CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

205395Orig1s000

SUMMARY REVIEW

Cross-Discipline Team Leader Review

Date	December 23, 2014
From	Mary Singer, MD PhD
Subject	Cross-Discipline Team Leader Review
NDA/BLA #	NDA 205395
Applicant	Janssen
Date of Submission	March 28, 2014
PDUFA Goal Date	January 31, 2015
Proprietary Name / Established (USAN) names	Prezcobix (Darunavir/cobicistat)
Dosage forms / Strength	Fixed dose combination tablet/ 800 mg darunavir and 150 mg cobicistat
Proposed Indication(s)	Treatment of HIV-1 infection in adults in combination with other antiretroviral agents
Recommended:	*Approval*

1. Introduction

Darunavir, an HIV protease inhibitor, coadministered with ritonavir, was initially approved for treatment of HIV-1 in combination with other antiretroviral agents in June, 2006. Darunavir (Prezista) is currently available as film coated tablets (75, 150, 600, and 800 mg) and as an oral suspension for use in pediatric patients 3 years and older. In treatment-naïve and treatment-experienced adults with no darunavir resistance- associated substitutions, darunavir is dosed as 800 mg with 100 mg ritonavir once daily. In treatment-experienced adults with at least one darunavir resistance-associated substitution, the darunavir dosage is 600 mg coadministered with 100 mg ritonavir twice daily. Pediatric dosing of darunavir with ritonavir is based on weight in patients 3 years of age and older. Darunavir (Prezista) was developed by Janssen Pharmaceuticals, Inc.

Cobicistat was developed by Gilead Sciences as an alternative pharmacokinetic "booster" to ritonavir, and was approved as a single entity on September, 2014 for the indication of increasing systemic exposure of atazanavir or darunavir (once daily dosing regimen) in combination with other antiretroviral agent in treatment of HIV-1 infection. Cobicistat, like ritonavir is a strong CYP3A inhibitor, but is has no antiretroviral activity. Cobicistat was initially approved in 2012 as part of the fixed dose combination tablet, Stribild, which contains cobicistat, elvitegravir, emtricitabine, and tenofovir disoproxil fumarate for treatment of HIV-1.

2. Background

Janssen, in collaboration with Gilead, developed a fixed dose combination tablet containing darunavir 800 mg and cobicistat150 mg. The proposed indication for this fixed dose tablet is treatment of HIV-1 infection in (b) (4)-naïve and (b) (4)-experienced adults with no darunavir resistance associated substitutions.

The safety and efficacy of the darunavir/cobicistat fixed dose combination tablet was based on that of the individual approved products, darunavir (in combination with low dose ritonavir used to increase darunavir exposure by virtue of its CYP3A inhibitory activity) and safety and activity of cobicistat. The safety and efficacy of darunavir in combination with ritonavir was based on randomized controlled trials of darunavir/ritonavir in treatment-naïve and treatment-experienced HIV-infected adults and pediatric patients, as reviewed for NDAs 21976 and 202895. The safety and activity of cobicistat was based on a trial comparing safety and efficacy of atazanavir/cobicistat (300 mg/100 mg) to atazanavir/ritonavir (300 mg/100 mg) in treatment-naïve adults, as well as on pharmacokinetic bridging data which showed atazanavir exposures similar to that when atazanavir was coadministered with ritonavir. Cobicistat is also approved for use with darunavir (administered as single entities), based on pharmacokinetic bridging data, as reviewed for NDA 203094. For this NDA submission, the following trials were submitted as a bridge to the individual components of the FDC:

1. TMC114IFD1001: a phase one oral bioavailability study which evaluated two FDCs of DRV/Cobi (G003 and G004) compared to darunavir/ritonavir 800 mg/100 mg daily;
2. TMC114IFD1003: a phase one bioequivalence study of the selected FDC formulation compared to DRV and Cobi administered as single agents; and
3. GS-US-216-0130: a phase 3 open-label, single arm study of DRV and Cobi administered as single agents in ART-naïve or experienced HIV-infected adults.

Note that the first bioavailability trial, TMC114IFD1001, was not considered essential for this submission and was not reviewed; while TMC114IFD1003 was considered the pivotal trial for this submission. Trial TMC114IFD1003 demonstrated that the darunavir exposures achieved with darunavir/cobicistat FDC tablet were similar to those observed with darunavir coadministered with cobicistat as single entities. The single-arm, open-label GS-US-216-0130 trial was considered supportive to provide 24 week safety information for DRV 800 mg coadministered with cobicistat 150 mg.

3. CMC/Device

The drug product, Prezcobix, is an immediate release film-coated tablet consisting of a fixed dose combination (FDC) of 800 mg equivalent of darunavir (b) (4) and 150 mg equivalent of cobicistat (b) (4) The tablets are oval shaped, debossed and film-coated with a pink color. The darunavir/cobicistat 800 mg/150 mg tablets are packaged in 120 mL, white, high density polyethylene (HDPE) bottles. Each bottle contains 30 tablets and is capped (b) (4) . A shelf life of 24 months is granted for all climatic zones for drug product packaged in the proposed commercial container closure system.

The Drug Master Files (DMFs) for the darunavir and cobicistat drug substances are adequate. The Drug Master Files (DMF 25188 and DMF 18825) for the cobicistat on silicon dioxide and darunavir ethanolate drug substances supporting this NDA are adequate. Information on characterization of impurities for darunavir and cobicistat drug substances is included in the respective DMFs, and no new impurities were observed in the 800/150 mg darunavir/cobicistat film-coated tablets. Information provided for NDA 205395 regarding drug product manufacturing, raw materials controls and specifications, analytical methods, and drug product stability is adequate to support the quality of the drug product through its shelf-life of 24 months.

All requested inspections of manufacturing sites for drug product and drug substance have been completed and the overall recommendation from the Office of Compliance is "Acceptable" for establishment evaluation. The Product Quality Microbiology Review by Dr. Erika Pfeiler recommends approval; and from a CMC perspective, the NDA has provided adequate information to assure the identity, strength, purity and quality of the drug product,

and is recommended for approval. For full details, see CMC review by Fuqiang Liu, Ph.D. and Stephen Miller, Ph.D.

4. Nonclinical Pharmacology/Toxicology

No new pharmacology/toxicology studies were submitted to the NDA and there have been no new safety concerns based on non-clinical studies identified with darunavir or cobicistat.

5. Clinical Pharmacology/Biopharmaceutics

Because the efficacy and safety of darunavir has been established as a single entity in combination with ritonavir for treatment of HIV-1 (see NDAs 21976 for 202895 for Prezista tablet and oral suspension, respectively), a clinical trial to evaluate the efficacy and safety of FDC darunavir/cobicistat tablet was not required; and the efficacy and safety of this new combination product relies on that previously established for darunavir, and on the safety and activity of cobicistat along with the pharmacokinetic bridging data discussed above. Cobicistat, a CYP3A inhibitor with no intrinsic antiviral activity was approved as a single entity as a pharmaco-enhancer for the HIV protease inhibitors, atazanavir and darunavir (NDA 203094, approved September 2014) and as part of the FDC Stribild (elvitegravir, cobicistat, emtricitabine, and tenofovir disoproxil fumarate (NDA 203100, approved 2012).

The pivotal trial for this NDA, TMC114IFD1003 (1003), compared the relative bioavailability of darunavir and cobicistat administered as part of the FDC tablet to single entity formulations of daruanvir (two 400 mg tablets) and cobicistat (150 mg tablets). This trial also evaluated the food effect data for the darunavir/cobicistat FDC tablet. The Clinical Pharmacology review evaluated the food effect data; while the Biopharmaceutics review evaluated the relative bioavailability data, the inspections findings by the Office of Scientific Investigations (OSI), as well as the relevant bioanalytical information. The Biopharmaceutics review also evaluated drug product dissolution method development and acceptance criteria as well as drug product formulation development and dissolution quality risks. For full details, please see Clinical Pharmacology review by Drs. Stanley Au and Kellie Reynolds, in the Office of Clinical Pharmacology; and the Biopharmaceutics review by Drs. Minerva Hughes and Angelica Dorantes, in the Office of New Drug Quality Assessment.

In brief, the 90% confidence intervals for darunavir exposure were within 80-125% for the FDC tablet compared to the single entity tablets of darunavir and cobicistat in trial 1003, as noted in the Biopharmaceutics review. The dissolution methods and acceptance criteria were considered acceptable by the Biopharmaceutics reviewers for product quality control. The Office of Scientific Investigation (OSI) was consulted to inspect the clinical and bioanalytical sites used for trial 1003 and found all clinical and analytical study data acceptable. The Biopharmaceutics reviewers have recommended approval of this NDA for the darunavir/cobicistat FDC tablet.

In trial 1003, a food effect was observed for darunavir when administered with cobicistat as a fixed dose combination tablet, as noted in the Clinical Pharmacology review. An increase in darunavir AUC and Cmax (70% and 127%, respectively) was demonstrated when the darunavir/cobicistat FDC tablet was administered with a high fat meal in comparison to fasting. This increase in exposure was somewhat higher than that observed in previous studies in which darunavir was administered with ritonavir as single entities (48% increase in darunavir AUC and 59% increase in Cmax) under high fat compared to fasted conditions. No food effect was observed for cobicistat administered as part of the darunavir/cobicistat FDC product in trial 1003. The darunavir (Prezista) full prescribing information includes a recommendation that darunavir in combination with ritonavir be administered with food; and because no specific exposure-related safety issues have been identified for darunavir at the recommended darunavir/ritonavir dosage regimens, the Applicant's recommendation to administer darunavir/cobicistat FDC tablet with food was considered acceptable; and the Clinical pharmacology reviewers have recommended approval for this NDA.

6. Clinical Microbiology

Please see Clinical Microbiology Review by Drs. Takashi Komatsu and Jules O'Rear for full details. In brief, the single arm, open-label trial, GS-US-216-0130, in which treatment-naïve and treatment-experienced HIV-1 infected subjects who had no darunavir resistance-associated substitutions were treated for 24 weeks with darunavir 800 mg plus cobicistat 150 mg as single entities in combination with 2 fully active NRTIs was reviewed to evaluate development of resistance-associated substitutions in subjects who experienced virologic failure. None of the subjects had primary resistance substitutions for darunavir at screening. A total of 36 subjects with evaluable resistance data (30/277, 11% treatment naïve and 6/17, 35% treatment-experienced subjects) were identified as having virologic failure. Among virologic failure subjects with available genotypic data, a total of 10 amino acid substitutions in the HIV protease developed on treatment. Five of these were identified in 5 treatment-naïve subjects and 5 were identified in 5 treatment-experienced subjects with virologic failure. One subject developed the DRV resistance-associated substitution, PI I84I/V; however the susceptibility to DRV was not reduced in the isolate from this subject possibly due to a mixture of wild type (I) and mutant (V) viruses. No new darunavir resistance-associated substitutions were identified; and none of the subjects with available genotypic data developed primary resistance-associated substitutions to any of the reverse transcriptase inhibitors.

7. Clinical/Statistical- Efficacy

The Applicant conducted an open-label, single arm, multicenter trial, GS-US-216-0130, to evaluate safety and efficacy of darunavir/cobicistat as single entities coadministered with 2 fully active NRTIs in HIV-1 infected, antiretroviral treatment-naïve (n=295) and treatment-experienced (n=18) adults with no DRV resistance-associated substitutions. As efficacy for the darunavir/cobicistat fixed dose combination tablet is extrapolated from that of darunavir/ritonavir, this trial was considered supportive for efficacy and safety. At baseline,

the median age of subjects was 35 years, 11% were female, 40% were non-white, 42% had HIV-1 RNA >100,000 copies/mL, and 19% had CD4+ cell count <200 cells/mm^3. At 24 weeks, 82% of subjects treated with darunavir coadministered with cobicistat plus two nucleoside reverse transcriptase inhibitors achieved HIV RNA <50 copies/mL. At 24 weeks, 247/295 (84%) treatment-naïve subjects and 11/18 (61%) treatment-experienced subjects achieved an HIV RNA < 50 copies/mL. In a cross-study comparison, at 48 weeks, HIV RNA < 50 copies/mL at 48 weeks was achieved in 84% treatment-naïve subjects treated with darunavir/ritonavir 800 mg/100 mg once daily and in 78% subjects treated with lopinavir/ritonavir 800 mg/200 mg once daily both in combination with tenofovir disoproxil fumarate and emtricitabine (Trial TMC114-C211, as reviewed for NDA 21976). In treatment-experienced patients with no darunavir associated resistance substitutions, 69% subjects who received darunavir/ritonavir 800 mg/100 mg once daily, and 69% subjects who received darunavir/ritonavir 600 mg/100 mg twice daily plus an optimized background regimen achieved HIV RNA < 50 copies/mL at week 48 in Study TMC114-C214 (NDA 21976). Acknowledging the limitations of cross-study comparisons and of interpreting data from a single arm, noncomparative trial, the results of GS-US-216-0130 provide support that DRV coadministered with cobicistat has adequate antiviral activity. See Dr. Sarita Boyd's clinical review for further details. A statistical review was not considered necessary for this application, as trial GS-US-216-0130 is not considered an adequate well-controlled trial and is considered solely as supportive information for this NDA.

8. Safety

The safety of darunavir/cobicistat FDC tablet is extrapolated from the safety of darunavir/ritonavir reviewed under NDA 21976. The ongoing open-label, single arm, multicenter trial, GS-US-216-0130 submitted with this application was considered supportive for safety. The 24 week safety data was reviewed by Dr. Sarita Boyd, and no new safety concerns were identified. The following table summarizes safety findings at the 24 week cut point for trial GS-US-216-0130. No deaths were reported in the trial, and overall, 88% subjects experienced at least one adverse event, 5% had a serious AE, 5% discontinued due to AE, and 6% experienced a Grade 3 or 4 AE.

Table 1. Safety Summary for GS-US-216-0130 (24 week timepoint)

	Darunavir 800 mg plus cobicistat 150 mg daily N= 313 n (%)
Any adverse event	275 (88)
Serious adverse event	15 (5)
Discontinuation due to adverse event	15 (5)
Death	0
Severe (grade 3 or 4 AE)	18 (6)

N= number of subjects

The most common SAEs in this trial were fever and rash, reported in 2 subjects each. Investigators considered 3 SAEs related or possibly related to study drugs: immune reconstitution syndrome, rash, and maculopapular rash. No cases of Stevens Johnson syndrome, DRESS, or TEN were reported in this trial. Darunavir and cobicistat have each been associated with rash (see full prescribing information for each), so rash is not unexpected with the darunavir/cobicistat FDC tablet. Immune reconstitution syndrome has been associated with antiretroviral therapy, and is found as a Warning in the prescribing information for HIV protease inhibitors.

The most common adverse events resulting in study drug discontinuation were rash in 9 subjects (3%), hypersensitivity in 2(0.6%) subjects (described as rash in one subject and rash with angioedema in one subject), and nausea in 2 subjects (0.6%). Overall, the most common AEs regardless of causality were rash (7%), diarrhea (5%), upper respiratory tract infection (4%), and nausea (3%). The most common AEs considered related to study drugs by investigators were rash (5%), nausea (2%) and diarrhea (2%). These adverse events have all been described in prescribing information for darunavir and/or cobicistat. Darunavir has been associated with rashes ranging from mild to severe, and the full prescribing information includes a Warning for severe skin reactions.

Grade 3 or 4 laboratory abnormalities were reported for ALT in 7 subjects (2%), and AST in 6 subjects (2%). ALT and AST elevation was not associated with bilirubin elevation fitting Hy's law criteria in any of these subjects. One subject with Gilbert's syndrome at baseline experienced a grade 3 bilirubin elevation with no concomitant ALT, AST or alkaline phosphatase elevation. No grade 3 or 4 creatinine elevation was reported, although 23 subjects (7%) had grade 1 or 2 creatinine elevation, as expected with cobicistat. Grade 3 or 4 amylase and lipase elevations were reported in 6 (2%) and 5 (2%) subjects, respectively; however amylase and/or lipase elevations were not associated with pancreatitis or symptoms of pancreatitis. Grade 3 or 4 hematologic abnormalities were reported in 4 subjects with neutropenia, 1 with thrombocytopenia, and 1 with anemia (hemoglobin 6.5- < 7.5). All 4 subjects with neutropenia received tenofovir/emtricitabine (TDF/FTC) in addition to darunavir and cobicistat. Neutropenia in these subjects was not associated with any reports of infection or other adverse events, and was not considered clinically significant. The single report of Grade 4 thrombocytopenia was associated with an SAE of idiopathic thrombocytopenic purpura (ITP), which is associated with HIV infection; and the Grade 3 hemoglobin decrease was reported in a patient with severe pelvic inflammatory disease.

Review of the 120-day safety update, which included additional safety information from the ongoing trial, GS-US-216-0130, and from the renal impairment trial, GS-US-236-0118, did not reveal any new or unexpected adverse reactions.

9. Advisory Committee Meeting

An Advisory Committee meeting was not held for this application.

10. Pediatrics

Efficacy of antiretroviral therapy can be extrapolated from adults to pediatric patients with HIV, because the pathophysiology of HIV infection is similar in both, and because suppression of HIV RNA is associated with decreased morbidity (i.e. AIDS or non-AIDS related morbidity) and mortality in both adult and pediatric patients. The cobicistat commercial sponsor has a PREA requirement to evaluate darunavir coadministered with cobicistat as single entities in pediatric patients to assess safety, antiviral activity and pharmacokinetics in order to determine appropriate dosing regimens.

This applicant will have a PREA requirement for each pediatric age group noted below to evaluate the pharmacokinetics, safety, and antiviral activity of darunavir/cobicistat fixed dose combination (FDC) age-appropriate formulation in HIV-infected pediatric subjects (ages 3 year to < 6 years weighing at least 15 kg, ages 6 years to < 12 years; and ages 12 to (b) (4) years of age). A pediatric clinical trial may not be required if the dosing recommendation for the FDC age-appropriate formulation can be supported by pediatric trials already conducted with the individual drug products and if the age-appropriate FDC formulation produces similar exposures as the individual components. The Applicant will also evaluate the relative oral bioavailability of the darunavir/cobicistat age-appropriate fixed dose formulation in comparison to the individual components in healthy adults once pediatric doses are established for darunavir and cobicistat. (b) (4)

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(b) (4)

The bioequivalence of the fixed dose combination product, darunavir/cobicistat 800 mg/150 mg has already been established in healthy adults in comparison to the single agents, and may be appropriate for some pediatric patients (e.g. adolescents).

The Applicant requested a waiver for a pediatric assessment in patients < 3 years old because of safety concerns with darunavir in this age group. Darunavir has been approved in pediatric patients ≥ 3 years of age, but not in younger patients because of increased mortality observed in a juvenile animal toxicity study. A waiver for pediatric assessments in pediatric patients ≥ 3 years of age weighing < 15 kg was also requested for the fixed dose combination because the product fails to represent a meaningful therapeutic benefit over existing therapies (i.e. darunavir and ritonavir are currently available as separate entities for this age group, (b) (4) and is unlikely to be used in a substantial number of pediatric patients. A deferral was requested for pediatric patients ≥ 3 years to < 18 years of age weighing ≥ 15 kg because adult studies are completed and ready for approval, and because the different darunavir/cobicistat FDC age-appropriate formulations necessary for weight based dosing cannot be developed until dosing recommendations are available for darunavir and cobicistat as single agents. The cobicistat sponsor is currently evaluating safety, antiviral activity and pharmacokinetics of darunavir and cobicistat as single agents in pediatric patients. The Division and the pediatric review committee (PeRC) agreed with the Applicant's proposed waiver and deferral.

11. Other Relevant Regulatory Issues

Financial disclosures were not required for investigators of the single arm, open-label trial of darunavir and cobicistat administered as single entities, GS-US-216-0130, because the trial was considered supportive. Financial disclosures were obtained for the pivotal bioequivalence trial, TMC114IFD1003, for 4 of the 5 clinical investigators. The Applicant was unable to obtained financial disclosure for one clinical investigator who participated in the trial despite numerous attempts. However, ORA inspection of the clinical site did not result in any citations, and there was no evidence to suggest any deficiencies, irregularities or biases. Thus, the lack of financial disclosure information from a single investigator should not preclude approval this supplement.

12. Labeling

The proposed proprietary name for darunavir/cobicistat fixed dose combination tablet, Prezcobix, was considered acceptable by DMEPA and DAVP. One issue raised by DMEPA concerned the Applicant's proposal to (b) (4)

(b) (4)

(b) (4)

Additional issues for the FPI included including lurasidone, an atypical antipsychotic, as a contraindicated medication due to a drug interaction (b) (4) if coadministered with darunavir/cobicistat FDC tablet. The Division of Psychiatry Products was consulted and recommended the contraindication because of safety concerns with coadministration (b) (4) Alternative antipsychotic agents are available which could potentially be substituted for lurasidone. The applicant agreed with this change.

For Section 8, Use in Specific Populations, 8.1 Pregnancy, the final Pregnancy Labeling Rule was published this month in the Federal Register, and will require removal of pregnancy category as well as reorganization of this section within a risk summary. Because these changes are not yet mandatory, they will not be made with this submission, pending revision of this section in the darunavir and cobicistat labeling.

Other content and formatting changes have been made in consultation with the acting associate director for labeling in DAVP, Dr. Katie Schumann. The Applicant has accepted these changes.

(b) (4)

[redacted]

13. Recommendations/Risk Benefit Assessment

- **Recommended Regulatory Action:** *Approval*

- **Risk Benefit Assessment**

  The review team found the risk-benefit profile of the darunavir/cobicistat FDC tablet acceptable. The risks and benefits are similar to those outlined for the individual entities as reviewed in the respective NDAs for darunavir and cobicistat. In addition, because cobicistat is used in combination with darunavir to increase darunavir exposures similar to the use of ritonavir in combination with darunavir or other HIV protease inhibitors, the risk-benefit considerations are similar to those assessed for darunavir/ritonavir. Efficacy and safety of the darunavir/cobicistat FDC tablets were extrapolated from clinical trials of darunavir/ritonavir in treatment-naïve and treatment experienced subjects with HIV-1, based on bioequivalence data between darunavir/cobicistat FDC tablet and the single entities and between darunavir and cobicistat administered as single entities and darunavir ritonavir administered as single entities. The single arm, open-label trial which evaluated darunavir and cobicistat as single entities was considered supportive for both efficacy and safety of the darunavir/cobicistat FDC tablet.

- **Recommendation for Postmarketing Risk Evaluation and Management Strategies:** A REMS is not recommended for this application.

- **Recommendation for other Postmarketing Requirements and Commitments:**

  Other than the pediatric postmarketing requirements (PMRs) required under PREA, no other postmarketing commitments or requirements are recommended. The PREA PMRs and proposed timelines for completion agreed to by the Applicant include:

1. Evaluate the pharmacokinetics, safety, and antiviral activity (efficacy) of darunavir/cobicistat fixed dose combination (FDC) age-appropriate formulation in HIV-infected pediatric subjects 3 years to less than 6 years of age and weighing at least 15 kg. The safety and antiviral activity (efficacy) of darunavir/cobicistat FDC age-appropriate formulation in pediatric subjects should be evaluated for a minimum of 24 weeks. A clinical trial in children ages 3 to less than 6 years may not be required if the dosing recommendation for the FDC age-appropriate formulation can be supported by pediatric trials already conducted with the individual drug products and if the age-appropriate FDC produces similar exposures as the individual components.

Final Protocol Submission:	03/31/2020
Study/Trial Completion:	12/31/2020
Final Report Submission:	12/31/2021

2. Evaluate the pharmacokinetics, safety, and antiviral activity (efficacy) of darunavir/cobicistat fixed dose combination (FDC) age-appropriate formulation in HIV-infected pediatric subjects 6 years to less than 12 years of age. The safety and antiviral activity (efficacy) of darunavir/cobicistat FDC age-appropriate in pediatric subjects should be evaluated for a minimum of 24 weeks. A clinical trial in children ages 6 to less than 12 years may not be required if the dosing recommendation for the FDC age-appropriate formulation can be supported by pediatric trials already conducted with the individual drug products and if the age-appropriate FDC produces similar exposures as the individual components.

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3. Evaluate the pharmacokinetics, safety, and antiviral activity (efficacy) of darunavir/cobicistat fixed-dose combination (FDC) tablets in HIV-infected pediatric subjects 12 years to less than 18 years of age (b) (4) . The safety and antiviral activity (efficacy) of darunavir/cobicistat FDC tablets in pediatric subjects should be evaluated for a minimum of 24 weeks. A clinical trial in children 12 years to less than 18 years of age (b) (4) may not be required if the dosing recommendation for the FDC tablets can be supported by pediatric trials already conducted with the individual drug products and if the FDC produces similar exposures as the individual components.

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As noted above, these PREA PMRs depend on development of age-appropriate formulations, and determination of appropriate dosing regimen for each of the proposed age groups in clinical trials of darunavir and cobicistat administered as single agents, as required by the cobicistat commercial sponsor with the cobicistat NDA.

- **Recommended Comments to Applicant**
  No additional comments will be conveyed to the applicant.

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/s/

MARY E SINGER
01/02/2015