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APPLICATION NUMBER:

202895Orig1s000

SUMMARY REVIEW

Cross-Discipline Team Leader Review- Amendment

Date	December 8, 2011
From	Yodit Belew, M.D.
Subject	Cross-Discipline Team Leader Review Amendment
NDA/NDA # **Supplement #**	202895/21976 S-20 (to NDA 21976)
Applicant	Tibotec, Inc.
Date of Submission	March 29, 2011
PDUFA Goal Date	September 30, 2011
Proprietary Name / Established (USAN) names	Prezista(darunavir)
Dosage forms / Strength	New proposed dosage form: Oral Suspension Approved dosage forms: 600, 400, 150, 75 mg tablets
Proposed Indication(s)	Treatment of HIV infection
Recommended:	Approval

This amendment summarizes two important events that occurred after review of the pediatric data to NDAs 202895 and 21976 were completed. The first section of this amendment addresses the revised dosing recommendations that have been made for children 3 years of age and older and weighing 10 to less than 15 kg. The second section addresses why an action was not taken on the PDUFA goal date, September 30, 2011. Specifically, it discusses the information submitted by the Applicant which was considered a major amendment, what conclusions the review team reached after review of the information, and what the final recommendation is for the application.

Section 1

A revision to the dosing recommendation has been made by the Division and subsequently accepted by the Applicant. Specifically, the Division recommended that for subjects 3 years of age and older and weighing 10 to less than 15 kg, the dose should be calculated based on darunavir 20 mg/kg co-administered with ritonavir 3mg/kg.

Several reasons led to the recommendation that the 20/3 mg/kg instead of (b) (4) mg/kg be approved for dosing in children 10- <15kg:

- The Applicant submitted a revision to the population PK analysis to correct for an error, primarily in subjects weighing 10 - <15 kg.

Table 1 Comparative result of the mean AUC in the initial and adjusted dosage regimens to the mean target adult exposure of 62.3 mcg/mL*hr

	Before Dose Adjustment			After Dose Adjustment		
	Overall	10 to <15 kg	15 to <20 kg	Overall	10 to <15 kg	15 to <20 kg
Original Analysis	107%	111%	104%	128%	140%	122%
Revised analysis	107%	110%	104%	129%	**153%**	113%

Source: Applicant's revised submission

Based on this revised analysis, subjects weighing 10 to <15 kg have mean AUC exposure that is 53% higher that the targeted mean adults exposure value.

- Changes in the dosing device

As discussed in the CDTL memo, DMEPA had recommended that the originally proposed (b) (4) be replaced by a syringe that is similar to what is currently available in the U.S. market. The Applicant submitted an alternative device (syringe) for marketing and has been accepted and recommended for approval by DMEPA. Although this syringe is similar to what is available in U.S. pharmacies, the dosing increments are much closer compared to the originally proposed (b) (4). Therefore, less precision could be expected when drawing the medication. Although this decrease in precision is likely to be by small amounts, it can potentially add to the overall increased dose of darunavir 25/3 mg/kg, in particular for those weighing 10 to <15 kg.

In addition to the already higher exposure expected with the 25/3 mg/kg dosing, one could consider adding yet another level of complexity: a drug-drug-interaction scenario where the exposure could be further pushed to significantly higher exposure where no supportive safety data is available from the adult or pediatric trials.

We therefore reevaluated the PK/PD, antiviral activity and safety data for the two doses as well as the adult trials C202 and C213.

Pharmacokinetics The pre-defined targeted exposure was to be within 80%-130% of the mean adult AUC value (62.3) at the 600/100 mg dose. The mean AUC value at the 20/3 mg/kg dose falls within this range. On the other hand, the mean AUC value at the 25/3 mg/kg falls outside the range of the target- i.e. 53% higher than adult mean AUC. As previously discussed and demonstrated, the data analysis exposure-response/efficacy in the treatment experienced adults did not demonstrate a relationship for the two variables even when considering doses as low as 400 mg QD. Therefore the exposure-response information does not support the need for a higher darunavir dose. Had the 20/3 mg/kg yielded exposures below the targeted adult mean value, it would be reasonable to consider and accept the (b) (4) mg/kg in order to avoid under dosing in children. But such is not the case.

The standard for pediatric HIV drugs approval within the Agency is primarily based on PK data- matching the pre-specified adult parameters. Efficacy (or antiviral activity) and safety data collected during the trials are used as supportive evidence. This is due to the nature of HIV pediatric trials- single arm, open label and not powered for true efficacy demonstration. In the case of C218, the primary endpoint- the pre-specified pharmacokinetic parameter was met with the 20/3 mg/kg dose.

One of the concerns about selecting the 20/3 mg/kg dose is the lack of long term antiviral activity/efficacy data. In order to address this issue, we looked at the mean exposure period for the 20/3 dose and also considered the patient population – what the average age is at the 10-<15 kg weight band and compared it to the treatment experienced adult population from studies C202 and C213.

Duration of exposure Although the 20/3 mg/kg dose is referred to as the initial dose (Week 2), the mean exposure time (weeks) for this dose is 12.9 weeks. Therefore there

is antiviral activity data for the 20/3 mg/kg dosing beyond a 2-week period. As summarized in the figure below, response rate was upward and positive during the first ~16 weeks.

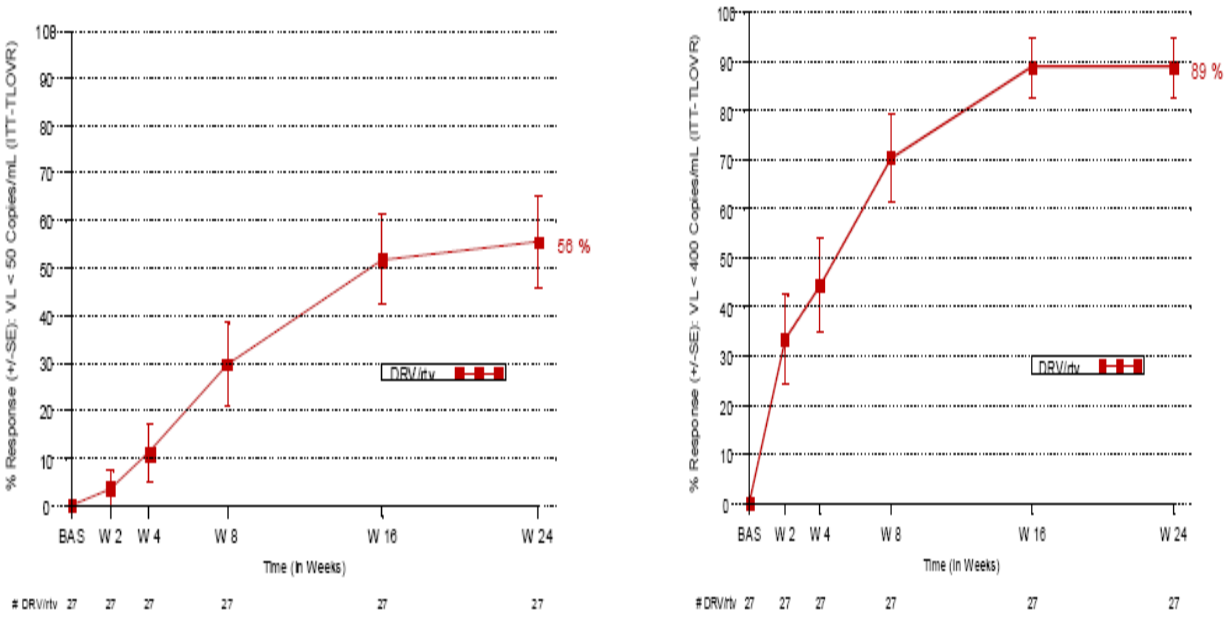


Figure 1A and B: Virologic Response Defined as the Percentage of Subjects with Viral Load <50 copies/mL (A) and <400 copies/mL (B) [ITT- TLOVR) Over Time

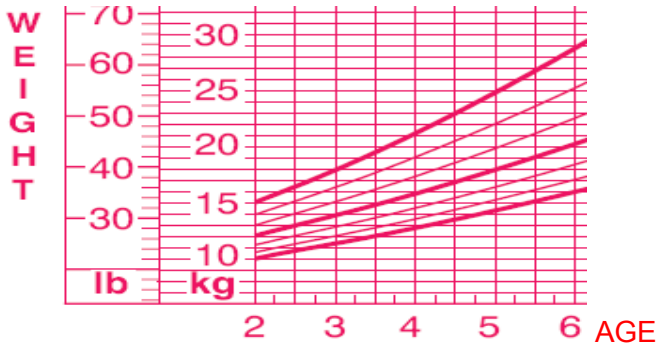
Patient population: The subjects enrolled in the adult clinical trials C202 and C213 were heavily treatment experienced. The mean time since first ART initiation (months) was 114 for C202 and 112 for C213. In addition, based on baseline phenotypic data, overall, 71% of the subjects in C202 and 63% of subjects in C213 were infected with virus resistant to all available PIs. Despite the significant amount of resistant viruses, 56-69% and 36-57% of the subjects had HIV-RNA <400 copies/mL and <50 copies/mL, respectively at the 600/100 mg dose. Similarly 52-68% and 37-54% of the subjects had HIV-RNA <400 copies/mL and <50 copies/mL, respectively, at the 400/100 mg dose (Table 2).

Table 2 Virologic outcome at Week 24

	<1 log drop in HIV RNA	VL<400 copies/mL	VL<50 copies/mL
Trial TMC114-C202			
400/100 qd	31/65=48%	25/65=38%	16/65=25%
800/100 qd	33/64=52%	26/64=41%	16/64=25%
400/100 bid	38/63=60%	33/63=52%	23/63=37%
600/100 bid	42/66=64%	37/66=56%	24/66=36% *
Trial TMC114-C213			
400/100 qd	45/64=70%	40/64=63%	27/64=42%
800/100 qd	45/63=71%	39/63=62% *	31/63=49%
400/100 bid	45/63=71%	43/63=68%	34/63=54%
600/100 bid	49/65=75%	45/65=69%	37/65=57%

Source: Analysis by FDA Statistical Reviewer- Dr Thomas Hammerstrom
* = to be marketed dose

The pediatric subjects in the 10 - <15 kg weight band are not expected to have comparative levels of baseline resistance as they are considerably younger. The CDC growth chart (below) can be utilized to estimate the age range for this weight band. Based on the CDC growth chart, approximately 50% of children weigh 15 kg by age 3.5 years and less than 3 percentile weigh 15 kg by age 5.5 years.



Therefore, many if not most children weighing 10- <15 kg should not be older than 4.5 years of age. It is extremely unlikely that pediatric patients at such age will harbor resistant viruses to the same extend as the adult patients did. As evident by the baseline disease characteristics information obtained from trial C228, there is less resistance in this overall 3 to <6 years-old subject population compared to adults.

According to the Applicant, the median number of ARVs previously used in the pediatric subjects enrolled in C228 was 4; the median number of PIs, NRTIs, and NNRTIs previously used was 1, 2, and 1, respectively. Eleven subjects (40%) had used no PI; twelve subjects (44%) had used 1 PI, and 4 subjects (15%) had used ≥ 2 PIs. The previous PI most frequently used was lopinavir; the previous NNRTI most frequently used was nevirapine.

Protease mutations, primary PI mutations, PI RAMs, and DRV RAMs at baseline were collected. The majority of subjects had no primary PI mutations (23 subjects, 85.2%) and no DRV RAMs (25 subjects, 92.6%) at baseline; 21 subjects (77.8%) had ≥ 3 PI RAMs. The median number of primary PI mutations was 0 (range: 0 - 3), the median number of DRV RAMs was 0 (range: 0 - 2), and the median number of PI RAMs was 4 (range: 1 - 13). DRV RAMs L76V and L33F were observed in 1 subject and L76V was observed in 1 other subject (CRF ID 228-0015).

Finally, the number of susceptible drugs per class at baseline was also provided. At baseline, all subjects enrolled in the trial were infected with virus susceptible to ≥ 5 ARVs (including PIs, NRTIs, NNRTIs, fusion inhibitor, integrase inhibitor). All subjects were infected with virus susceptible to DRV and most subjects had also virus susceptible to the other commercially available PIs (ranging between 85.7% and 95.2% for the different PIs).

In summary, based on the baseline genotypic and phenotypic resistance profile, the baseline IC_{50} is not expected to be higher than what was observed in trials C202 and C213. This is an important factor as response to treatment is related to inhibitory quotient (IQ)- the ratio between steady state trough concentration and baseline IC_{50} (see below).

Pharmacometrics: Based on the adult data (C202 and C213), virologic response is related to the subject's darunavir IQ- the higher the IQ, the more likely that a subject will respond. The IQ appears to be primarily influenced by baseline IC_{50}. The 600/100 mg BID dose in adults correlated with an IQ sufficient enough to have an acceptable virologic success rate. Because the 20/3 mg/kg dose leads to exposures that are within 80 to 130% range of the adult exposure (from the 600/100 mg BID dose), and because the IC_{50} is not expected to be higher in this age group, the long term efficacy or durability of the 20/3 mg/kg can be expected to be similar to what was observed in treatment experienced adults.

Safety The overall mean duration of treatment from trial start up to the cut-off date of the analysis was 30.5 weeks. The mean duration of treatment after dose adjustment was 18.4 weeks. Although the 25/3 mg/kg dose appears to be generally safe and well tolerated for the 18.4 weeks it was administered, sparse data is available for subjects weighing 10 to <15 kg and with exposure >130%. Post dose adjustment, 6 subjects out of a total of 9 in the 10 to < 15 kg group had exposures above 130% of the target range for adults. Although no significant adverse events were reported, the lack of sufficient number of subjects in that weight band supporting higher exposure is concerning.

In conclusion, I recommend the approval of this pediatric NDA (202895) with the following dosing recommendations:

- 10 kg to < 15 kg: darunavir 20 mg/kg with ritonavir 3 mg/kg twice daily
- 15 kg to < 20 kg: darunavir 375 mg with 50 mg of ritonavir twice daily

The Applicant agrees with the dosing recommendations. Labeling revisions to the dosing section of the USPI are currently underway.

Section 2

- Background

Trial TMC114-C228 is an international trial evaluating the pharmacokinetic, antiviral activity and safety of darunavir in children 3 to less than 6 years of age. The study report was submitted to both the US and European regulatory agencies in support of dosing recommendations for subjects 3 to less than 6 years of age and weighing between 10 and 20 kg.

Twenty-seven subjects were enrolled and stratified by weight band- 14 subjects (52%) in the 10 to < 15 kg weight group, and 13 subjects (48%) in the 15 to < 20 kg weight group. Table 3 summarizes the distribution of subjects by country.

Table 3 Subjects enrolled in Trial 228

Country	Number of Sites Enrolling	Number of Subjects Enrolled	Number Prematurely Discontinued
Argentina	3	4	0
Brazil	3 (2 enrolled)	6	1
Kenya	2	6	0
South Africa	3	10	0
India	1	1	0

As a part of the review process for marketing authorization, the EMA Inspectorate conducted clinical site inspections at 3 locations. On September 27, 2011, unsolicited new information [submission number (SN) 41] was submitted by the Applicant to NDA 202-895. The submission contained interim clinical sites inspection reports issued by the EMA for trial TMC114-C228.

DAVP has not routinely requested clinical site inspections for pediatric trials of antiretroviral drugs unless there was a specific concern identified. It should also be noted that the FDA does not rely on inspections conducted by other regulatory agencies to make regulatory decisions. As such, although the inspection reports were taken into consideration and reviewed, the final regulatory decision by the FDA is independent of other agencies.

The inspection reports generated concerns about the quality of the data from the 3 sites inspected by EMA: a Kenyan site, which enrolled six subjects, and two South African sites, which together enrolled nine subjects. Because the information was submitted 3 days before the PDUFA goal date, there was insufficient time for review of the data. Therefore, the information submitted was deemed a major amendment and the review time was extended to December 30, 2011. Furthermore, the review team needed additional information from the Applicant in order to conduct an adequate review. After the Applicant submitted the additional information requested, a full review of the information was conducted by the review team, in consultation with the Office of Scientific Inspection (OSI).

- Deficiencies identified by the report

The inspection reports identified several issues, ranging from 'minor' to 'critical', although most were considered 'minor' by the inspectorate.

In addition, there were 2 stability/storage temperature issues identified during inspections: 1) storage and stability of drug product (darunavir oral suspension, and possibly ritonavir) at temperatures in the range of 10-30º C and 2) storage of blood/plasma PK samples at (b) (4)º C rather than -20º C.

Please refer to the amendments by the chemistry reviewer and the clinical pharmacology reviewer for further detail on the issues related to plasma sample storage and drug product stability. In summary, it is unlikely that, storage of the drug product over the range of temperatures noted, before administration to patients would adversely affect product quality or performance. Further, storage of plasma at (b) (4) C would not likely adversely impact chemical stability of the analytes (darunavir, metabolites).

The following are among the clinical violations noted from the South African sites:

- Inconsistencies in data in the Week 24 dataset when compared to the source document and when compared to the subset data included in the Week 48 data

- Procedure for identifying and classifying protocol deviations were insufficient

However, in addition to the data inconsistencies between source documents and datasets, the violations from the Kenyan sites appear to be more serious, and also include ethical violations:

- Issues with the Informed Consent Form (ICF) which arose during language translation:
  - The quality of translation was not adequately assessed.
  - The ICF lacked dosing and storing instructions that were included in the master version.
  - Risks associated with darunavir that were included in the master version were omitted.
  - Risks associated with ritonavir that were included in the master version were omitted.
  - Questionable if the signatures of the parents for some subjects were personally dated by the parents or the staff.
  - Unclear if counselors who administered the ICF had medical background and/or if they received training for ICF administration

- Subject identifiers on source documentation were not adequate.

- The clinical site, in general lacked experience and there were insufficient monitoring visits from the clinical research organization (CRO)

- Handling and processing of biological samples was not adequate. Issues with the local laboratory (which was used for diagnostics) included: lack of daily QC checks of analytical methods; failing to establish its own reference range but instead used outside laboratory reference ranges; incorrect patient identifiers were used on laboratory reports. Of note, per trial design, all laboratory testing were to be performed by a central laboratory ((b) (4)).

- Applicant's response to the inspection reports

The Applicant acknowledged the issues identified by the reports and believes it to be an indicative of "sloppy work" and plans to implement corrective actions for future projects.

With regards to the inconsistencies found between the 24 and 48 week datasets across the sites, the Applicant performed a detailed assessment of the datasets. Per Applicant, the inconsistencies identified are either additions or corrections of the Week-24 dataset, generally pertaining to screening and baseline data. There were no consequences of the inspection findings on the handling on the safety of the subjects in the trial (the trial subjects were monitored according to local medical standards). There were no negative consequences for the pharmacokinetic, safety and efficacy conclusions of the primary Week-24 and Week-48 analyses.

- DAVP's review of the inspection report and Applicant's response

After reviewing the inspection reports and the Applicant's response to the reports, the assessment made by the review team is that none of the issues identified in the two South African sites were considered significant enough to recommend exclusion of the data from these sites. The sites generally followed GCP and the data were not fraudulent or fabricated. In addition, there were no ethical violations related to the Informed Consent Form (ICF).

In addition to the major laboratory and clinical site concerns, of paramount concerns of the Kenyan site are the violations relating to the ICF. Based on review of the report, the events appear to be due to 'sloppy work' but the investigator had good intent. Nonetheless, these violations can be considered as ethical violations. Although the violations did not necessarily lead to unsound clinical data, it is questionable if the data was ethically obtained and thus questions the usability of the data to support the application.

Darunavir is an antiretroviral drug considered essential for this pediatric age group as it adds meaningful therapeutic benefit for treatment of HIV infection. Therefore, it is not without serious deliberation that the review team concluded the data from the Kenya site should be excluded. When considering the necessity of the data from this site, it is arguable that there is no critical need of the Kenyan data to justify its inclusion because adequate pharmacokinetic, safety and efficacy data exists from the other clinical sites. Therefore, the data from the Kenyan site should be excluded from analyses used to support dosing recommendation in this pediatric age group. The revised efficacy analysis after excluding the Kenyan data is comparable to the original result: 59% (original dataset) vs. 58% (revised dataset).

- Conclusions and recommendation

In addition to the types of clinical trial violations, one has to consider the type of disease, the patient population for which the study was conducted and the unmet medical need that exists for the patient population. Consider the following: HIV infection is a life-threatening disease, if untreated; the pediatric patient population is in need of additional antiretroviral drugs; and darunavir has been shown to be safe and effective for treatment

of HIV infection in patients 6 years of age and older. Therefore, the data from this trial should be considered crucial. Unless there is ethical misconduct or fraudulent data, every effort should be made to utilize the data. In addition, data collected from pediatric research subjects (i.e. children 3 to 6 years of age) who participated with full consent should not be easily discarded.

As stated previously, the Kenya site violations are serious and question the ethics in which the trial was conducted. Therefore, the data from this site should be excluded. However, the violations from the South African sites do not lead to conclusions that question the integrity of the data. In lieu of the fact that the data remains uncompromised, there are no scientific or ethical bases to exclude the South African data from analyses.

In summary, the trial results were re-analyzed excluding subjects from the Kenyan site. The final pharmacokinetic, safety and efficacy conclusions generally remained unchanged.

The overall recommendation for this NDA application is approval. The Applicant has agreed with the recommendations made by the Division (i.e. exclusion of the Kenyan data). Labeling changes to reflect the revised number of subjects who contributed to the analyses have been made by the Applicant and are acceptable.

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/s/

YODIT BELEW
12/14/2011

Cross-Discipline Team Leader Review

Date	September 9, 2011
From	Yodit Belew, M.D.
Subject	Cross-Discipline Team Leader Review
NDA/NDA # **Supplement #**	202895/21976 S-20 (to NDA 21976)
Applicant	Tibotec, Inc.
Date of Submission	March 29, 2011
PDUFA Goal Date	September 30, 2011
Proprietary Name / Established (USAN) names	Prezista(darunavir)
Dosage forms / Strength	New proposed dosage form: Oral Suspension Approved dosage forms: 300 mg tablets, 150 mg tablets
Proposed Indication(s)	Treatment of HIV infection
Recommended:	Approval

1. Introduction

This review summarizes the main issues for Tibotec's NDA seeking approval for Prezista Oral Suspension in pediatric patients 3 to 6 years of age and for older pediatric patients who are unable to swallow tablets. This review highlights the supporting pharmacokinetic, safety and efficacy (antiviral activity) data. Of note, Prezista Tablet Formulation is approved for use in HIV infected children 6 years of age and older weighing at least 20 kg. This application extends the intended population to 3 years of age and weighing at least 10 kg, and provides alternative dosing formulations for older children who cannot take the tablet formulation. Additionally, the NDA was granted a priority review as it pertains to pediatric population.

2. Background

Prezista, originally approved in June 2006, is an important product for adults and pediatric patients receiving antiretroviral treatment for HIV-1 infection. Prezista is recommended as a preferred protease inhibitor for initiation of ART in naïve adult and is recommended as an alternative regimen to pediatric patients 6 years of age and older. The recommended dose of Prezista in treatment naïve and experienced adult patients with no darunavir resistance associated substitutions is 800 mg of darunavir co-administered with 100 mg of ritonavir once daily. In treatment experienced adult patients with one or more darunavir resistance associated substitutions, the recommended dosage regimen is 600 mg of darunavir co-administered with 100 mg of ritonavir twice daily. The weight based dosing recommended in pediatric patients 6 years of age and older and weighing at least 20 kg is summarized in Table 1. Once daily dosing is not approved for pediatric patients (b) (4)

Table 1 Currently Approved Darunavir/ritonavir Dose for Pediatric Patients 6 to Less Than 18 Years of Age Weighing at Least 20 kg

Body Weight		Dose
(Kg)	(lbs)	
≥ 20 kg – < 30 kg	≥ 44 lbs – < 66 lbs	375 mg PREZISTA/50 mg ritonavir twice daily
≥ 30 kg – < 40 kg	≥ 66 lbs – < 88 lbs	450 mg PREZISTA/60 mg ritonavir twice daily
≥ 40 kg	≥ 88 lbs	600 mg PREZISTA/100 mg ritonavir twice daily

The proposed dosing regimen for pediatric patients 3 to 6 years of age who weigh at least 10 kg is also weight based:

- 10 kg to < 15 kg: darunavir (b) (4) mg/kg with ritonavir 3 mg/kg twice daily
- 15 kg to < (b) (4) kg: darunavir 375 mg with 50 mg of ritonavir twice daily

This current application fulfills one of the outstanding postmarketing requirements under Pediatric Research Equity Act (PREA): 'Deferred pediatric study under PREA for the treatment of HIV-1 infection in pediatric patients 3 to 6 years of age. Please evaluate dose requirements and safety in treatment-experienced pediatric patients 3 to 6 years of age with HIV-1 infection after preliminary review of data from the 6 to 17 year olds in trial TMC114-C212 with the Division of Antiviral Products (DAVP)' [requirement/commitment Number 1 under NDA 21976 S-6]. In addition, the current application, in combination with the previously submitted and reviewed pediatric study in children 6 years of age and older, fulfills the Pediatric Written Request issued in November 2006. The Applicant has been granted pediatric exclusivity.

3. CMC

With the exception of setting dissolution test acceptance criteria, no other issues have been identified by the CMC reviewer. Please refer to ONDQA's review by Mark Seggel for full detail. The Applicant and the ONDQA review team have agreed to the establishment of an interim dissolution test acceptance criterion. A Q of (b) (4) % at 45 minutes will be accepted as the interim setting while the Applicant continues to collect dissolution profiles at release and on stability. Refer to 'Recommendation for other Postmarketing Requirements and Commitments' under Section 9 for additional details.

In addition, the Division of Medication Error Prevention and Risk Management (DMEPA) identified potential dosing errors with use of the proposed dosing (b) (4). The Applicant included a dosing devise (b) (4) as part of the packaging for Darunavir Oral Suspension. Therefore, the (b) (4) was reviewed by DMEPA. Please refer to review by Loretta Holmes, Pharm.D for details. In summary, DMEPA was concerned that the (b) (4) is not generally used in the US and thus may lead to dosing errors. In addition to the lack of familiarity, DMEPA is concerned that the device is confusing as the measurement markings are displayed on the (b) (4) (i.e. opposite to the typical syringe markings found in the U.S.). DMEPA also reviewed dosing errors reported (via AERS) for (b) (4), a suspension medication (b) (4). DMEPA identified 2 cases of dosing errors that appear to be related to parent/s being confused about the devise. DMEPA recommended that that the proposed dosing (b) (4) be replaced with a standard oral dosing syringe.

The Applicant submitted a response to the concerns outlined by DMEPA. In summary, the Applicant believes it is in the 'best interests' of their patients and their caregivers to proceed with the originally submitted (b) (4). Their proposal considers the following points:

- Dosing accuracy of the originally submitted (b) (4) is confirmed with the oral suspension throughout the range suggested for dosing at increments of 0.2 mL
- Filling of the (b) (4) with the correct dose is achieved without inverting the (b) (4). Other products currently on the US market employing the (b) (4) dosing configuration include (b) (4).
- To assist caregivers in the proper use of the dosing (b) (4), a written instructions and pictographs as an aid to understanding the correct use of the (b) (4) has been prepared.

The Applicant also submitted an alternative dosing device- a syringe, similar to the standard oral dosing syringe used in the U.S., along with an adaptor to aid in drawing the medication directly from the bottle without spillage. A 'Use for Instruction' has also been included with the devise.

I agree with the Applicant that the original (b) (4) provides dosing measurement with such accuracy that it is superior to the alternative (b) (4) which is similar to the standard U.S. syringes. This is an important point to consider as it affects the daily administration of the medication. However, DMEPA remains concerned about potential dosing error because the devise differs from the standard syringe that patients are used to. The alternative dosing device is currently under review by CMC and DMEPA.

4. Nonclinical Pharmacology/Toxicology

The Applicant submitted the results of a toxicology study conducted to fulfill a post-marketing requirement (PMR) issued at the time of an sNDA 21,976 approval (2008). The PMR requested that the Applicant "perform a nonclinical reproductive study in a relevant species which achieves an adequate AUC exposure margin (compared to human serum exposure) in order to establish the safety profile of darunavir *in-utero'*. Refer to Dr. Laine (Peyton) Myer's review for further details. The Applicant conducted the study and confirmed the *in-utero* toxicity of darunavir - incomplete ossification of a number of bones and delayed thymus development. The Pharmacology/Toxicology review team has determined that the study fulfills the PMR requirement; the label has been updated with the new reproductive toxicology study information.

5. Summary of Pharmacokinetic Data

Two clinical studies were conducted under the current NDA- TMC114-C228 and TMC114-C169.

Trial C169 was a bioequivalence trial comparing a darunavir oral suspension formulation to darunavir tablets in healthy adult subjects. The trial was considered a pivotal trial by the Agency as it provided linkage between the oral suspension and tablet formulation. This is

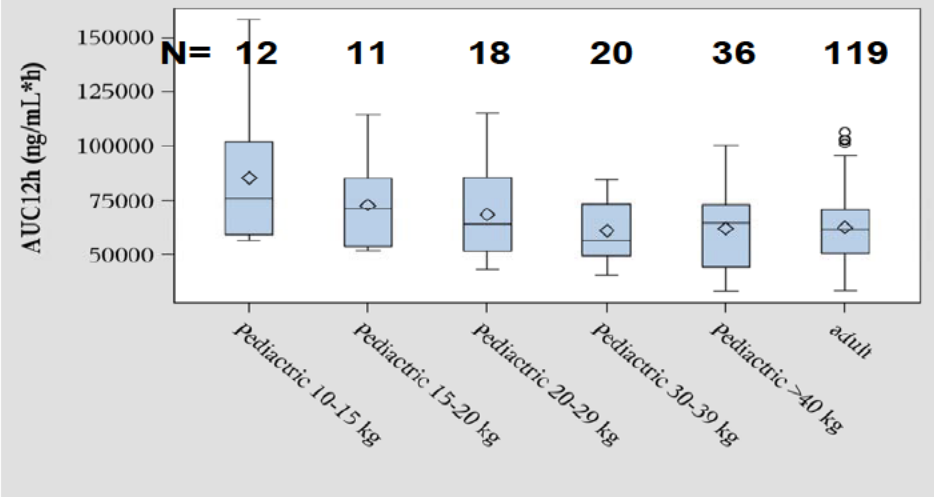
important as it would support allowing pediatric patients 6 years of age and older (and adult patients) who are unable to swallow tablets to be able to take the suspension formulation. Of note, the suspension formulation was used only in trial C228; no suspension formulation was used in trial C212 (pediatric patients 6 years of age and older) or in any of the HIV infected adult clinical trials. Therefore, a consultation for site investigation was issued by the Clinical Pharmacology Division to the Office of Scientific Investigations (OSI). Although no 483 observation was issued, OSI recommended that the bioequivalence results of the trial not be accepted because the trial did not retain samples of the drug products (i.e. test drug- suspension formulation or the reference drug- tablet formulation). However, it was left up to the review team whether the multiple pharmacokinetic data of the suspension formulation could be used to support dosing recommendations. The Office of Clinical Pharmacology determined that it was acceptable to rely on the pharmacokinetic data from the multiple dosing portion of the trial.

Despite this limitation of lack of supportive bioequivalence data, the review team was able to use alternative methods to allow dosing recommendations with the oral suspension formulation for older pediatric patients and adult patients. This recommendation is based on assumption that the two formulations have similar bioavailability. Please refer to the Clinical Pharmacology review for further details.

In summary, comparing the exposure (AUC, Cmax) data of darunavir suspension in healthy volunteer adults to the historical exposure data of darunavir tablets in HIV infected adults, the suspension formulation leads to higher exposure (AUC higher by up to 31%; Cmax higher by up to 35%). However, such increases are not anticipated to result in clinically significant safety issues based on review of previous adult darunavir exposure-safety data.

If the two formulations generally lead to similar exposures in adults, similar conclusions can be reached in children- that is, the two formulations would lead to generally similar exposures. Additionally, although there is no pharmacokinetic data available comparing exposures of darunavir suspension to tablets in pediatric subjects from within the same weight group, the exposures (AUC) observed in pediatric subjects 10-15 kg and 15-20 kg (suspension formulation) is generally similar to the exposures (AUC) observed in pediatric subjects weighing ≥ 20 kg and in adults (tablet formulations):

Figure 1 Darunavir exposures (suspension and tablets) in pediatrics and adults



Source: Pharmacometrics review team analysis

In conclusion, for adult and pediatric patients 6 years of age and older, the dosing recommendations for the suspension formulation is supported primarily by comparing the data from the adult multiple dosing pharmacokinetic data from C169 (suspension formulation) to the historical adult multiple dosing pharmacokinetic data. In addition, there is a secondary supportive data demonstrating that exposures of the tablet and suspension formulation are similar among the weight ranges.

TMC114-C228 which is currently ongoing, is a pediatric clinical trial evaluating the safety, pharmacokinetics and antiviral activity of darunavir/ritonavir twice daily administered in combination with other ART in HIV infected pediatric subjects 3 to less than 6 years of age and weighing 10 to < 20 kg. Twenty seven (27) treatment-experienced pediatric subjects were enrolled in the trial; the suspension formulation proposed for marketing was administered to all subjects. The pharmacokinetic, safety and efficacy data are discussed in details in the Clinical Review by Dr. Regina Alivisatos and in the Clinical Pharmacology and Pharmacometrics Review by Stanley Au (Pharm.D) and Dr. Jiang Liu. Please refer to the respective reviews for additional details. The main pharmacokinetic, safety and efficacy results are addressed in this review.

Summary of Important Clinical Pharmacology and Biopharaceutics Finding (C228)

Pediatric subjects who were on a stable but failing ART and with baseline HIV-1 RNA >1000 copies/mL, and with less than three darunavir associated substitutions were allowed for enrollment. The background regimen (BR) consisted of at least two ART, as selected by the investigators. The initial dosing was approximately 20 mg/kg of darunavir oral suspension combined with approximately 3 mg/kg of ritonavir oral suspension BID. The Week 2 pharmacokinetic (AUC) data showed that the darunavir exposure for both the 10 kg to < 15 kg and the 15 kg to < 20 kg groups were within 80% to 130% of the target AUC (62.3 µg*hr/mL). However based on simulated population pharmacokinetic analysis, the applicant revised the dosing to approximately: darunavir/ritonavir 25/3 mg/kg twice daily for subjects weighing between 10 kg to < than 15 kg and 375/50 mg twice daily for subjects weighing between 15 kg to < 20 kg. Two weeks after dosage adjustment, the population PK analysis was repeated and was concluded that the trial could proceed using the adjusted darunavir dosage regimens. Comparative results of the mean AUC in the initial and adjusted dosage regimens to the mean target adult exposure of 62.3 µg/mL*hr are summarized below:

Before Dose Adjustment			After Dose Adjustment		
Overall	10 to < 15 kg	15 to < 20 kg	Overall	10 to < 15 kg	15 to < 20 kg
107%	111%	104%	128%	140%	122%

Source: Clinical Pharmacology and Pharmacometrics Review

After the darunavir dosage regimens were adjusted, for subjects weighing 15 kg to < 20 kg, the darunavir mean exposure (AUC) value was within 80% to 130% of the target mean adult AUC (i.e. 128%). But for subjects weighing 10 kg to < 15 kg, the exposure was greater than 130% (i.e. 140%). In other words, compared to the targeted mean adult darunavir exposure, the exposure (AUC) was 22% higher in pediatric subjects weighing 15 kg to < 20 kg and 40% higher in pediatric subjects weighing 10 kg to < 15 kg. The Agency generally suggests a pediatric exposure range of 80%-130% of the targeted mean adult exposure (AUC). A 22% higher exposure is similar to what would be observed during a drug-drug interactions where no dose adjustment would be recommended; a 40% higher exposure is only 10% higher than the upper bound recommended range (i.e. 30%). But more importantly, the applicant has

provided clinical safety data to support the higher exposure in subjects weighing 10 to <15kg. The 40% higher exposure is not expected to result in clinically significant safety issues based on the exposure-safety analysis performed as well as on the overall safety analysis conducted for darunavir when administered in pediatric subjects (see Safety Section below).

6. Efficacy Evaluation

The primary efficacy endpoint was plasma viral load < 50 copies/mL at Week 24. The proportion of subjects with plasma viral load < 50 copies/mL at Week 24 (based on FDA snapshot algorithm) was 59% (16/27). Eleven subjects were considered non-responders: nine subjects were classified as virologic failures (HIV RNA >50 copies/mL), one subject had missing data, and one subject had no data due to early discontinuation. Of note, all subjects considered to be virologic failures had HIV RNA < 400 copies/mL at Week 24. Refer to Dr. Alivisatos' review for additional details.

Table 2 Virologic Outcome at Week 24

	DRV/r N = 27
Virologic Success (HIV RNA <50 copies/mL), n (%)	16 (59)
Non-responders, n (%)	11(40)
Virologic Failure*	9 (33)
No virologic data week 24-discontinued due to AE/death#	1 (4)
Missing data week 24	1 (4)

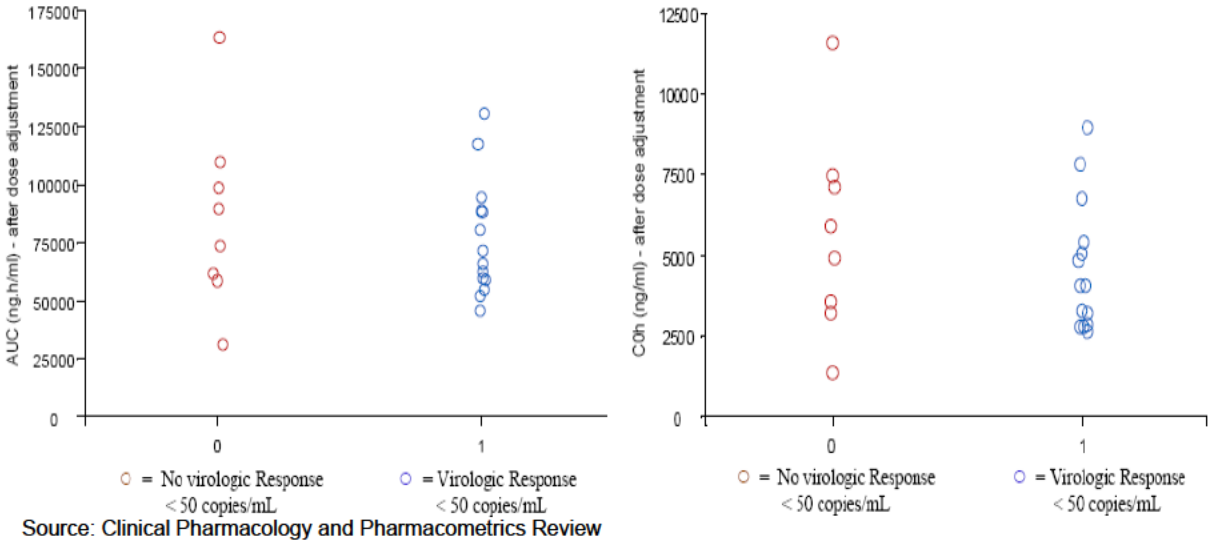
* Includes a) subjects who had ≥ 50 copies/mL in the Week-24 window, b) subjects who discontinued prior to Week 24 for lack or loss of efficacy, c) subjects who had a switch in their OBR that was not permitted by the protocol (provided the switch occurred before the earliest onset of an AE leading to permanent stop of trial medication), and d) subjects who discontinued for reasons other than AEs/death, and lack or loss of efficacy (provided their last available viral load was detectable).
#Includes subjects who discontinued due to AE or death at any time point from Day 1 through the Week-24 time window if this resulted in no virologic data on treatment during the specified window (provided the earliest AE leading to permanent stop was not preceded by a switch in the OBR that was not permitted by the protocol).

The observed success rate (HIV RNA <50 copies/mL) in this pediatric age group (i.e. 3 to 6 years of age) is similar to the overall observed success rate in TMC114-C212 (pediatric study in children 6 years of age and older) – 57%; the proportion of subjects with HIV RNA <50 copies/mL at Week 24 was 75% in the 6 to12 year old group and 39% in the 12 to 18 year old group. The overall virologic success rates in treatment experienced adult subjects range from 58%- 69%.

In subjects 3 to <6 years of age, the virologic success rate, defined as proportion of subjects with HIV RNA < 400 copies/mL at Week 24, was 93% (25/27). The overall response rates observed in trial TMC114-C212 was 65%: 88% in the 6 to12 year old age group and 54% in the 12 to 18 years group. The observed virologic success rate (<400 copies/mL) in treatment experienced adult subjects during Phase 2b trials was 55%.

The exposure response analysis conducted by the Applicant compared the range of darunavir exposure (AUC and Ct) in subjects with virologic success to subjects who were virologic failures- HIV RNA ≥ 50 copies/mL (see Figure 2). There was no exposure-response relationship identified between the two groups.

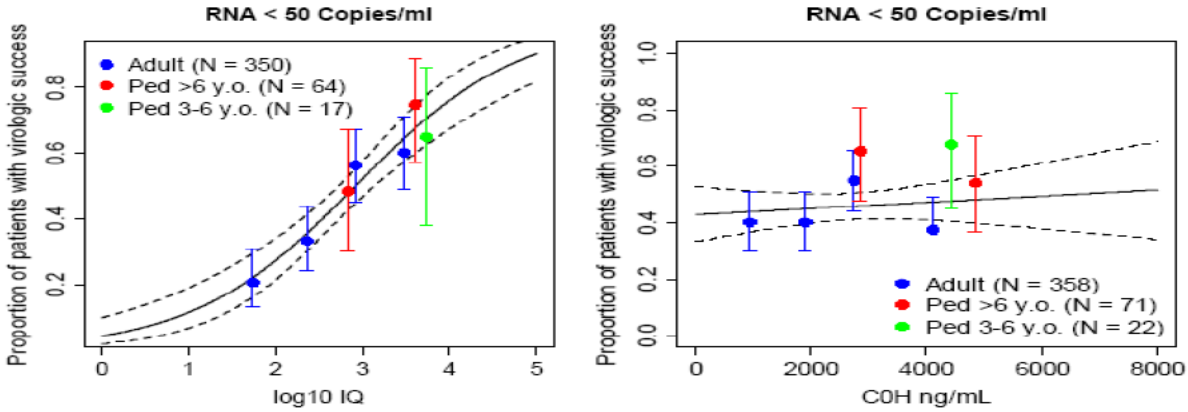
Figure 2 Comparison of AUC and C_t for subjects either achieving virologic response or not achieving virologic response (HIV RNA <50 copies/mL).



Source: Clinical Pharmacology and Pharmacometrics Review

Additional analyses evaluated the inhibitory quotient (IQ) and the proportion of subjects achieving HIV RNA < 50 copies/mL. Refer to Clinical Pharmacology and Pharmacometrics Review for details. For the purpose of the review analyses, the IQ was defined as the ratio of the darunavir C_t to IC_{50}. Previously conducted analysis in older pediatric subjects and adults had demonstrated positive relationship between IQ and virologic success (Figure 3). Although direct comparison between the IQ and virologic success could not be made for the 3 to <6 years of age group (unable to break down data into multiple groups), the proportion of subjects with virologic success at the median (C_t) was generally consistent with the previous results from older pediatric subjects and adults.

Figure 3 Evaluation of IQ and darunavir C_t and the proportion of subjects achieving virologic response (HIV RNA < 50 copies/mL)



Source: Clinical Pharmacology and Pharmacometrics Review

Analysis of virologic outcome by baseline mutations showed that at baseline, two patients harbored darunavir resistance associated mutations (DRV RAMs) - one subject with L33F

and L76V mutations, another subjects with L76V mutation. Both subjects had HIV RNA <50 copies/mL at Week 24.

In summary, although the trial did not have a comparative arm, when cross trial comparisons are made, the virologic success rates (HIV RNA <50 copies/mL or <400 copies/mL) observed in this pediatric trial were generally similar to previously reported rates in older pediatric subjects and in adults. No exposure-response relationship was identified.

7. Safety Evaluation

The data submitted support safety and tolerability of darunavir when co-administered with ritonavir in combination with other ARVs. The Applicant has submitted safety data on 27 pediatric patients with at least 24 week safety data. Darunavir, when co-administered with ritonavir in combination with other antiretroviral drugs, was generally safe and tolerated in pediatric subjects 3 to < 6 years of age. No new safety issues were identified. The adverse events (AEs) reported were similar to those reported in adults and in older pediatric subjects. No exposure-safety relationships were identified for hepatic, cardiac or rash adverse events.

As with most pediatric HIV trials, this clinical trial did not have an active comparator arm. Therefore, the results discussed below have some limitations. Refer to Dr. Alivisatos' review for additional details.

During the 24 week treatment period, 1 patient (5 year old female) discontinued the trial due to AE (vomiting). The vomiting (Grade 2) started on Day 1 of the treatment period and continued through study day 14. The investigator considered the event to be very likely related to ritonavir, but not darunavir. The vomiting resolved immediately after treatment discontinuation (D14). The viral load at the time of discontinuation was 8,540 copies/mL (Baseline 214,000 copies/mL).

There were no deaths reported during the 24 week treatment period.

The most common adverse events (all grades, regardless of causality) reported in at least 3 subjects were (by preferred term): upper respiratory tract infection (33%, n=9), diarrhea (30%, n=8), hypokalemia (19%, n=5), alkalosis, cough and nasopharyngitis (15%, n=4 each).

No treatment related grade 3 or higher adverse events were reported after the darunavir dosage regimens were adjusted (i.e. after Week 2).

Hepatic-related events were considered submission specific primary safety concerns. Three patients (11%) had 1 liver-related adverse event during the treatment period (AST increased, ALP increased, hepatosplenomegaly). All were grade 2 in severity. AST increased was considered possibly related to DRV. None of the events were reported as an SAE, or led to permanent treatment discontinuation. There were no subjects meeting Hy's Law criteria (i.e., ALT or AST > 3 x ULN, in combination with total bilirubin elevation > 2 x ULN, or INR > 1.5).

Rash or skin reactions were also considered as submission specific primary safety concerns. Terminologies such as rash, papular, macular, maculo-papular, urticaria, drug rash, hypersensitivity, pruritic rash and pruritis were selected for analysis. Four events (regardless of causality, severity) were reported from three subjects. The events included: erythema (1

patient), rash (1 patient), and rash papular and rash pruritic (both in the same patient). One subjects had grade 1 rash (papular) considered possibly treatment-related. No rash-related AEs were reported as serious events, or led to permanent treatment discontinuation.

With the exception of the one subject with grade 2 increased AST (referenced above), there were no additional liver-related laboratory parameters reported as abnormal.

All except 1 hematology laboratory abnormality were grade 1 in severity. Grade 3 decreased neutrophils was observed in 1 patient at Week 24; this patient had grade 1 decreased neutrophils at screening, and marked fluctuations during treatment period.

In summary, darunavir when co-administered with ritonavir and other ARTs, was generally safe and tolerated. There were no deaths, non-fatal serious or severe (grade 3 or higher) treatment-related events reported. There were no significant hepatic- or skin- related events. There were no grade 3 or higher liver-related laboratory abnormalities. No subject discontinued treatment due to darunavir toxicity.

8. Labeling

Package Insert

The following revisions to the Dosing and Administrations section of the USPI were successfully negotiated:

Dosing recommendations for pediatric patients weighing at least 10 kg but less than 15 kg

The weight-based dose in pediatric patients weighing less than 15 kg is PREZISTA (b) (4) mg/kg with ritonavir 3 mg/kg which can be dosed using the following table:

Table 1: Recommended Dose for Pediatric Patients with PREZISTA Oral Suspension (100 mg/mL) and Ritonavir Oral Solution* for Pediatric Patients Weighing 10 kg to Less Than 15 kg

Body weight (kg)	Dose (twice daily with food)
Greater than or equal to 10 kg to less than 11 kg	PREZISTA (b) (4) mg ((b) (4) mL) with ritonavir 32 mg (0.4 mL)
Greater than or equal to 11 kg to less than 12 kg	PREZISTA (b) (4) mg ((b) (4) mL) with ritonavir 32 mg (0.4 mL)
Greater than or equal to 12 kg to less than 13 kg	PREZISTA (b) (4) mg ((b) (4) mL) with ritonavir 40 mg (0.5 mL)
Greater than or equal to13 kg to less than 14 kg	PREZISTA (b) (4) mg ((b) (4) mL) with ritonavir 40 mg (0.5 mL)
Greater than or equal to 14 kg to less than 15 kg	PREZISTA (b) (4) mg ((b) (4) mL) with ritonavir 48 mg (0.6 mL)
*with ritonavir oral solution: 80 mg/mL	

Dosing recommendations for pediatric patients weighing at least 15 kg

Pediatric patients who weigh at least 15 kg and are able to swallow tablets can be dosed using the following table:

Table 2: Recommended Dose for Pediatric Patients with PREZISTA Tablets and Ritonavir Oral Solution or Tablets/Capsules for Pediatric Patients Weighing At Least 15 kg

Body Weight (kg)	Dose (twice daily with food)
Greater than or equal to 15 kg to less than 30 kg	PREZISTA 375 mg with ritonavir* 50 mg (0.6 mL)
Greater than or equal to 30 kg to less than 40 kg	PREZISTA 450 mg with ritonavir* 60 mg (0.75 mL)
Greater than or equal to 40 kg	PREZISTA 600 mg with ritonavir† 100 mg

*with ritonavir oral solution: 80 mg/mL
† with ritonavir capsules or tablets: 100 mg

Pediatric patients who weigh at least 15 kg but are unable to swallow tablets can be dosed using the following table:

Table 3: Recommended Dose for Pediatric Patients with PREZISTA Oral Suspension (100 mg/mL) and Ritonavir Oral Solution* for Pediatric Patients Weighing At Least 15 kg

Body Weight (kg)	Dose (twice daily with food)
Greater than or equal to 15 kg to less than 30 kg	PREZISTA 375 mg† (3.8 mL) with ritonavir 50 mg (0.6 mL)
Greater than or equal to 30 kg to less than 40 kg	PREZISTA 450 mg# (4.6 mL) with ritonavir 60 mg (0.75 mL)
Greater than or equal to 40 kg	PREZISTA 600 mg (6.0 mL) with ritonavir 100 mg (1.25 mL)

*with ritonavir oral solution: 80 mg/mL
† The 375 mg dose refers to the dose using darunavir tablets for this weight group, which is rounded off to 3.8 mL for suspension dosing.
# The 450 mg dose refers to the dose using darunavir tablets for this weight group, which is rounded off to 4.6 mL for suspension dosing.

Patient Package Insert

After routine consultation to the Division of Risk Management (DRISK) was made, significant updates to the PPI were recommended. The primary content of the recommendations are formatting and reorganization of the information contained within the PPI. These recommendations have been incorporated into the label.

Dosing Devise

The Applicant included a dosing devise (b) (4) as part of the packaging for Darunavir Oral Suspension. As discussed earlier, DMEPA recommended that alternative dosing device be used for administration of darunavir oral suspension.

The Applicant favors the originally proposed (b) (4) as it allows for better precision when drawing the medication. The proposed alternative dosing device is currently under review.

9. Outstanding Issues

The following item need to be resolved prior to approval of this NDA:

- Dosing device: The alternative dosing device, along with the 'Instruction for Use' as proposed by the Sponsor, is currently under review by DMEPA and ONDQA.

10. Recommendations/ Risk Benefit Assessment

I recommend the approval of this NDA, pending the resolution of all outstanding CMC/dosing device issues. The data from the current NDA provides sufficient pharmacokinetic evidence to recommend darunavir twice daily dosing, co-administered with ritonavir in combination with other ART for the treatment of HIV-1 infection in pediatric patients 3 to < 6 years of age. The dose selected and administered after the Week 2 pharmacokinetic analysis led to darunavir exposure (AUC) that was within (80% to 130%) or higher (140%) of the target mean adult AUC. As no exposure-safety relationship was identified during the analysis, the 40% higher exposure is not expected to result in clinically significant safety issues.

Results from C228 demonstrated that darunavir was an effective treatment in suppressing HIV RNA below assay limits of detection. Overall the proportion of subjects with HIV RNA < 50 copies/mL and <400 copies/mL at Week 24 were 59% and 93%, respectively. In addition, all nine subjects considered to be virologic failures (≥ 50 copies/mL at Week 24) had HIV RNA < 400 copies/mL. No subject discontinued due to virologic failure. One subject discontinued due to vomiting. Although this subject had HIV RNA >400 at the time of discontinuation, the subject had only been on treatment for 14 days before treatment discontinuation.

There were neither new safety signals identified nor were there safety differences identified between pediatric subjects 3 to <6 years of age and the older pediatric subjects or adults.

Recommendation for other Postmarketing Requirements and Commitments

A Phase IV Post-Marketing Commitment (PMC) has been recommended by ONDQA reviewers. The objective of the PMC is to provide the additional dissolution data from full-scale manufactured batches that are needed for the setting of the final regulatory dissolution specification, specifically, to collect dissolution profile data from all available full-scale manufactured batches, during the first 12 months after approval of the NDA.

The collection of dissolution data will target the dissolution specification recommended by the FDA (see bullet below) and will include dissolution testing at Stage 1, 2, or 3 as appropriate.

- Q = (b) (4) % at 30 minutes

(b) (4)

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/s/

YODIT BELEW
09/16/2011