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APPLICATION NUMBER:

21-814s005/22-292

SUMMARY REVIEW

CROSS DISCIPLINE TEAM LEADER REVIEW

Date	June 19, 2008
From	Kimberly A. Struble, PharmD Clinical Analyst Team Leader Division of Antiviral Products
Subject	Cross Discipline Team Leader Review
NDA/BLA # **Supplement#**	21-814 SE1 (005) 21-822 (000)- response to approvable 22-292 (000)
Applicant	Boehringer Ingelheim Pharmaceuticals, Inc
Date of Submission	December 20, 2007
PDUFA Goal Date	June 20, 2008
Proprietary Name / Established (USAN) names	Aptivus (tipranavir)
Dosage forms / Strength	Capsules 250 mg (approved) Oral Solution 100 mg/mL (Proposed)
Proposed Indication(s)	Aptivus co-administered with ritonavir, is indicated for treatment of HIV-1 infected pediatric patients at least 2 years of age and adults who are treatment-experienced and infected with HIV-1 strains resistant to more than one protease inhibitor.
Recommended:	Approval for expanded indication to include children 2-18 years of age Approval of Oral Solution 100 mg/mL

1. Introduction

This cross-discipline team leader review summarizes the main issues for Boehringer Ingelheim Pharmaceutical's (BI) supplemental New Drug Application (sNDA) to provide pharmacokinetic, safety, activity data and dose recommendations for Aptivus (tipranavir; TPV) co-administered with ritonavir in treatment-experienced pediatric patients 2 -18 years of age. The submitted data are in response to a Pediatric Written Request. BI submitted results from one open-label study (1182.14), to determine the pharmacokinetic, safety and activity profile of TPV oral solution and capsules in children 2-18 years of age. Children were randomized to one of two doses (TPV/ritonavir 290 mg/m^2/115 mg/m^2 or TPV/ritonavir 375 mg/m^2/150 mg/m^2) and stratified by age. Review of submitted data completes the evaluation of all necessary pediatric age groups. Studies in children less than two years of age were waived because TPV will not receive an indication in treatment-naïve patients based on the risk/benefit assessment in a study conducted in adults comparing TPV/ritonavir and lopinavir/ritonavir (see NDA 21-814 003, review by Dr. Chan Tack). Children less than

two years of age are not likely to be treatment experienced, harboring protease inhibitor resistant HIV-1 virus and failing their current regimen; therefore, studies in children < 2 years of age were waived. Pediatric Exclusivity was granted on March 7, 2008.

In addition, BI submitted a complete response to the approvable letter for NDA 21-822 for Oral Solution for use in adults. The approvable letter stated the following data are needed prior to approval.

- steady-state relative bioavailability or bioequivalence data compared to capsules or
- adequate exposure data in the relevant patient population to demonstrate the selected dose of oral solution achieves tipranavir concentrations similar to those achieved following administration of tipranavir capsules at a dose of 500 mg with 200 mg ritonavir twice daily in adults

Data from a steady-state bioavailability study and data from the pediatric study, as described below, satisfies the deficiencies described in the approvable letter. As a result, BI submitted a new NDA 22-292 seeking approval for the oral solution for dosing in children and adults. This review highlights the pharmacokinetic, activity and safety findings in children and briefly summarizes the data supporting the oral solution formulation.

These applications received a priority review because treatment options for children with protease inhibitor resistance virus are limited. The new oral solution formulation along with the approved capsule formulation provides dosing flexibility for children ages 2-18 years.

2. Background

Aptivus (tipranavir; TPV) co-administered with ritonavir 200 mg was approved in June 22, 2005, for combination antiretroviral treatment of HIV-1 infected adult patients with evidence of viral replication, who are highly treatment-experienced or have HIV-1 strains resistant to multiple protease inhibitors. The accelerated approval was based on two 24 week phase 3 studies. Traditional approval was granted October 4, 2007, based on the 48 week results from the two studies submitted for accelerated approval. The pediatric written request and PREA requirements as amended included multiple-dose pharmacokinetic, safety and activity of TPV in combination with low dose ritonavir together with other antiretroviral agents in HIV-infected treatment-experienced patients ages 2-18 years. The primary objective of the study was to identify dosing for TPV co-administered with ritonavir in children and evaluate safety. As stated in Dr. Belew's review, the Division bases the approval of pediatric indications on extrapolation of efficacy from adequate and well-controlled studies in adults with supportive pharmacokinetic and safety data from the representative pediatric population as specified in the PWR. The Division has concluded the disease course is similar between HIV infected adults and children; therefore, extrapolation of

efficacy data is clinically relevant. Studies in children are conducted to determine: (1) a dose or doses for which exposures are similar to those achieved in adults, (2) the overall safety profile compared to adults and to identify any safety concerns specific to children, and (3) virologic and immunologic response rates and to ensure these rates are similar to adults.

Of note, five patients from one site in Mexico were excluded from the overall analyses conducted by Dr. Belew. The five patients were in the 2-< 6 age group and were excluded due to Good Clinical Practice Issues, including inadequate informed consent (form completed by investigator and signed by parent/guardian), lack of required baseline testing (chest X-ray and ECG), and omission of study visits. Even with the five excluded patients we were able to evaluate safety and activity and make dosing recommendations. At least 100 patients were evaluable for safety as specified in the PWR. The data from the five patients were taken into consideration to better characterize the pharmacokinetic-pharmacodynamic and resistance profile.

3. CMC/Device

BI submitted a New NDA (22-292) for an oral solution formulation. The supporting CMC data were previously submitted and reviewed under 21-822. NDA 21-822 received an approvable action due to inadequate bioavailability data. The CMC data were deemed acceptable. Please refer to Dr. Ko-Yu Lo's review for details. The oral solution contains 100 mg TPV in each mL and is supplied in 95 mL bottles. A 5 mL plastic oral dispensing syringe is provided.

4. Nonclinical Pharmacology/Toxicology

In vitro, TPV inhibits human platelet aggregation at levels consistent with exposures observed in patients receiving TPV/ritonavir. Studies in rats show TPV induced dose-dependent changes in coagulation parameters (increased prothrombin time, increased activated partial thromboplastin time, and a decrease in some vitamin K dependent factors). In some rats, the changes in coagulation parameters led to bleeding in multiple organs and death. The co-administration of vitamin E in the form of TPGS (d-alpha-tocopherol polyethylene glycol 1000 succinate) with TPV resulted in significant increase in effects on coagulation parameters, bleeding events, and death. Of note coagulation parameters were not affected in dogs.

Given nonclinical findings of changes in coagulation parameters, the TPV label currently includes a warning to use TPV with caution in patients who may be at risk for increased bleeding from trauma, surgery or other medical conditions, or who are receiving medications known to increase the risk of bleeding such as antiplatelet agents and anticoagulants, or who are taking supplemental high doses of vitamin E.

Based on the data from the TPV coagulation, BI conducted and submitted the results of a 10-week oral (gavage) study in male rats to explore the effects of TPV on coagulation parameters when co-administered with an excipient in TPV oral solution, Vitamin E TPGS. This study evaluated the effects of TPV and TPGS on the coagulation cascade and impact of Vitamin K_1 administration on these changes. As noted in Dr. Anita Bigger's review, the key findings from the rat study show vitamin E TPGS co-administered with TPV exacerbates the anti-coagulant effect of TPV. A previous study demonstrated the effects of TPV, administered alone, on vitamin K related factors as well as arachidonic acid-induced platelet aggregation. Based on literature review, vitamin E has also been shown to affect vitamin K-related factors.

Based on the in vitro and nonclinical results, patients receiving TPV oral solution should not take supplemental vitamin E greater than a standard multivitamin as TPV oral solution contains 116 IU/mL of vitamin E which is higher than the reference daily intake (adults 30 IU, pediatrics approximately 10 IU). Given these concerns, BI also conducted an analysis of stored plasma from adults and children treated with capsules and oral solution, respectively, to determine the effects on vitamin K dependent coagulation factors, PT or aPPT. Please refer to section 8 and Dr. Yodit Belew's review for details on this study.

5. Clinical Pharmacology/Biopharmaceutics

Pharmacokinetics in pediatric patients:

Two twice daily dosing regimens were evaluated in pediatric patients: TPV/ritonavir 290/115 mg/m^2 (TPV low dose) and TPV/ritonavir 375 /150 mg/m^2 (TPV high dose). TPV/ritonavir 290/115 mg/m^2 was allometrically scaled by body surface area to the 500/200 mg adult dose (BSA 1.73 m^2). The 375/150 mg/m^2 dose was projected to have a 30% increase in TPV exposures compared to the adult dose. This dose was selected to account for potential increases in metabolism and clearance of TPV in pediatric patients. The dose in children was not to exceed the adult dose of TPV/ritonavir 500/200 mg twice daily. Patients were randomized to dose and stratified by age group (2- < 6 years, 6-<12 years and 12-18 years). All patients initiated treatment with the oral solution formulation.

Dr. Zhang concluded the TPV/ritonavir low dose more closely resembled the TPV exposure observed in adults receiving TPV/ritonavir 500/200 mg twice daily. The TPV/ritonavir high dose resulted in higher TPV exposure in the 2 to <6 and 6 to <12 age groups compared to the TPV/ritonavir low dose, while smaller increases in exposure were seen in the 12 to 18 age group. This is a reflection of limiting the dose to 500/200 mg and many older patients in the TPV/ritonavir high dose group reached the maximum dose of 500/200 mg. The TPV/ritonavir high dose provided TPV exposures 37% higher than those obtained in adults receiving TPV/ritonavir 500/200 mg.

Bioavailability of Oral Solution Formulation:

NDA 21-822 received an approvable action in June 2005 for the oral solution formulation due to lack of acceptable relative bioavailability data. The single dose bioavailability data was not sufficient due to the complex enzyme/transporter interactions during absorption; therefore, steady-state bioavailability data are needed. In the absence of this information, exposure-response data could have been used to support the approval of the oral solution formulation; however, limited pharmacokinetic and safety data from pediatric patients were submitted for review and we could not make dosing recommendations for pediatric patients. Therefore, BI conducted a study to determine the relative bioavailability to TPV/ritonavir administered as oral solution or capsules. TPV/ritonavir capsules were given and dosed to steady-state (10.5 days) then subjects received oral solution for 3.5 days (fed and fasted). TPV/ritonavir oral solution formulation administered as a 500/200 mg dose twice-daily to steady state was slightly more bioavailable (AUC_{0-12h} increased by 23%) than the marketed TPV/ritonavir capsule formulation at steady state, and C_{max} was about 21% lower when TPV/ritonavir oral solutions are administered with food. These differences are not sufficient to change the dose regimen from the current recommended dose of TPV/ritonavir 500/200 mg bid. Thus oral solution and capsule are interchangeable.

6. Clinical Microbiology

The clinical virology evaluation is included in the clinical efficacy section below. Please refer to Dr. Lisa Naeger's review for further details.

7. Clinical/Statistical- Efficacy

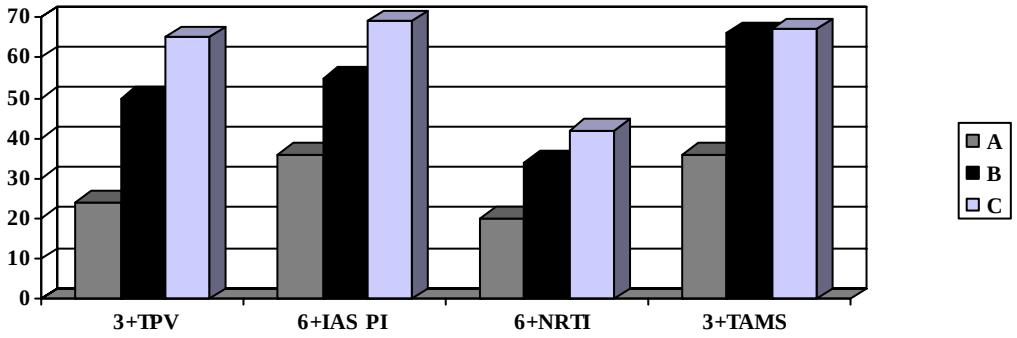
Study 1182.14 provided evidence of virologic and immunologic activity through 48 weeks of treatment. Through Week 48, 40% of patients in the low dose group (TPV/ritonavir 290/115 mg/m^2) and 46% of patients in the high dose group (TPV/ritonavir 375 /150 mg/m^2) achieved HIV RNA < 400 copies/mL, respectively. Similarly, increases in CD4 cell counts were seen in all patients. CD4 cell counts increased by 100 cells/mm^3 and 59 cells/mm^3 in the low dose and high dose groups, respectively, through Week 48. Children ages 12-18 were permitted to receive TPV capsules after Week 4. Response rates for the oral solution formation and capsule formulation were similar in the 12-18 age group. Overall, the observed virologic and immunologic responses were consistent with those seen in two phase 3 trials in treatment-experienced adults.

To determine the optimal dose recommendations for children, several exploratory analyses were conducted and included response rates by age and dose, baseline mutations (TPV key mutations, TPV-resistance associated mutations, all baseline mutations; overall NRTI, NNRTI and PI mutations), and TPV exposure, including genotypic inhibitory quotient (GIQ). Appendix A includes a tabular display for some of the key analyses conducted by Drs. Belew, Hammerstrom, Naeger, Lee and Jadhav. Drs. Lee and Jadhav conducted extensive exposure-response and exposure-safety analysis to justify the proposed dose regimens.

Overall, response rates were numerically greater for the TPV high dose group compared to the TPV low dose group. Other key efficacy findings include:

- As the number of baseline key TPV mutations, TPV-resistance associated mutations or overall mutation score increased, patients receiving TPV high dose tended to have better response rates compared to patients receiving the TPV low dose.
- Patients with greater than five TPV associated mutations had better response rates if they received TPV high dose compared to TPV low dose.
- GIQ was also a predictor of virologic success. Virologic response rates increased with higher TPV exposure.
- Response rates were greater in the 2 to < 6 year old group compared to the 6-< 18 group. This finding was expected given the baseline resistance observed by age group as outlined in Figure 1.

Figure 1: Prevalence of Mutations by Age



Source: Dr. Naegar's review
A= 2-<6 years; B= 6-<12 years; C=12-18 years

Based on these findings BI proposed the high dose for all patients. The DSMB for the study and BI's pediatric advisory board also recommended the high dose for all patients. Upon further examination, response rates by age and dose showed similar efficacy results between the high and low dose groups for children 2 - < 6 years of age. The analysis by FDA shows the proportion of patients with HIV RNA < 400 copies/mL (<50 copies/mL) was 70% (54%) for 2 to < 6 year olds receiving TPV low dose compared to 70% (42%) for 2 to < 6 year olds receiving TPV high dose. Thus, no efficacy advantage was apparent to recommend the high dose over the low dose in children 2 - < 6 years of age. However, after internal discussions and discussions with BI, we concluded the high dose was appropriate for all patients based on the following factors.

First, the enrollment criteria for study 1182.14 included children with HIV RNA > 1500 copies/mL regardless of prior ARV therapy or baseline HIV resistance status. As a result, the baseline characteristics for the 2 - < 6 year old group may not be representive of the treatment-experienced child for whom TPV is indicated. TPV is indicated for patients with resistant virus (resistant to more than one protease inhibitor). Of note, in the adult studies, patients were required to have previously

received at least two protease inhibitor-based antiretroviral regimens and were failing a protease inhibitor-based regimen at the time of study entry with baseline HIV-1 RNA at least 1000 copies/mL and any CD4+ cell count. At least one primary protease gene mutation from among 30N, 46I, 46L, 48V, 50V, 82A, 82F, 82L, 82T, 84V or 90M had to be present at baseline, with not more than two mutations at codons 33, 82, 84 or 90. If the adult enrollment criteria were used for the pediatric study, the baseline resistance profile for children 2 - < 6 years of age would most likely have been more similar to those seen in children 6-< 18 years of age and adults. Secondly, overall, the high dose group had numerically greater response rates compared to the low dose group. Furthermore, the treatment effect appears more durable for the high dose group compared to the low dose group. At Week 96, 27% of patients in the low dose group achieved HIV RNA < 400 copies/mL compared to 36% of patients in the high dose group. Additionally, at Week 96 31% of patients in the high dose group and 16% of patients in the low dose group achieved HIV RNA < 50 copies/mL. Also six patients (5%) in the low dose group developed a new AIDS defining event compared to no patients in the high dose group. Taking into consideration the treatment-experienced population as a whole (patients who are resistant to more than one PI), ensuring higher TPV exposures, without compromising safety could theoretically help overcome some baseline resistance, improve response rates, and increase the therapeutic barrier to emergence of resistance and treatment failure. Additionally, simplification to a single dose schedule for all patients could potentially reduce dosing errors. As a result the TPV high dose is recommended for children 2- < 18 years of age.

Given the labeled indication of TPV is for patients who are treatment-experienced and infected with HIV-1 strains resistant to more than one PI, children receiving TPV are at the stage of disease for which effective available therapies are limited. These children are in need of receiving therapy to treat their HIV infection; otherwise untreated HIV infection will result in death. As previously stated, the high dose group appears more consistently effective compared to low dose group, particularly in patients with more baseline resistance. As shown in the table below, the low dose group did demonstrate activity and response rates were reasonable. TPV low dose provided similar TPV exposures compared to adults. If a child does not have other therapeutic options, and is experiencing intolerance or toxicity at the higher dose, a dose reduction to TPV/ritonavir dose of 290 mg/m^2/115 mg/m^2 or 12 mg/5mg/kg can be considered for patients who do not have extensive baseline PI resistance. A dose reduction consideration was allowed because alternative options are limited for children at this stage of disease for which TPV is needed. Therefore, preserving TPV as an option, even at a reduced dose is worth considering for an individual patient providing the patient does not have extensive baseline PI resistance.

Proportion of patients with HIV RNA < 400 copies/mL (<50 copies/mL) by age and dose (48 weeks)

	2-<6 years N =20	6 - < 12 years N=38	12-18 years N=52
APTIVUS/ritonavir dose of 290 mg/m^2/115 mg/m^2	n=10 70% (53.8%)	n=19 36.8% (31.6%)	n=26 30.8% (23.1%)
APTIVUS/ritonavir dose regimens: 375 mg/m^2/150 mg/m^2	n= 10 70% (41.7%)	n=19 50% (38.9%)	n=26 33.3% (29.6%)

8. Safety

TPV/ritonavir was studied in 135 HIV-infected children age 2-18 years, of which 110 were enrolled in study 1182.14 and 25 children were enrolled in other studies including Expanded Access and Emergency Use programs. In study 1182.14, 83 and 73 patients received TPV for at least 48 and 100 weeks, respectively. The number of patients followed for safety exceeded the PWR requirements of a minimum of 100 patients with 24 week safety data at the to-be-marketed dose or higher. The adverse event profile was similar in children and adults. Vomiting (38%), cough (31%), pyrexia (31%), diarrhea (28%), rash (21%) and nausea (20%) were the most frequently reported adverse reactions (all severity, all causes) in pediatric patients. Only Grade 2-4 rash was reported more frequently in children compared to adults.

Two deaths occurred during the study; both were reported during the optional extended treatment period (> 48 weeks) and not considered related to TPV by the investigator. The first death occurred in a 17 year old male following 22 months of treatment. After one day of treatment discontinuation he presented with gastric pain, oral candidiasis and wasting. He had an enlarged spleen and pancreas head, dilated hepatic biliary ducts, free liquid in peritoneal cavity and retroperitoneal lymphadenopathy were noted. The patient was also coagulopathic and received fresh plasma and platelets transfusions. The patient did not have hepatic failure. The cause of coagulopathy was believed to be due to gastrointestinal lymphoma or alternatively due to malnutrition, wasting, advanced HIV disease and vitamin K deficiency.

The second death was due to renal failure secondary to B-cell lymphoma.
Two additional deaths were reported in other studies; one due to acute respiratory distress in a patient with cerebral toxoplasmosis and another death due to sepsis in a patient with cryptococcosis and atypical mycobacterial infection.

Twenty-seven patients (25%) reported an SAE during study 1182.14. The proportion of patients with SAEs was similar between the high and low dose group and were similar among the three stratified age groups. The most common SAEs were related

to infections/infestations followed by GI disorders. These findings were consistent with the adult studies.

Through Week 48, the proportion of patients who discontinued treatment due to an AE was 9% in the low dose group and 7% in the high dose group. No discontinuations occurred in children 2- < 6 years of age. The most commonly reported reason for discontinuation was GI (5%) or hepatic related (4%) events. Elevated GGT was cited as a reason for discontinuation in 3 patients, of note no GGT elevation was considered serious or clinically significant. One patient in the high dose group discontinued due to increased ALT.

The safety concerns of interest included bleeding events, rash and hepatic toxicity. Due to the in vitro findings of inhibition of human platelet aggregation and nonclinical finding of dose-dependent changes in coagulation parameters in rats and the additive effect on changes in coagulation parameters with the vitamin E excipient in the oral solution formulation, the bleeding events were reviewed in detail by Dr. Belew. Through 100 weeks of treatment, 13 patients (12%) experienced a bleeding event. The most common reported bleeding event was epistaxis (4.5%). Epistaxis is commonly seen in pediatrics. No other bleeding events were reported in >1% and no drug related serious bleeding events were seen. Overall, more bleeding events were seen in the high dose group (15%) compared to low dose group (9%). More bleeding events were seen with the oral solution group (69%) compared to the capsule group (31%). Of note the observed difference between formulations may also be due to more patients receiving oral solution compared to capsules.

As noted in Dr. Belew's review of stored plasma from adult patients treated with TPV capsules and pediatric patients treated with TPV oral solution (which contains a vitamin E derivative) showed no effect of TPV/ritonavir on vitamin K-dependent coagulation factors (Factor II and Factor VII), Factor V, or on prothrombin or activated partial thromboplastin times.

The incidence of rash was similar between dose groups and occurred in 21% of children overall. The incidence of rash was higher in children compared to adults (12%). However, the type and severity of rash appears similar in children and adults.

Drs. Lee and Jadhov conducted several exposure-safety analyses. No apparent relationship between bleeding event or rash and exposure was seen.

Grade 3/4 ALT elevations were more frequently reported in the high dose group (11%) compared to the low dose group (5%). ALT elevations were more frequently seen in the 12-18 year old group compared to children 2-< 12 years of age. Of note, the proportion of children with ALT elevations was not greater than the adult experience. In an exposure-safety analyses, the proportion of patients with Grade 2 or greater increase in LFT's increased from 16% in patients with the lowest quartile for Cmin (median Cmin = 14 uM) to 53.8% in patients with the highest quartile for Cmin (median Cmin = 74 uM). Only one patient in the 2- < 6 age group had any Grade 3 or

4 ALT abnormalities. In the 6 - < 12 group, 3 children had a Grade 3 or 4 ALT abnormality compared to 6 children in the 12-18 age group. No concomitant Grade 3/4 ALT and total bilirubin increases were seen. Based on an analysis conducted by Dr. Lee, decreasing the TPV dose could lessen the ALT abnormalities; however, efficacy would be compromised, particularly for those patients with extensive PI resistance and in need of higher TPV exposures. Overall, the ALT abnormalities observed were no higher than those seen in adults and these changes are easily monitored and well documented in the current label (including Box Warning) to ensure safe use.

No new or unexpected safety findings were observed in the pediatric population. The events seen were previously reported in adults and are adequately described in the package insert.

9. Advisory Committee Meeting

An advisory committee meeting was not held for this application.

10. Pediatrics

This sNDA fulfilled the terms of the PWR and the outstanding postmarketing commitment. Pediatric Exclusivity was granted on March 7, 2008. No additional pediatric specific postmarketing commitments are needed. NDA 22-292 provided sufficient data to recommend approval for the oral solution formulation for use in children and adults unable to swallow the capsule formulation.

11. Other Relevant Regulatory Issues

No outstanding relevant regulatory issues are pending for this sNDA.

12. Labeling

Please refer to Dr. Belew's review for a detailed description of the labeling changes. Dosing recommendations are provided based on the pharmacokinetic, activity and safety data from study 1182.14 in children 2-18 years of age. Dosing based on mg/kg and body surface area is provided. A description of study 1182.14 including the pharmacokinetic, safety and efficacy results, and detailed rationale for dose selection for children were included in Section 6 Adverse Reactions, Section 8 Use in Specific Populations, Section 12 Clinical Pharmacology and Section 14 Clinical Studies.

13. Recommendations/Risk Benefit Assessment

I agree with the review team's recommendations for granting approval for TPV/ritonavir use in HIV-1 infected treatment-experienced pediatric patients 2 to 18 years of age.

Virologic and immunologic activity of TPV/ritonavir was demonstrated in children. No apparent trend toward increased rates in AEs in the high dose group compared to low dose group was seen. With the exception of diarrhea and vomiting, the types of AEs observed were similar between doses. Differences between the dose groups were seen for Grade 3/4 elevations in ALT. More patients in the high dose group (11%) developed Grade 3/4 ALT elevations compared to the low dose group (4%). The higher frequency in ALT elevations was driven by the 12-18 year old age group. The 12-18 year old group is in need of higher TPV exposures for efficacy given the extent of baseline resistance. No Hy's Law cases or reports of concomitant Grade 3/4 ALT and total bilirubin cases were seen. Patients with ALT increases were asymptomatic.

The observed benefit of TPV high dose for patients with resistance to more than one PI outweighs the identified safety risks. The risks of TPV use, including hepatotoxicity are well-characterized and adequately labeled (Box Warning) event. The observed safety profile in children was similar between doses, with few exceptions. The incidence of ALT elevations in children was slightly less than those observed in the adults. Overall no clinically significant increase in adverse event rates was observed with the high dose group. The available safety data in children support use of either dose studied in 1182.14. The high dose is recommended because an efficacy benefit was seen with the high dose in patients with extensive baseline resistance and no untoward safety issues were identified. Although TPV was found safe and effective for use in treatment-experienced adult patients, TPV use is limited by a complex drug-drug interaction profile and higher rates of Grade 2-4 GI events and transaminase elevations compared to other PIs. As a result, patients in need of TPV treatment are those with limited remaining options and multiple resistance mutations. The advantage of higher TPV exposures for children with extensive baseline resistance outweighs the higher frequency of ALT elevations and GI events with the high dose compared to the low dose. High dose TPV could theoretically help overcome some baseline resistance, improve response rates, and increase the therapeutic barrier to emergence of resistance and treatment failure. As previously emphasized, the risks are well identified and easily monitored and do not preclude use of TPV high dose in patients at need for alternative therapies given the extent of baseline resistance.

Additionally the AE and efficacy profile were similar between formulations for the 12-18 year old group. The oral solution and capsule formulation are suitable formulations for children and adults who are unable to swallow solid oral formulations.

- Recommendation for Postmarketing Risk Management Activities

No postmarketing risk management activities are required for this application.

- Recommendation for other Postmarketing Study Commitments

See Section 10

Appendix A

Table A: Proportion of patients with HIV RNA < 400 copies/mL (<50 copies/mL) by age and dose

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

Table B: Proportion of patients with HIV RNA < 400 copies/mL by Key TPV Mutations and TPV-Associated Mutations

TPV Dose	APTIVUS/ritonavir dose regimen: 375 mg/m^2/150 mg/m^2				APTIVUS/ritonavir dose regimen: 290 mg/m^2/115 mg/m^2			
Age	**ALL**	**2 to <6**	**6 to <12**	**12 to 18**	**ALL**	**2 to <6**	**6 to <12**	**12 to 18**
Key TPV muations								
0	**50% (11/22)**	**71% (5/7)**	**63% (5/8)**	**14% (1/7)**	**53% (10/19)**	**88% (7/8)**	**0/4**	**43% (3/7)**
1	**77% (10/13)**	**75% (3/4)**	**100% (5/5)**	**50% (2/5)**	**38% (6/16)**	**50% (2/4)**	**33% (3/9)**	**33% (1/3)**
2	**11% (1/9)**	**0/1**	**0/3**	**20% (1/5)**	**36% (4/11)**	**-**	**50% (1/2)**	**33% (3/9)**
3	**25% (3/12)**	**-**	**0/3**	**33% (3/9)**	**17% (2/12)**	**0/1**	**50% (2/4)**	**0/7**
4	**1/1**			**1/1**				
≥2	**23% (5/22)**	**0/1**	**0/6**	**33% (5/15)**	**26% (6/23)**	**0/1**	**50% (3/6)**	**19% (3/16)**
Age	**ALL**	**2 to <6**	**6 to <12**	**12 to 18**	**ALL**	**2 to <6**	**6 to <12**	**12 to 18**
TPV-associated mutations								
0-1	**14/25 (56%)**	**5/7 (71%)**	**7/10 (70%)**	**2/8 (25%)**	**8/15 (53%)**	**5/6 (83%)**	**0/2**	**3/7 (43%)**
2-4	**7/20 (35%)**	**2/4 (50%)**	**3/8 (38%)**	**2/8 (25%)**	**13/28 (46%)**	**4/6 (67%)**	**6/12 (50%)**	**3/10 (30%)**
≥5	**5/12 (42%)**	**1/1**	**0/1**	**4/10 (40%)**	**1/15 (7%)**	**0/1**	**0/5**	**1/9 (11%)**

Key TPV Mutations include amino acid substitutions at position 33, 82, 94 and 90

TPV associated mutations include amino acid substitutions in HIV protease among L10V, I13V, K20M/R/V, L33F, E35G, M36I, K43T, M46L, I47V, I54A/M/V, Q58E, H69K, T74P, V82L/T, N83D or I84V

The Effect of GIQ (Cmin/IC50) on Virologic Response by TPV Dose and Age Group

Dose	High				Low			
Age Group	**All**	**2 to <6**	**6 to <12**	**12 to 18**	**All**	**2 to <6**	**6 to <12**	**12 to 18**
GIQ Quartile*								
Q1	0% (0/10)	-	0/3	0/7	13% (2/15)	0	13% (1/8)	14% (1/7)
Q2	58% (7/12)	40% (2/5)	33% (1/3)	100% (4/4)	36% (5/14)	33% (1/3)	50% (2/4)	29% (2/7)
Q3	50% (6/12)	1/1	75% (3/4)	29% (2/7)	57% (8/14)	67% (4/6)	67% (2/3)	40% (2/5)
Q4	77% (13/17)	83% (5/6)	83% (5/6)	60% (3/5)	89% (8/9)	4/4	67% (2/3)	2/2

*GIQ Quartiles: QI 0.48-5.85, Q2 6.05-14.2, Q3 14.38-36.23, Q4 36.48-215.38

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