

New pediatric dosing information for Aptivus, patients 2-18 years of age, approval of New Oral Solution and information on coadministration with midazolam

Aptivus (tipranavir) is now available as an oral solution (100 mg/mL). The label was updated to include dosing recommendations for pediatric patients 2-18 years of age. In addition, information regarding oral and parenterally administered midazolam was updated in the Contraindication and Drug Interactions section.

Pediatric Patient Information:

The dose selection for children ages 2-18 years of age including possible dose reduction was based on the following information. This information is also contained in section 14.2 Pediatric Studies

- A greater proportion of patients receiving APTIVUS/ritonavir 375 mg/m²/150 mg/m² compared to 290 mg/m²/115 mg/m² achieved HIV-1 RNA < 400 and < 50 copies/mL.
- A greater proportion of patients 6 to 18 years of age with multiple baseline protease inhibitor resistance-associated substitutions receiving APTIVUS/ritonavir 375 mg/m²/150 mg/m² achieved HIV-1 RNA < 400 copies/mL at 48 weeks compared to patients receiving APTIVUS/ritonavir 290 mg/m²/115 mg/m².
- No clinically significant increase in adverse event rates observed with 375 mg/m²/150 mg/m² compared to 290 mg/m²/115 mg/m²
- Overall, 6 (5%) patients ages 6 to 18 had AIDS defining illness during the treatment period and all received the 290 mg/m²/115 mg/m² dose.

The guidance for possible dose reduction for patients who develop intolerance or toxicity and cannot continue with APTIVUS/ritonavir 14 mg/kg/6 mg/kg (or 375 mg/m²/150 mg/m²) is based on the following:

- The 290 mg/m²/115 mg/m² twice daily regimen provided tipranavir plasma concentrations similar to those obtained in adults receiving 500/200 mg twice-daily. The 375 mg/m²/150 mg/m² twice daily regimen provided tipranavir plasma concentrations 37% higher than those obtained in adults receiving 500/200 mg twice-daily.
- The observed response rates for APTIVUS/ritonavir dose of 290 mg/m²/115 mg/m²

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

Dosing in children (2 – 18 years of age) is based on body weight or body surface area (size). The Dosage and Administration section 2.2 Pediatric Patients was updated to include the following.

APTIVUS must be co-administered with ritonavir and can be taken with or without food

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

2.2 Pediatric Patients (age 2 to 18 years)

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

Prescribers should calculate the appropriate dose of APTIVUS for each individual child based on body weight (kg) or body surface area (BSA, m²) and should not exceed the recommended adult dose.

Before prescribing APTIVUS 250 mg capsules, children should be assessed for the ability to swallow capsules. If a child is unable to reliably swallow an APTIVUS capsule, the APTIVUS oral solution formulation should be prescribed.

The recommended pediatric dose of APTIVUS is 14 mg/kg with 6 mg/kg ritonavir (or 375 mg/m² co-administered with ritonavir 150 mg/m²) taken twice daily not to exceed a maximum dose of APTIVUS 500 mg co-administered with ritonavir 200 mg twice daily. For children who develop intolerance or toxicity and cannot continue with APTIVUS 14 mg/kg with 6 mg/kg ritonavir, physicians may consider decreasing the dose to APTIVUS 12 mg/kg with 5 mg/kg ritonavir (or APTIVUS 290 mg/m² co-administered with 115 mg/m² ritonavir) taken twice daily provided their virus is not resistant to multiple protease inhibitors. [See *Adverse Reactions (6.2)*, *Use in Specific Populations (8.4)* and *Clinical Studies (14.2)*].

Body surface area can be calculated as follows:

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

Section 5 Warnings and Precautions subsection 5.4 Effects on Platelet Aggregation and Coagulation was updated as follows:

In rats, tipranavir treatment alone induced dose-dependent changes in coagulation parameters, bleeding events and death. Co-administration with vitamin E significantly increased these effects. However, analyses of stored

plasma from adult patients treated with APTIVUS capsules and pediatric patients treated with APTIVUS oral solution (which contains a vitamin E derivative) showed no effect of APTIVUS/ritonavir on vitamin K-dependent coagulation factors (Factor II and Factor VII), Factor V, or on prothrombin or activated partial thromboplastin times.

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

A new Warning and Precaution was added for patients receiving the oral solution formulation.

5.5 Vitamin E Intake

Patients taking APTIVUS oral solution should be advised not to take supplemental vitamin E greater than a standard multivitamin as APTIVUS oral solution contains 116 IU/mL of vitamin E which is higher than the Reference Daily Intake (adults 30 IU, pediatrics approximately 10 IU).

Subsection 5.6 Rash was revised to include rash information in children

In the pediatric clinical trial, the frequency of rash (all grades, all causality) through 48 weeks of treatment was 21%. Overall, most of the pediatric patients had mild rash and 5 (5%) had moderate rash. Overall 3% of pediatric patients interrupted APTIVUS treatment due to rash and the discontinuation rate for rash in pediatric patients was 0.9%.

The following information was added to section 6 Adverse Reactions subsection 6.2 Pediatric Patients - Clinical Trials Experience

6.2 Clinical Trials in Pediatric Patients

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

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

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

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

The following information was added to Section 8 Use in Specific Populations subsection 8.4 Pediatric Use

The safety, pharmacokinetic profile, and virologic and immunologic responses of APTIVUS oral solution and capsules were evaluated in HIV-1 infected pediatric patients age 2 to 18 years.

The most frequent adverse reactions (grades 2-4) were similar to those described in adults. However, rash was reported more frequently in pediatric patients than in adults

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

Section 12.3 Pharmacokinetics was updated as follows

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

Table 6 Pharmacokinetic Parameters^a of tipranavir/ritonavir 375 mg/m²/150 mg/m² for HIV-1 Positive Pediatric Patients by Age

Parameter	2 to <6 years (n=12)	6 to <12 years (n=8)	12 to 18 years (n=6)
C _p trough (μM)	59.6 ± 23.6	66.3 ± 12.5	53.3 ± 32.4
C _{max} (μM)	135 ± 44	151 ± 32	138 ± 52
T _{max} (h)	2.5	2.6	2.7
AUC _{0-12h} (μM•h)	1190 ± 332	1354 ± 256	1194 ± 517
CL/F (L/h)	0.34	0.45	0.99
V (L)	4.0	4.7	5.3
t _{1/2} (h)	8.1	7.1	5.2

^a Population pharmacokinetic parameters reported as mean ± standard deviation

Section 12.4 Microbiology was updated to include statements regarding the similar resistance profile in adults and pediatric patients. Also substitution at position I54V/A/M was included in the list of other substitutions that developed in 10-20% of Aptivus/ritonavir virologic failure isolates.

Section 14 Clinical Studies subsection 14.4 Pediatric Studies was also updated with the following study results.

The pharmacokinetic profile, safety and activity of APTIVUS/ritonavir was evaluated in a randomized, open-label, multicenter study. This study enrolled HIV-1 infected, treatment-experienced pediatric patients (with the exception of 3 treatment naïve patients), with baseline HIV-1 RNA of at least 1500 copies/mL. The age ranged from 2 through 18 years and patients were stratified by age (2 to < 6 years, 6 to < 12 years and 12 to 18 years). One hundred and ten (110) patients were randomized to receive one of two APTIVUS/ritonavir dose regimens: 375 mg/m²/150 mg/m² dose (N=55) or 290 mg/m²/115 mg/m² dose (N=55), plus background therapy of at least two non-protease inhibitor antiretroviral drugs, optimized using baseline genotypic resistance testing. All patients initially received APTIVUS oral solution. Pediatric patients who were 12 years or older and received the maximum dose of 500/200 mg BID could subsequently change to APTIVUS capsules at day.

Demographics and baseline characteristics were balanced between the APTIVUS/ritonavir dose groups. The 110 randomized pediatric patients had a median age of 11.7 years (range 2 to 18), and were 57.2% male, 68.1% white, 30% black, and 1.8% Asian. The median baseline plasma HIV-1 RNA was 4.7 (range 3.0 to 6.8) \log_{10} copies/mL and median baseline CD4+ cell count was 379 (range 2 to 2578) cells/mm³. Overall, 37.4% of patients had a baseline HIV-1 RNA of >100,000 copies/mL; 28.7% had a baseline CD4+ cell count \leq 200 cells/mm³, and 48% had experienced a prior AIDS defining Class C event at baseline. Patients had prior exposure to a median of 4 NRTIs, 1 NNRTI, and 2 PIs.

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

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

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

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

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

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

- A greater proportion of patients receiving APTIVUS/ritonavir 375 mg/m²/150 mg/m² compared to 290 mg/m²/115 mg/m² achieved HIV-1 RNA < 400 and < 50 copies/mL.
- A greater proportion of patients 6 to 18 years of age with multiple baseline protease inhibitor resistance-associated substitutions receiving APTIVUS/ritonavir 375 mg/m²/150 mg/m² achieved HIV-1 RNA <400 copies/mL at 48 weeks compared to patients receiving APTIVUS/ritonavir 290 mg/m²/115 mg/m².

- No clinically significant increase in adverse event rates observed with 375 mg/m²/150 mg/m² compared to 290 mg/m²/115 mg/m²
- Overall, 6 (5%) patients ages 6 to 18 had AIDS defining illness during the treatment period and all received the 290 mg/m²/115 mg/m² dose.

The guidance for possible dose reduction for patients who develop intolerance or toxicity and cannot continue with APTIVUS/ritonavir 14 mg/kg/6 mg/kg (or 375 mg/m²/150 mg/m²) is based on the following:

- The 290 mg/m²/115 mg/m² twice daily regimen provided tipranavir plasma concentrations similar to those obtained in adults receiving 500/200 mg twice-daily. The 375 mg/m²/150 mg/m² twice daily regimen provided tipranavir plasma concentrations 37% higher than those obtained in adults receiving 500/200 mg twice-daily.
- The observed response rates for APTIVUS/ritonavir dose of 290 mg/m²/115 mg/m² as shown in Table 13.

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

When body surface area (BSA) dosing is converted to mg/kg dosing, the APTIVUS/ritonavir 375 mg/m²/150 mg/m² twice daily regimen is similar to 14 mg/kg/6 mg/kg and APTIVUS/ritonavir 290 mg/m²/115 mg/m² twice daily regimen is similar to 12 mg/kg/5 mg/kg twice daily .

Section 16 How Supplied/Storage and Handling was updated to provide information for the oral solution formulation as follows:

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

Storage

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

Midazolam Information:

Orally administered midazolam is contraindicated for use with Aptivus. This change is reflected in section 4 Contraindications.

Section 7 Drug Interactions Table 4 Established and Other Potentially Significant Drug Interactions was updated to include information on parenterally administered midazolam and includes the following statement.

Midazolam is extensively metabolized by CYP3A4. Increases in the concentration of midazolam are expected to be significantly higher with oral than parenteral administration. Therefore, Aptivus should not be given with orally administered midazolam. If Aptivus is coadministered with parenteral midazolam, close clinical monitoring for respiratory depression and/or prolonged sedation should be exercised and dosage adjustment should be considered.