nor induce QT prolongation. APTIVUS/ritonavir at therapeutic doses did not induce clinically relevant ECG effects in healthy subjects.

**Pharmacokinetics in Adult Patients**

In order to achieve effective tipranavir plasma concentrations and a b.i.d. dosing regimen, co-administration of APTIVUS with 200mg ritonavir (low-dose) b.i.d. is essential. Ritonavir acts by inhibiting hepatic cytochrome P450 CYP3A, the intestinal P-glycoprotein (P-gp) 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 b.i.d.) was associated with a 29-fold increase in the geometric mean morning steady-state trough plasma concentrations compared to APTIVUS 500 mg b.i.d. without ritonavir.

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:** Absorption of tipranavir in humans is limited, though no absolute quantification of absorption is yet available. Tipranavir is a P-gp substrate.

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 enzyme and transporter 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 or oral solution co-administered with ritonavir at steady state, no clinically significant changes in $C_{p12h}$, $C_{max}$ and $AUC_{0\text{-}12h}$ were observed under fed conditions (500-682 Kcal, 23-25% calories from fat) compared to fasted conditions. Since ritonavir is advised to be taken with food, APTIVUS co-administered with ritonavir should be taken with food.

When APTIVUS, co-administered with low-dose ritonavir, was co-administered with 20 mL of aluminium and magnesium-based antacid, APTIVUS $AUC_{12h}$, $C_{max}$ 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%) *in vitro*. It binds to both human serum albumin and $\alpha$-1-acid glycoprotein. 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% $\pm$ 0.006%; HIV positive subjects 0.019% $\pm$ 0.076%). Total plasma tipranavir concentrations for these samples ranged from 9 to 82 $\mu$M. 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 200 mg ritonavir is minimal. In a $^{14}$C-tipranavir human study ($^{14}$C-tipranavir/ritonavir, 500 mg/200 mg b.i.d), 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 faeces, unchanged tipranavir represented the majority of faecal radioactivity (79.9% of faecal radioactivity). The most abundant faecal metabolite, at 4.9% of faecal 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) who received APTIVUS/ritonavir 500 mg/200 mg b.i.d 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 b.i.d. daily with a light meal.

**Pharmacokinetics in Paediatric Patients**

Among paediatric patients in clinical trial 1182.14, steady state plasma tipranavir trough concentrations were obtained 10 to 14 hours following study drug administration. The geometric mean tipranavir trough concentrations evaluated among 50 patients taking 375 mg/m$^2$/150 mg/m$^2$ b.i.d. were between 46.9 and 61.3 µM. The geometric mean tipranavir trough concentrations evaluated among 81 patients taking 290 mg/m$^2$/115 mg/m$^2$ b.i.d. were between 32.7 and 49.8 µM. Older paediatric patients tended to have higher geometric mean trough concentrations than younger paediatrics.

Clinical trial 1182.100 assessed the relative bioavailabilities at steady state for tipranavir/ritonavir oral solution and capsule formulation (500/200 mg), under fed and fasting conditions. Among 32 healthy adult subjects, the rate and extent of systemic availability for tipranavir oral solution in the presence of ritonavir solution increased 14% to 23% ($C_{max}$, AUC) when compared to tipranavir capsules in the presence of ritonavir capsules, under fed conditions. Since the differences in exposures are well within the clinically accepted range for maintaining efficacy and safety, no dose adjustment is recommended when switching between capsule and oral solution.

*Special populations*

***Age related pharmacokinetic differences:*** Evaluation of steady-state plasma tipranavir trough concentrations at 10-14 h after dosing from the RESIST-1 and RESIST-2 studies (see Description of Clinical 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 related pharmacokinetic differences:*** 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 b.i.d., 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 related pharmacokinetic differences:*** 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 dysfunction:*** Tipranavir 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 dysfunction:*** In a study comparing 9 patients with mild (Child-Pugh A) hepatic impairment to 9 controls, the single and multiple dose pharmacokinetic disposition 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.

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 moderate or severe hepatic impairment (see CONTRAINDICATIONS).

## CLINICAL TRIALS

### Description of Clinical Studies

### Treatment Experienced Adult Patients

*Studies RESIST-1 and RESIST-2: APTIVUS/Ritonavir 500/200 mg b.i.d. + optimised background regimen (OBR) vs. Comparator protease inhibitor (PI)/Ritonavir b.i.d. + OBR*

The following clinical data are 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 studies evaluating the effect of APTIVUS/ritonavir on clinical progression of HIV.

RESIST-1 and RESIST-2 are ongoing, randomised, open-label, multicentre studies in HIV-positive, triple-class experienced patients, evaluating treatment with APTIVUS, co-administered with low-dose 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 (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 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 interim 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).

### Analysis of Efficacy of APTIVUS in Treatment-Experienced Patients

*- Efficacy data at 48 weeks*

Treatment response and outcomes of randomised treatment at week 48 are presented in Table 1 below.

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

| | **APTIVUS/RTV (500/200 mg b.i.d.) + OBR**<br><br>**n=746** | **Comparator PI/RTV*** + OBR**<br><br>**n=737** |
|---|---|---|
| Treatment Response* | 34.2 % | 15.5 % |
| - With New Enfuvirtide (patients) | 60.5 % (n=75/124) | 22.7 % (n=22/97) |
| - Without Enfuvirtide | 29.5 % (n=170/576) | 14.3 % (n=86/602) |
| Median HIV VL log change from baseline ($log_{10}$ copies/mL) | -0.64 | -0.22 |
| HIV VL <400 copies/mL | 30.3 % | 13.6 % |
| HIV VL <50 copies/mL | 22.7 % | 10.2 % |
| Median increase in CD4+ cell count (cells/$mm^3$) | 23 | 4 |
| Treatment Failure | 65.8 % | 84.5 % |
| Reasons for treatment failure | | |
| Death | 1.6 % | 0.7 % |
| Discontinued study drug or OBR change due to lack of efficacy | 12.5 % | 45.9 % |
| Virologic rebound | 23.1 % | 18.3 % |
| No confirmed virologic response | 49.5 % | 69.9 % |
| Discontinued due to any adverse event | 8.7 % | 4.7 % |
| Discontinued due to other reasons** | 6.0 % | 9.2 % |

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

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

*** Comparator PI/RTV: LPV/r 400/100 mg b.i.d., IDV/r 800/100 mg t.i.d., SQV/r 1000/100 mg b.i.d. or 800/200 mg b.i.d., APV/r 600/100 mg b.i.d.

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

*- Efficacy data at 96 weeks*

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 previously naïve to enfuvirtide, the median time to treatment failure was 587 days among APTIVUS/ritonavir treated patients and 60 days among CPI/ritonavir treated patients.

At 96 weeks, 26.4% of patients in the TPV/ritonavir group achieved a treatment response compared with 10.7% of patients in the comparator group (CPI/ritonavir group). Response rates were higher in both groups (45.2% in TPV/ritonavir, 16.5% in CPI/ritonavir) when new enfuvirtide was included in the treatment regimens compared to when no enfuvirtide was included in the treatment regimen (23.1% in TPV/ritonavir and 9.5% in CPI/ritonavir).

**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-associated 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 (Table 2).

**Table 2: 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-associated mutation score and ENF use in RESIST patients.**

| Number of Tipranavir-associated mutation scores | New ENF | | No New ENF[1] | |
|---|---|---|---|---|
| | 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 2) 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 3: Mean decrease in viral load from baseline to Week 48, according to tipranavir baseline mutation score and ENF use in RESIST patients.**

| Number of Tipranavir Score Mutations | New ENF | | No New ENF[1] | |
|---|---|---|---|---|
| | 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.

**Paediatric Patients**

Clinical information on paediatric patients is derived from analyses of 48-week data from ongoing clinical trial 1182.14, a randomised, open-label, multicentre study enrolling HIV-positive, paediatric patients. The primary objective was to compare the two dose regimens for safety and tolerability based on adverse reactions and laboratory findings. The secondary objectives were to evaluate pharmacokinetics, virologic and immunologic response including HIV-1 RNA levels and CD4% and CD4+ cell counts, and time to treatment failure at 48 weeks.

Participants were aged 2 to 18 years of age, with a baseline HIV-1 RNA concentration of at least 1,500 copies/mL. One hundred and fifteen (115) patients were stratified by age (2 to <6 years, 6 to <12 years and 12 to 18 years) and randomised to receive one of two APTIVUS/ritonavir dose regimens: 375 mg/m$^2$/150 mg/m$^2$ dose (N=57) or 290 mg/m$^2$/115 mg/m$^2$ dose (N=58). All patients initially received APTIVUS oral solution. Paediatric patients who were 12 years or older and received the maximum dose of 500/200 mg b.i.d. could subsequently change to APTIVUS capsules at day 28. Background therapy consisted of at least two non-protease inhibitors and was optimised using baseline genotypic resistance testing.

Demographics and baseline characteristics were balanced between the APTIVUS, co-administered with low-dose ritonavir, dose groups. All but three patients were treatment-experienced. The 115 randomised paediatric patients had a median age of 11.5 years (range 2 -18), and were 56.5% male, 69.6% white, 28.7% black and 1.7% Asian. The median baseline plasma HIV-1 RNA was 4.7 (range 3.0 to 6.8) $\log_{10}$ copies/mL and median baseline CD4+ cell count was 379 (range 2 to 2578) cells/mm$^3$, and the CD4% was 20.1% (range 0.6-44.0). Overall, 37.4% of patients had a baseline HIV-1 RNA of >100,000 copies/mL; 28.7% had a baseline CD4+ cell count ≤ 200 cells/mm$^3$, and 48% had experienced a prior AIDS defining Class C event at baseline. Patients had prior exposure to a median of 4 NRTIs, 1 NNRTI, and 2 PIs.

Eighty eight (76.5%) completed the 48 week period while 23.5% discontinued prematurely. Of the patients who discontinued prematurely, 9 (7.8%) discontinued due to virological failure and 10 (8.7%) discontinued due to adverse reactions.

At 48 weeks, 42.6% of patients had viral load <400 copies/mL. The proportion of patients with viral load <400 copies/mL tended to be larger (72.0%) in the youngest group of patients, who had less baseline viral resistance, compared to the older groups (36.8% and 32.7%). Among the older paediatric patients, who had greater baseline viral resistance, those receiving the 375 mg/m$^2$/150 mg/m$^2$ dose tended to have a higher likelihood of achieving a viral load <400 copies/mL at 48 weeks, compared to the 290 mg/m$^2$/115 mg/m$^2$ dose (Table 4).

**Table 4: Proportion of paediatric patients with <400 copies/mL RNA at 48 weeks by age group**

| APTIVUS/ritonavir Dose Regimen | 2 to <6 years | 6 to <12 years | 12 to 18 years | All |
|---|---|---|---|---|
| 290 mg/m$^2$/115 mg/m$^2$ and 375 mg/m$^2$/150 mg/m$^2$ | 72.0% | 36.8% | 32.7% | 42.6% |
| 290 mg/m$^2$/115 mg/m$^2$ | 76.9% | 31.6% | 26.9% | 39.7% |
| 375 mg/m$^2$/150 mg/m$^2$ | 66.7% | 42.1% | 38.5% | 45.6% |

Multivariate analysis results suggested that better adherence to treatment and higher genotypic inhibitory quotient (GIQs) were predictors of better response.

At 48 weeks for the 375 mg/m$^2$/150 mg/m$^2$ and 290 mg/m$^2$/115 mg/m$^2$ dose groups, the median changes from baseline in viral load were -1.24 copies/mL and -0.80 copies/mL, respectively, and the median changes from baseline in CD4+ cell count were 59 cells/mm$^3$ and 100 cells/mm$^3$ respectively, and for CD4% were 3% and 5%, respectively (Table 5).

**Table 5: Other efficacy parameter changes from baseline at week 48 by dose group**

| APTIVUS/ritonavir Dose Regimen | Median VL change $Log_{10}$ copies/mL | Median CD4+ increase cells/mm$^3$ | Median CD4% increase |
|---|---|---|---|
| 290 mg/m$^2$/115 mg/m$^2$ | -0.80 | 100 | 5 |
| 375 mg/m$^2$/150 mg/m$^2$ | -1.24 | 59 | 3 |

## INDICATIONS

APTIVUS (tipranavir), co-administered with low dose ritonavir, is indicated for combination treatment of HIV infection in antiretroviral treatment experienced patients from 2 years of age, with evidence of viral replication, who have HIV-1 strains resistant to more than one protease inhibitor.

In deciding to initiate therapy with APTIVUS/ritonavir, careful consideration should be given to treatment history of the individual patient and the patterns of mutations associated with different agents. Genotypic testing should be performed to guide the use of APTIVUS.

There are insufficient data in paediatric patients less than 2 years of age and treatment of these children with APTIVUS is therefore not recommended.

## CONTRAINDICATIONS

APTIVUS is contraindicated in patients with:

- known hypersensitivity to the active ingredient or any of the excipients,
- moderate or severe (Child-Pugh Class B or C) hepatic insufficiency,
- vardenafil is contraindicated with APTIVUS/ritonavir.

Co-administration of APTIVUS with low-dose 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 include:

- antiarrhythmics (such as amiodarone, bepridil, flecainide, propafenone, quinidine),
- antihistamines (such as astemizole, terfenadine),
- ergot derivatives (such as dihydroergotamine, ergonovine, ergotamine, methylergonovine),

- GI motility agents (such as cisapride),
- antipsychotics (such as pimozide and quetiapine),
- sedatives/hypnotics (such as orally administered midazolam and triazolam),
- alpha-1 adrenoceptor antagonist alfuzosin and sildenafil when used for the treatment of pulmonary arterial hypertension (see Interactions with other medicines).

Combination of HMG CoA reductase inhibitors (lovastatin, simvastatin) with APTIVUS with concomitant low dose ritonavir is contraindicated (see also Interactions with other medicines).

Combination of rifampicin (rifampin) with APTIVUS with concomitant low dose ritonavir is contraindicated (see also Interactions with other medicines).

Herbal preparations containing St. John's Wort (Hypericum perforatum) must not be used while taking APTIVUS, co-administered with low dose ritonavir, due to the risk of decreased plasma concentrations and reduced clinical effects of tipranavir (see also Interactions with other medicines).

Patients with rare hereditary conditions of fructose intolerance should not take APTIVUS capsules, as the capsules contain up to 50.4 mg sorbitol per maximum recommended daily dose.

Co-administration of colchicine with APTIVUS/ritonavir is contraindicated in patients with renal or hepatic impairment (see Interactions with other medicines).

## PRECAUTIONS

**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.**

APTIVUS must be administered with low-dose 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. Doses of ritonavir lower than 200 mg twice daily should not be used as they might affect efficacy of the combination.

Due to the need for co-administration of APTIVUS with low-dose ritonavir, please also refer to the ritonavir prescribing information for additional precautionary measures (such as contraindications, precautions/warnings, side effects and potential drug interactions for ritonavir).

Patients receiving APTIVUS or any other antiretroviral therapy may continue to develop opportunistic infections and other complications of HIV-1 infection. APTIVUS therapy has not been shown to reduce the risk of transmission of HIV-1 to others.

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.

**Hepatic Impairment and Toxicity:** Appropriate laboratory testing should be conducted prior to initiating therapy with APTIVUS and low-dose ritonavir, and frequently during treatment. Increased monitoring should be considered when APTIVUS and low-dose ritonavir are administered to patients with elevated baseline AST and ALT levels, or with 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.

If asymptomatic elevations in AST or ALT greater than 10X ULN occur, APTIVUS therapy should be discontinued.

If another cause is identified (e.g. acute hepatitis A, B or C virus, gallbladder disease, other medications), or if the potential benefit outweighs the risk, then rechallenge with APTIVUS may be considered when AST/ALT have returned to baseline levels.

If symptomatic hepatitis occurs APTIVUS therapy should be discontinued.

If another cause is identified (e.g. acute hepatitis A, B or C virus, gallbladder disease, other medications) then rechallenge with APTIVUS may be considered when AST/ALT have returned to baseline levels.

APTIVUS co-administered with low-dose 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 low dose ritonavir, could not be established. Patients with signs or symptoms of hepatitis should discontinue APTIVUS/ritonavir treatment and seek medical evaluation. Caution should be exercised when administering APTIVUS/ritonavir to patients with liver enzyme abnormalities or history of hepatitis.

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.

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

**Treatment-naïve patients:** In a study of treatment-naïve patients, 16.2% of patients experienced grade 3 or 4 ALT elevations while receiving APTIVUS, co-administered with low dose ritonavir, through week 48. The use of APTIVUS, co-administered with low dose ritonavir, in treatment-naïve patients infected with wild-type virus is not recommended.

**Haemophilia:** 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.

**Effects on Platelet Aggregation and Coagulation:** APTIVUS, co-administered with low dose 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 with 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 low dose ritonavir.

In rats, co-administration of a vitamin E derivative increased the bleeding effects of tipranavir (see Toxicological Studies). Analyses of Vitamin-K dependent coagulation factors was done on stored frozen K-EDTA plasma samples from adults treated with APTIVUS capsules (RESIST studies), and paediatric patients treated with APTIVUS capsules or oral solution

(Trial 1182.14). No effect was shown on Factor II, Factor VII, Factor V, or on prothrombin or activated partial thromboplastin times.

**Vitamin E Intake:** Patients taking APTIVUS oral solution should be advised not to take supplemental vitamin E as APTIVUS oral solution contains 116 IU/mL of vitamin E which is higher than the Recommended Daily Intake (adults 30 IU, paediatrics approximately 10 IU).

**Intracranial Haemorrhage:** APTIVUS, co-administered with low dose ritonavir, has been associated with fatal and non-fatal intracranial haemorrhage (ICH) among some patients, many of whom had other medical conditions or were receiving concomitant medications that may have caused or contributed to these events. No pattern of abnormal haematologic or 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.

An increased risk of ICH has previously been observed in patients with advanced HIV disease / AIDS such as those treated in the APTIVUS clinical trials. A cause of a relationship between APTIVUS and ICH has not been established.

**Diabetes Mellitus/Hyperglycaemia:** New onset diabetes mellitus, exacerbation of pre-existing diabetes mellitus and hyperglycaemia 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 hypoglycaemic agents for treatment of these events. In some cases, diabetic ketoacidosis has occurred.

In those patients who discontinued protease inhibitor therapy, hyperglycaemia 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 elevations:** Treatment with APTIVUS, co-administered with low-dose 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 (see Interactions with other medicines - for information on potential drug interactions with APTIVUS/ritonavir and HMG-CoA reductase inhibitors).

**Fat redistribution:** Combination antiretroviral therapy has been associated with the redistribution of body fat (lipodystrophy) in HIV infected patients. The long-term consequences of these events are currently unknown. Knowledge about the mechanism is incomplete. A connection between visceral lipomatosis and protease inhibitors and lipoatrophy and nucleoside reverse transcriptase inhibitors has been hypothesised. A higher risk of lipodystrophy has been associated with individual factors such as older age, and with drug related factors such as longer duration of antiretroviral treatment and associated metabolic disturbances. Clinical examination should include evaluation for physical signs of fat redistribution. Consideration should be given to the measurement of fasting serum lipids and blood glucose. Lipid disorders should be managed as clinically appropriate.

**Immune Reactivation Syndrome:** Immune reactivation syndrome has been reported in patients treated with combination antiretroviral therapy, including APTIVUS. During the initial phase of combination antiretroviral treatment, patients whose immune system response may develop an inflammatory response to indolent or residual opportunistic infections (such as Mycobacterium avium infection, cytomegalovirus, Pneumocystis pneumonia, tuberculosis, or reactivation of herpes simplex and herpes zoster), which may necessitate further evaluation and treatment. Autoimmune disorders (such as Graves' disease) have also been reported to occur in the setting of immune reactivation; however, the reported time to onset is more variable and these events can occur many months after initiation of treatment.

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

**Rash:** Mild to moderate rashes including urticarial rash, maculopapular rash, and possible photosensitivity have been reported in subjects receiving APTIVUS/ritonavir. In Phase II and III 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 generalised pruritus has been reported in both men and women receiving APTIVUS/ritonavir.

**Warnings on concomitant use with other drugs:** APTIVUS co-administered with low dose ritonavir can alter plasma exposure of other drugs and other drugs can alter plasma exposure of tipranavir and ritonavir (see CONTRAINDICATION; Interactions with other medicines).

**Effects on fertility:** In a fertility and early embryonic study conducted in rats at tipranavir oral gavage doses up to 1000 mg/kg/day (approximately 0.8-fold the human exposure at the adult clinical dose, based on AUC), no adverse effects on mating, fertility or early embryonic development were observed. Clinical data on fertility are not available for tipranavir.

**Carcinogenicity:** Long-term carcinogenicity bioassays in rats and mice have been completed. Tipranavir was evaluated for carcinogenic potential by oral gavage administration to mice and rats up to 104 weeks. Mice were administered 30, 150 and 300 mg/kg/day tipranavir, 150/40 mg/kg/day tipranavir/ritonavir in combination, or 40 mg/kg/day ritonavir. The incidences of hepatocellular adenomas, and adenomas and carcinomas combined were significantly increased in females at all doses, except the low dose of tipranavir. The incidences of these tumours were also increased in males at the high dose of tipranavir, and tipranavir/ritonavir in combination. The incidence of hepatocellular carcinoma was increased in females given the high-dose of tipranavir, and both sexes given tipranavir/ritonavir. Higher incidences of this tumour type with the combination were associated with higher drug exposure. This finding is probably specific to rodents, and is unlikely to have clinical relevance. Mouse systemic exposures (estimated AUCs) at all doses were lower than in humans at the recommended therapeutic dose. 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. Tumour incidences were not significantly increased in males. The incidence of follicular cell adenoma of the thyroid gland was increased in female rats at the highest dose of tipranavir. This finding is probably specific to rodents, and is unlikely to have clinical relevance. Rat systemic exposure at the highest dose (estimated AUCs) was approximately equal to that in humans at the recommended therapeutic dose.

**Genotoxicity:** Tipranavir showed no evidence of mutagenic or clastogenic activity in *in vitro* and *in vivo* genetic toxicology assays. These studies included Ames bacterial mutation assays in *Salmonella typhimurium* and *Escherichia coli*, unscheduled DNA synthesis assays in rat hepatocytes, an AS52/XPRT mammalian cell mutation assay, a chromosomal aberration assay in human peripheral lymphocytes, and *in vivo* micronucleus assays in mice and rats.

**Toxicological Studies:** In nonclinical studies in rats, tipranavir treatment induced dose-dependent changes in coagulation parameters (increased prothrombin time, increased activated partial thromboplastin times, and a decrease in some vitamin K dependent factors). In some rats, these changes led to bleeding in multiple organs and death. The co-administration of 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 nonclinical 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.

**Use in Pregnancy (Category B3):** No teratogenicity was detected in embryo-foetal development studies in pregnant rats and rabbits administered tipranavir gavage doses up to 1000 mg/kg/day and 150 mg/kg/day, respectively, at systemic exposures (AUCs) approximately 0.8-fold (rats) or 0.1-fold (rabbits) the exposure at the recommended adult clinical dose. However, foetal toxicity (decreased sternebrae ossification and body weights) was observed in rats at doses of 400 mg/kg/day (approximately 0.7-fold the adult clinical exposure) and above. No foetal toxicity was observed in rats and rabbits at respective tipranavir doses of 40 and 150 mg/kg/day, at approximately 0.2-fold and 0.1-fold the adult clinical exposure.

In a pre- and post-natal development study with tipranavir at oral gavage doses up to 1000 mg/kg/day in rats, no adverse effects were noted at 40 mg/kg/day (0.2-fold the adult clinical exposure, based on AUC), but growth inhibition of pups was observed at maternally toxic gavage doses of 400 (approximately 0.8-fold the clinical exposure) and 1000 mg/kg/day.

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 foetus.

**Use in Lactation:** 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. Tipranavir has been detected in the milk of lactating rats administered radiolabelled tipranavir by oral gavage.

**Use in Children:** Safety and efficacy in children less than 2 years of age has not been established.

**Warnings related to certain excipients:** 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.

**Effects on ability to drive and use 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.

**Information for patients:** 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.

## INTERACTIONS WITH OTHER MEDICINES

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 low-dose 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.

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

administered with ritonavir capsules demonstrated similar effects as APTIVUS capsules co-administrated with ritonavir.

There was no net effect on CYP2C9 or hepatic P-gp at first dose or steady state. There was no net effect after first dose on CYP1A2, but there was moderate induction at steady state. There was 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 P-gp activity was inhibited after first dose but there was no net effect at steady state.

APTIVUS is metabolised by CYP3A and is a P-gp substrate. Co-administration of tipranavir and agents that induce CYP3A and/or P-gp may decrease tipranavir concentrations and reduce its therapeutic effect. Co-administration of APTIVUS and medicinal products that inhibit P-gp may increase tipranavir plasma concentrations.

Drug interaction information for drugs that are likely to be co-administered with APTIVUS/ritonavir is summarised in Table 6 below.

**Table 6: Summary of Drug Interaction Information and relevant Clinical Comments for drugs likely to be co-administered with APTIVUS/ritonavir**

| Concomitant Drug Class/ Name | Effect on Concentration of Tipranavir (TPV) or Concomitant Drug | Clinical Comment |
|---|---|---|
| HIV-Antiviral Agents | | |
| **Fusion Inhibitors:** | | |
| Enfuvirtide | ↑ Tipranavir plasma trough concentration by approximately 45% | The co-administration of enfuvirtide with APTIVUS, co-administered with low-dose 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 | ↓ raltegravir AUC, $C_{max}$ and $C_{12}$ | Favourable efficacy data collected in phase III studies substantiate that APTIVUS/ritonavir may be co-administered with raltegravir without a dose adjustment. There were no serious adverse experiences or discontinuations due to study drug-related adverse experiences, and raltegravir coadministered with APTIVUS/ritonavir was generally well tolerated in healthy subjects. |
| **Nucleoside reverse transcriptase inhibitors:** | | |
| Abacavir | ↓ Abacavir AUC | APTIVUS, co-administered with low-dose ritonavir, decreases the AUC of abacavir by approximately 40%. The clinical relevance of the reduction in abacavir levels has not been established and a dosage adjustment of abacavir cannot be recommended at this time. |

| | | |
|---|---|---|
| Didanosine | ↓ Didanosine AUC | APTIVUS, co-administered with low-dose ritonavir, causes a reduction in the AUC of didanosine. The clinical relevance of the reduction in didanosine plasma levels has not been established. Dosing of enteric-coated didanosine and APTIVUS, co-administered with low-dose ritonavir, should be separated by at least 2 hours to avoid formulation incompatibility. |
| Lamivudine<br>Stavudine<br>Emtricitabine | No significant change in AUC of lamivudine, stavudine or emtricitabine. | APTIVUS, co-administered with low-dose ritonavir, does not cause a significant change in the AUC of lamivudine, stavudine or emtricitabine. No dosage adjustment of lamivudine, stavudine or emtricitabine is recommended. |
| Zidovudine (AZT) | ↓ Zidovudine AUC | APTIVUS, co-administered with low-dose ritonavir, decreases the AUC of zidovudine by 36%; with 500 mg/100 mg the reduction was 77%. |
| **Nucleotide reverse transcriptase inhibitors:** | | |
| Tenofovir | No significant change in plasma concentrations of tenofovir. | APTIVUS, co-administered with low-dose ritonavir, did not cause a significant change in the plasma concentrations of tenofovir. No dosage adjustment of tenofovir is recommended. |
| **Non-nucleoside reverse transcriptase inhibitors:** | | |
| Efavirenz | No significant impact on AUC and $C_{min}$ of efavirenz. | Steady-state efavirenz 600 mg q.d. co-administered with steady-state APTIVUS and low dose ritonavir (500/200 mg b.i.d.) 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 $C_{p12h}$ (19.2%). APTIVUS, co-administered with low-dose ritonavir, has no significant impact on the AUC and $C_{min}$ of efavirenz. |
| Nevirapine | ↓ Nevirapine AUC and $C_{min}$<br>↓ TPV AUC and $C_{min}$ | No significant interaction between APTIVUS, co-administered with low dose ritonavir and nevirapine was observed (Nevirapine AUC and $C_{min}$ decreased by approximately 10%; TPV AUC decreased by 15% and $C_{min}$ by <5%). Therefore no dose adjustments are necessary. |
| 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. |
| 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, but no dose adjustment is recommended. If APTIVUS/ritonavir is co-administered with rilpivirine, close monitoring and/or dose adjustment of either drug may be required. |

| | | |
|---|---|---|
| **Protease inhibitors (co-administered with low dose ritonavir):** | | |
| Amprenavir<br>Lopinavir<br>Saquinavir<br>Atazanavir | ↓ Amprenavir $C_{min}$<br>↓ Lopinavir $C_{min}$<br>↓ Saquinavir $C_{min}$<br>↓ Atazanavir $C_{min}$ | Concomitant use of APTIVUS, co-administered with low-dose ritonavir, with the protease inhibitors amprenavir, atazanavir, lopinavir or saquinavir (each co-administered with low-dose ritonavir), results in significant decreases in plasma concentrations of these protease inhibitors. Combining a protease inhibitor with APTIVUS/ritonavir is not recommended.<br><br>Patients receiving the combination of APTIVUS/amprenavir, both co-administered with low-dose ritonavir, may have an increased risk of Grade 3/4 hepatic transaminase elevations.<br><br>In a clinical study of dual-boosted protease inhibitor combination therapy in multiple-treatment experienced HIV-positive adults, APTIVUS, co-administered with low dose 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. Therefore the concomitant administration of APTIVUS, co-administered with low dose ritonavir, with amprenavir/ritonavir, atazanavir/ritonavir, lopinavir/ritonavir or saquinavir/ritonavir, is not recommended, as the clinical relevance of the reduction in their levels has not been established. If concomitant administration is considered absolutely necessary no dose adjustments can be recommended at this time.<br><br>No data are currently available on interactions of APTIVUS, co-administered with low-dose ritonavir, with protease inhibitors other than those listed above. |
| **Alpha 1-adrenoreceptor antagonist:** | | |
| Alfuzosin | ↑ Alfuzosin | Tipranavir coadministered with ritonavir and concomitant use with alfuzosin results in increased alfuzosin concentrations and may result in hypotension. |
| Other Agents for Opportunistic Infections | | |
| **Antifungals:** | | |
| Fluconazole | No substantial effects on steady state pharmacokinetics of Fluconazole;<br>↑ TPV AUC and $C_{min}$ | APTIVUS, co-administered with low-dose ritonavir, does not substantially affect the steady-state pharmacokinetics of fluconazole. Fluconazole increases the AUC and $C_{min}$ of tipranavir by 56% and 104%, respectively, when compared to historical data. No dosage adjustments are recommended. Fluconazole doses >200 mg/day are not recommended. |

| | | |
|---|---|---|
| Itraconazole<br>Ketoconazole | Combination with TPV/ritonavir not studied.<br>↑ Itraconazole<br>↑ Ketoconazole | Based on theoretical considerations APTIVUS, co-administered with low-dose ritonavir, is expected to increase itraconazole or ketoconazole concentrations. Itraconazole and ketoconazole should be used with caution (doses >200 mg/day are not recommended). |
| Voriconazole | Combination with TPV/ritonavir not studied.<br>↕ Voriconazole | Due to multiple CYP isoenzyme systems involved in voriconazole metabolism, it is difficult to predict the interaction with APTIVUS, co-administered with low-dose ritonavir. |
| **Antimycobacterials:** | | |
| Clarithromycin | ↑ TPV $C_{min}$<br>↑ Clarithromycin AUC and $C_{min}$<br>↓ 14-hydroxy-clarithromycin metabolite AUC. | APTIVUS, co-administered with low-dose ritonavir, increases the AUC and $C_{min}$ of clarithromycin by 19% and 68%, respectively, and decreases the AUC of the 14-hydroxy active metabolite by over 95%. These changes are not considered clinically relevant. Clarithromycin increases the $C_{min}$ of tipranavir by more than 100%. This large increase in $C_{min}$ may be clinically relevant.<br><br>Patients using clarithromycin at doses of 500 mg b.i.d or higher should be carefully monitored for signs of toxicity.<br>For patients with renal impairment the following dosage adjustments should be considered:<br>• For patients with $CL_{CR}$ 30 to 60 mL/min the dose of clarithromycin should be reduced by 50%.<br>• For patients with $CL_{CR}$ < 30 mL/min the dose of clarithromycin should be decreased by 75%.<br>No dose adjustment for patients with normal renal function is necessary. |
| Rifabutin | ↑ TPV $C_{min}$<br>↑ Rifabutin plasma concentrations<br>↑ 25-O-desacetyl-rifabutin active metabolite | APTIVUS, co-administered with low-dose ritonavir, increases plasma concentrations of rifabutin by up to 3 fold, and the 25-O-desacetyl-rifabutin active metabolite by up to 20 fold. Rifabutin increases the $C_{min}$ of tipranavir by 16%.<br>Dosage reductions of rifabutin by at least 75% of the usual 300 mg/day dose are recommended (i.e. 150 mg on alternate days, or three times per week). Patients receiving rifabutin with APTIVUS/ritonavir should be closely monitored for emergence of adverse events associated with rifabutin therapy. Further dosage reduction may be necessary. |
| Rifampicin | Combination with TPV/ritonavir not studied.<br>↓ TPV levels | Concomitant use of APTIVUS and rifampicin is contraindicated.<br>Co-administration of protease inhibitors, including APTIVUS, with rifampicin 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. |
| Other Agents Commonly used | | |
| **CYP isoenzyme inhibitors:** | | |
| Cobicistat and cobicistat-containing products | | APTIVUS/ritonavir should not be administered concomitantly with cobicistat or cobicistat-containing products. Cobicistat significantly inhibits hepatic enzymes, as well as other metabolic pathways. When co-administered, tipranavir and cobicistat exposures are markedly lower compared to that of tipranavir when boosted with low dose ritonavir. |

| | | |
|---|---|---|
| **Anti-HCV agents:** | | |
| Boceprevir | | 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 | | Co-administration of APTIVUS and telaprevir has not been studied. Telaprevir is metabolised in the liver by CYP3A and is a P-glycoprotein (P-gp) substrate, but other enzymes may be involved in the metabolism. When co-administered 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. |
| **Anti-gout:** | | |
| Colchicine | | Co-administration of colchicines with drugs known to inhibit CYP3A4 and/or p-glycoprotein (P-gp) increases the risk of colchicines toxic effects.<br><br>Colchicine is a substrate of CYP3A4 and P-gp. In combination with APTIVUS/ritonavir a dose reduction of colchicine or an interruption of colchicine treatment is recommended in patients with normal renal and hepatic function. For treatment of gout flares, the recommended colchicine dose in patients receiving APTIVUS/ritonavir is 0.6 mg (1 tablet), followed by 0.3 mg (half tablet) 1 hour later. The next dose of colchicine (0.6 mg, 1 tablet) should be taken after 72 hours at the earliest.<br><br>In patients with renal or hepatic impairment, co-administration of colchicine in patients on APTIVUS/ritonavir is contraindicated. |
| **Antidepressants:** | | |
| Desipramine | Combination with TPV/low-dose ritonavir not studied.<br>↑ Desipramine | Dosage reduction and concentration monitoring of desipramine is recommended. |
| Trazadone | Combination with TPV/low-dose ritonavir not studied.<br>↑ Trazadone | Concomitant use of trazadone and APTIVUS co-administered with low dose ritonavir may increase plasma concentrations of trazadone. Adverse events of nausea, dizziness, hypotension, and syncope have been observed following co-administration of trazadone and ritonavir. If trazadone is used with APTIVUS/ritonavir, the combination should be used with caution and a lower dose of trazadone should be considered. |

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| **Selective Serotonin-Reuptake Inhibitors (SSRIs):** | | |
| Fluoxetine<br>Paroxetine<br>Sertraline | Combination with TPV/ritonavir not studied.<br>↑ Fluoxetine<br>↑ Paroxetine<br>↑ Sertraline | Doses of SSRIs may need to be adjusted upon initiation of APTIVUS/ritonavir therapy as SSRI concentration is expected to increase. |
| Disulfiram/ Metronidazole | Combination with TPV/ritonavir not studied. | APTIVUS soft 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 | | In normal volunteers, co-administration of bosentan 125 mg twice daily and lopinavir/ritonavir 400/100 mg twice daily increased the trough concentrations of bosentan on Days 4 and 10 approximately 48-fold and 5-fold, respectively, compared with those measured after bosentan administered alone. Therefore, adjust the dose of bosentan when initiating ritonavir combination products.<br><br>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.<br><br>In patients who are currently not receiving APTIVUS/ritonavir: 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:** | | |
| Atorvastatin | No significant change in TPV AUC, $C_{max}$ or $C_{min}$;<br>↑ Atorvastatin plasma concentrations<br>↓ Hydroxyl-atorvastatin metabolites AUCs | Caution must also be exercised and the lowest possible doses of atorvastatin should be considered if APTIVUS, co-administered with low-dose ritonavir, is used concurrently with atorvastatin, which is metabolised to lesser extent by CYP3A4. The use of HMG-CoA reductase inhibitors other than atorvastatin should be considered.<br>APTIVUS, co-administered with low-dose ritonavir, increases the plasma concentrations of atorvastatin by approximately 8-10 fold and reduces the AUCs of the hydroxyl-metabolites by approximately 85%. Atorvastatin does not significantly change the AUC, $C_{max}$ or $C_{min}$ of tipranavir.<br>Co-administration of atorvastatin and APTIVUS/ritonavir is not recommended. In cases where co-administration is necessary, the dose of 10 mg atorvastatin daily should not be exceeded. It is recommended to start treatment with the lowest possible dose of atorvastatin with careful clinical monitoring or consider other HMG-CoA reductase inhibitors such as pravastatin, fluvastatin or rosuvastatin. |

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| Lovastatin<br>Simvastatin | Combination with TPV/ritonavir not studied. | The HMG-CoA reductase inhibitors simvastatin and lovastatin are highly dependent on CYP3A4 for metabolism, thus concomitant use of APTIVUS, co-administered with low-dose ritonavir with these medicinal products is not recommended due to an increased risk of myopathy, including rhabdomyolysis. |
| Rosuvastatin | ↑ Rosuvastatin AUC by 37% and $C_{max}$ by 123% | Co-administration of APTIVUS/ritonavir and rosuvastatin should be initiated with the lowest dose (5 mg/day) of rosuvastatin, titrated to treatment response, and accompanied with careful clinical monitoring for rosuvastatin associated symptoms. |
| Pravastatin | Combination with TPV/ritonavir 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 mg/day) with careful monitoring for pravastatin associated symptoms. |
| **Hypoglycaemics:** | | |
| Glimepiride<br>Glipizide<br>Glibenclamide<br>Pioglitazone<br>Repaglinide<br>Tolbutamide | Combination with TPV/ritonavir not studied.<br>↕ Glimepiride (CYP 2C9)<br>↕ Glipizide (CYP 2C9)<br>↕ Glibenclamide (CYP 2C9)<br>↕ Pioglitazone (CYP 2C8 and CYP 3A4)<br>↕ Repaglinide (CYP 2C8 and CYP 3A4)<br>↕ Tolbutamide (CYP 2C9) | The effect of TPV/ritonavir on CYP 2C8 and CYP 2C9 substrates is not known.<br>Careful glucose monitoring is warranted. |
| **Proton Pump Inhibitors:** | | |
| Omeprazole | ↓ Omeprazole AUC and $C_{max}$ by 71 and 73% | APTIVUS, co-administered with low-dose ritonavir, decreases the AUC and $C_{max}$ of omeprazole by 71% and 73% respectively. No clinically important changes in tipranavir/ritonavir at steady state were observed. The dosage of omeprazole may need to be increased when co-administered with APTIVUS and ritonavir. |
| **Immunosuppressants:** | | |
| Ciclosporin<br>Sirolimus<br>Tacrolimus | Combination with TPV/ritonavir not studied. Cannot predict effect of TPV/ritonavir on immunosuppressants due to conflicting effect of TPV/ritonavir on CYP 3A and P-gp.<br><br>↕ Ciclosporin<br>↕ Sirolimus<br>↕ Tacrolimus | The effect of co-administration of APTIVUS with low dose ritonavir on a substrate for CYP3A4/5 showed potent inhibition at both first-dose and steady-state APTIVUS/ritonavir. When APTIVUS with low dose 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. Monitoring the concentrations of these immunosuppressants is recommended when these medicinal products are combined with APTIVUS/ritonavir. |

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| **Inhaled / nasal steroids:** | | |
| Fluticasone propionate | ↑ Fluticasone | A drug interaction study in healthy subjects has shown that ritonavir significantly increases plasma fluticasone propionate levels, resulting in significantly decreased serum cortisol concentrations. Concomitant use of APTIVUS,co-administered with low dose 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. |
| Loperamide | ↓ TPV $C_{min}$<br>↓ Loperamide AUC and $C_{max}$ | A 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. 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. |
| **Inhaled beta agonist:** | | |
| Salmeterol | | Concurrent administration of APTIVUS/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:** | | |
| Methadone | ↓ Methadone AUC and $C_{max}$ | Co-administration of APTIVUS and low-dose ritonavir with single dose methadone results in approximately 50% reductions in methadone concentrations (AUC and $C_{max}$). Therefore in such cases, patients should be monitored for opiate withdrawal syndrome. Dosage of methadone may need to be increased. |
| Pethidine | Combinations with TPV/ritonavir not studied.<br>↓ Pethidine<br>↑ Norpethidine metabolite | APTIVUS, co-administered with low-dose ritonavir, is expected to decrease pethidine concentrations and increase norpethidine metabolite concentrations. Dosage increase and long-term use of pethidine with APTIVUS, co-administered with low-dose ritonavir, are not recommended due to increased concentrations of the metabolite norpethidine which has both analgesic activity and CNS stimulant activity (e.g. seizures). |
| Buprenorphine/ naloxone | ↓ TPV $C_{min}$ by 39% | Co-administration of buprenorphine/naloxone with APTIVUS/ritonavir did not result in changes in the clinical effect of buprenorphine/naloxone.<br><br>The clinical relevance of change in plasma concentration of tipranavir is unknown. |

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| **Sedatives/Hypnotics:** | | |
| Midazolam | ↑ Midazolam | Concomitant use of APTIVUS/ritonavir and oral midazolam is contraindicated. 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 ($AUC_{0-24h}$) when co-administered with APTIVUS/ritonavir at steady state. If APTIVUS/ritonavir is co-administered with parenteral midazolam, close clinical monitoring for respiratory depression and/or prolonged sedation should be instituted and dosage adjustment should be considered. |
| **Anticonvulsants:** | | |
| Carbamazepine, Phenobarbital, Phenytoin | Combinations with TPV/ritonavir not studied.<br><br>↓ Tipranavir | Carbamazepine, phenobarbital and phenytoin should be used with caution in combination with APTIVUS/ritonavir. Concomitant use of carbamazepine at a dose of 200 mg B.I.D. 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 controls), which may result in decreased effectiveness. Caution should be used when prescribing carbamazepine, phenobarbital or phenytoin. APTIVUS may be less effective due to decreased tipranavir plasma concentration in patients taking these agents concomitantly. |
| **Antipsychotics:** | | |
| Pimozide, sertindole and quetiapine | | Co-administration of APTIVUS/ritonavir with pimozide, sertindole or quetiapine is contraindicated due to CYP3A inhibition by APTIVUS/ritonavir, which may lead to serious life-threatening events including coma. |
| **Nucleoside analogue DNA polymerase inhibitor:** | | |
| Valaciclovir | | Co-administration of valaciclovir, APTIVUS and ritonavir in HIV-negative adults was not associated with clinically relevant pharmacokinetic effects. However, an increase of (up to grade 4) hepatic transaminases and/or discontinuations due to study drug-related adverse experiences was observed in these subjects.<br><br>Therefore, these agents can be co-administered without dose adjustment. Monitoring of clinical laboratory parameters is beneficial when co-administration of valaciclovir, with tipranavir and ritonavir in HIV-infected patients. |

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| **Oral contraceptives/Oestrogens:** | | |
| Ethinyl estradiol | ↓ Ethinyl estradiol AUC and $C_{max}$ | APTIVUS, co-administered with low-dose ritonavir, decreases the AUC and $C_{max}$ of ethinyl estradiol by 50%, but does not significantly alter the pharmaco-kinetic behaviour of norethindrone.<br><br>Since levels of ethinyl estradiol are decreased alternative or additional contraceptive measures are to be used when oestrogen based oral contraceptives are co-administered with APTIVUS, co-administered with low-dose ritonavir.<br><br>Patients using oestrogens as hormone replacement therapy should be clinically monitored for signs of oestrogen deficiency.<br><br>It should be noted that other compounds that are substrates of CYP3A might have increased plasma concentrations when co-administered with APTIVUS and low-dose ritonavir.<br><br>Women using oestrogens may have an increased risk of non serious rash. |
| **Phosphodiesterase (PDE5) inhibitors:** | | |
| Sildenafil<br>Tadalafil<br>Vardenafil | Combinations with TPV/ritonavir not studied.<br>↑ Sildenafil<br>↑ Tadalafil<br>↑ Vardenafil | Particular caution should be used when prescribing in patients receiving APTIVUS.<br><br>Co-administration of APTIVUS and low-dose ritonavir with PDE5 inhibitors is expected to substantially increase PDE5 inhibitors concentrations and may result in an increase in PDE5 inhibitor-associated adverse events including hypotension, visual changes and priapism. Particular caution should be used when prescribing phosphodiesterase (PDE5) inhibitors (e.g. sildenafil, vardenafil or tadalafil) in patients receiving APTIVUS, co-administered with low-dose ritonavir and in no case should the starting dose of:<br><br>• Sildenafil exceed 25 mg within 48 hours<br>• Tadalafil exceed 10 mg every 72 hours.<br><br>Vardenafil is contraindicated with APTIVUS/ritonavir.<br><br>Concomitant use of APTIVUS, co-administered with low dose ritonavir, and tadalafil resulted in a 2.3 fold increase in tadalafil exposure with first-dose APTIVUS/ritonavir and no change in tadalafil exposure with steady-state APTIVUS/ritonavir. If tadalafil is used within the first days of APTIVUS/ ritonavir treatment, then the lowest tadalafil dose should be administered. However, after 7-10 days of APTIVUS/ritonavir dosing, steady-state for tipranavir and ritonavir is achieved and the dose of tadalafil may be increased, as clinically necessary.<br><br>A safe and effective dose has not been established when sildenafil is used with APTIVUS/ritonavir. There is increased potential for sildenafil-associated adverse events (which include visual disturbances, hypotension, prolonged erection, and syncope). Co-administration APTIVUS/ritonavir with sildenafil when used to treat pulmonary arterial hypertension is contraindicated. |

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| St. John's Wort (Hypericum perforatum) | Combinations with TPV/ritonavir not studied.<br>↓ TPV | Concomitant use of APTIVUS and St. John's Wort (Hypericum perforatum), or products containing St. John's Wort, is contraindicated. 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. |
| Theophylline | Combinations with TPV/ritonavir not studied.<br>↓ 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 | Combination with TPV/ritonavir not studied.<br>Cannot predict the effect of TPV/ritonavir on S-warfarin due to conflicting effect of TPV and ritonavir on CYP 2C9. | The effect of co-administration of APTIVUS with low dose ritonavir on S-warfarin resulted in an 18% increase in S-warfarin exposure with first-dose APTIVUS/ritonavir, and a 12% decrease in S-warfarin exposure with steady-state APTIVUS/ritonavir. Clinical and biological (INR measurement) monitoring is recommended when these medicinal products are combined. |
| Bupropion | ↓ Bupropion $C_{max}$ and AUC by approximately 50% | Careful clinical monitoring should be recommended when combining these three drugs. |

It should be noted that other compounds that are substrates of CYP3A might have increased plasma concentrations when co-administered with APTIVUS and 200 mg ritonavir.

## ADVERSE EFFECTS

### Adults:

APTIVUS, co-administered with low-dose ritonavir has been studied in a total of 6308 HIV-positive adults as combination therapy in clinical studies. Of these, 1299 treatment-experienced patients received the dose of 500 mg/200 mg b.i.d. in clinical trials. 909 of these treatment-experienced 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 (see Description of Clinical Studies).

In RESIST-1 and RESIST-2 in the APTIVUS/ritonavir arm, the most frequent adverse events were diarrhoea/loose stools, nausea, headache, pyrexia, vomiting, fatigue and abdominal pain. At 48 weeks, the probability estimate (Kaplan-Meier probability estimates) for time to first adverse event leading to discontinuation of study medication was 13.3% for APTIVUS/ritonavir treated patients and 10.8% for the comparator arm patients.

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

- 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 (including hypertriglyceridaemia and hypercholesterolaemia): 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.

The most frequent adverse reactions of any intensity (Grades 1-4) reported in the Phase III clinical studies in the APTIVUS/ritonavir arms (n=749) are listed below by system organ class and frequency according to the following categories:

Very common ≥ 1/10, Common ≥ 1/100 – <1/10.

Metabolism and nutrition disorders:

Common: hypertriglyceridaemia, hyperlipidaemia, decreased appetite

Nervous system disorders:

Common: headache

Gastro-intestinal disorders:

Very common: diarrhoea, nausea
Common: vomiting, flatulence, abdominal distension, abdominal pain, dyspepsia

Skin and subcutaneous tissue disorders

Common: rash, pruritus

General disorders

Common: fatigue

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 twice daily (n=1397) are listed below by system organ class and frequency according to the following categories:

Uncommon ≥ 1/1000 – <1/100; Rare ≥ 1/10000 – <1/1000

Blood and lymphatic system disorders:

Uncommon: anaemia, neutropenia, thrombocytopenia

Immune system disorders:

Uncommon: hypersensitivity

Metabolism and nutrition disorders:

Uncommon: diabetes mellitus, hyperamylasaemia, hypercholesterolaemia, hyperglycaemia

Rare: dehydration, facial wasting

Psychiatric disorders:

Uncommon: insomnia, sleep disorder

Nervous system disorders:

Uncommon: intracranial hemorrhage, dizziness, neuropathy peripheral, somnolence

Respiratory, thoracic and mediastinal disorders:

Uncommon: dyspnoea

Gastrointestinal disorders:

Uncommon: gastro oesophageal reflux disease, pancreatitis

Hepatobiliary disorders:

Uncommon: hepatitis, toxic hepatitis, hepatic steatosis

Rare: hepatic failure (including fatal outcome), hyperbilirubinaemia

Skin and subcutaneous system disorders:

Uncommon: exanthem, lipoatrophy, lipodystrophy acquired, lipohypertrophy

Musculoskeletal and connective tissue disorders:

Uncommon: muscle spasms, myalgia

Renal and urinary disorders:

Uncommon: renal failure

General Disorders:

Uncommon: influenza like illness, malaise, pyrexia

Investigations:

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

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

In addition the following events were observed as well: Asthenia, bronchitis, depression and cough.

Laboratory Abnormalities

Frequencies of marked clinical laboratory abnormalities (Grade 3 or 4) reported in at least 2% of patients in the APTIVUS/ritonavir 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 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. The Kaplan-Meier probability estimate for the first occurrence of Grade 3/4 ALT and/or AST elevations continued to increase from 10.0% at week 48 to 14.7% at week 96 for APTIVUS/ritonavir, and from 3.4% to 4.5% at weeks 48 and 96 for comparator PI/ritonavir, respectively.

**Table 7 Summary of Grade 3 and 4 (Combined) Laboratory Abnormalities Reported in ≥ 2% of Adult Patients**

| Laboratory Test | RESIST-1 / RESIST-2 (48 weeks) | |
|---|---|---|
| | Tipranavir/RTV Group[a] (n = 738) % Patients[c] | Comparator PI/RTV Group[b] (n = 724) % Patients[c] |
| *Hematology* | | |
| WBC count (decrease) | 5.7 | 5.9 |
| *Chemistry* | | |
| ALT | 9.6 | 2.1 |
| AST | 6.1 | 1.8 |
| ALT and/or AST | 10.3 | 2.9 |
| Amylase | 6.0 | 7.0 |
| Lipase | 2.8 | 2.6 |
| Total cholesterol | 4.2 | 0.4 |
| Triglycerides | 24.9 | 13.0 |

[a] Tipranavir/RTV 500/200 mg b.i.d..
[b] Comparator PI/RTV doses are LPV/r 400/100 mg b.i.d., IDV/r 800/100 mg t.i.d., SQV/r 1000/100 mg b.i.d. or SQV/r 800/200 mg b.i.d., APV/r 600/100 mg b.i.d.
[c] Total combined number of patients with Grade 3 or 4 abnormality as worst intensity.

**Paediatrics:**

APTIVUS, co-administered with low-dose ritonavir, has been studied in 115 HIV-infected paediatric patients 2 through 18 years of age in clinical trial 1182.14. During the first 48 weeks of treatment, 58 paediatric patients were randomised to tipranavir/ritonavir doses of 290 mg/m$^2$/115 mg/m$^2$ b.i.d. and 57 were randomised to tipranavir/ritonavir doses of 375 mg/m$^2$/150 mg/m$^2$ b.i.d.. All paediatric patients except three were treatment-experienced.

The most frequent adverse reactions were similar to those described in adults and the frequency of most adverse reactions tended to be lower in paediatrics. Vomiting and rash were more frequent in paediatrics than in adults.

The most frequent treatment-emergent laboratory abnormalities were similar to those seen in adults.

## DOSAGE AND ADMINISTRATION

APTIVUS must be co-administered with low-dose ritonavir to ensure its therapeutic effect. Patients should be instructed accordingly. 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. Please also refer to the ritonavir prescribing information for contraindications, warnings, side effects and potential drug interactions.

APTIVUS must be co-administered with low-dose ritonavir which should be administered with food.

APTIVUS, co-administered with low-dose ritonavir, should be taken with at least two additional antiretroviral agents. The manufacturers' prescribing information of the antiretroviral agents should be followed.

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

**Paediatrics:** The recommended dose of APTIVUS for children 2 years of age or older is 375 mg/m$^2$ co-administered with ritonavir 150 mg/m$^2$ taken twice daily not to exceed a maximum

dose of APTIVUS 500 mg co-administered with ritonavir 200 mg twice daily. For children who develop intolerance or toxicity and cannot continue with APTIVUS 375 mg/$m^2$ with 150 mg/$m^2$ ritonavir, physicians may consider decreasing the dose to APTIVUS 290 mg/$m^2$ co-administered with 115 mg/$m^2$ ritonavir taken twice daily provided their virus is not resistant to multiple protease inhibitors.

To calculate the BSA in $m^2$ use the Mosteller formula given below:

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

## OVERDOSAGE

There is no known antidote for APTIVUS overdose. Treatment of overdose should consist of general supportive measures.

In case of poisoning or overdose, advice should be sought from the Poisons Information Centre on 131126 (Australia).

## PRESENTATION AND STORAGE CONDITIONS

APTIVUS (tipranavir) 250 mg capsules are pink, oblong, soft gelatine capsules imprinted in black with “TPV 250”. The capsules are available in a plastic bottle. Each bottle contains 120 capsules.

APTIVUS (tipranavir) 250 mg capsules should be stored at 2°C to 8°C (Refrigerate. Do not freeze). After first opening of the bottle, the capsules may be stored below 25°C and must be used within 60 days.

APTIVUS (tipranavir) 100 mg/mL oral solution* is a yellow viscous clear liquid. The oral solution is available as bottles of 95 mL of solution, with a 5 mL dispensing syringe and bottle-syringe adapter.

APTIVUS oral solution* should be stored at 15°C to 30°C. Do not refrigerate or freeze. After first opening the bottle, the oral solution should be used within 60 days.

* not currently distributed in Australia

## NAME AND ADDRESS OF THE SPONSOR

Boehringer Ingelheim Pty Limited

ABN 52 000 452 308

78 Waterloo Road

North Ryde NSW 2113

## POISON SCHEDULE OF THE MEDICINE

S4 – Prescription Only Medicine

**DATE OF FIRST INCLUSION IN THE AUSTRALIAN REGISTER OF THERAPEUTIC GOODS (THE ARTG)**

| | |
|---|---|
| APTIVUS tipranavir 250 mg soft capsule bottle | 8 June 2006 |
| APTIVUS tipranavir 100 mg/mL oral solution bottle | 26 October 2009 |

**DATE OF MOST RECENT AMENDMENT**

24 October 2016