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APPLICATION NUMBER:

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021567Orig1s035

SUMMARY REVIEW

Cross-Discipline Team Leader Review

Date	May 19, 2014
From	Mary Singer, M.D., Ph.D.
Subject	Cross-Discipline Team Leader Review
NDA/BLA # **Supplement#**	NDA 206352 NDA 21567 S-035
Applicant	Bristol Myers Squibb
Date of Submission	December 2, 2013
PDUFA Goal Date	June 2, 2014
Proprietary Name / Established (USAN) names	REYATAZ (atazanavir sulfate)
Dosage forms / Strength	Powder/50 mg atazanavir (b) (4)
Proposed Indication(s)	1. Treatment of HIV-1 infection in pediatric patients at least 3 months to (b) (4) weighing 10 to 25 kg
Recommended Action:	*Approval with recommended changes in labeling*

Cross Discipline Team Leader Review Template

1. Introduction

NDA 206352 includes data from 2 single-arm, open-label pediatric trials for safety, pharmacokinetics and antiviral activity of Reyataz powder formulation. Because HIV pathogenesis is similar in adults and pediatric patients, the efficacy of atazanavir in adults can be extrapolated from adults. This is a new powder formulation for oral use provided as (b) (4) which each contain 50 mg atazanvir. The contents of the Reyataz powder (b) (4) are to be mixed with liquid or food for administration.

2. Background

Reyataz capsules are currently approved for adults and pediatric patients ≥ 6 years old. Studies in pediatric patients less than 3 months of age have been waived because of the potential risk of kernicterus in that population. Studies in pediatric patients older than 3 months and (b) (4) have been deferred, pending development of a formulation for use in patients who cannot swallow capsules and studies of that formulation to determine the appropriate Reyataz dose. This NDA includes pharmacokinetic (PK), safety and antiviral activity data from one completed pediatric trial (PRINCE I, AI424397) which enrolled patients ≥ 3 months to less than 6 years old, and interim data from an ongoing trial (PRINCE II, AI424451) which enrolled patients ≥ 3 months to 11 years old. In previous communications with the Applicant the Division had recommended that the Reyataz dose be increased in patients weighing 5-10 kg because on preliminary review of the pharmacokinetic data from AI424397, atazanavir exposures were considerably lower than expected, suggesting under dosing in this weight band with ATV/RTV 150/80 mg. The applicant agreed to increase the ATV/RTV dose to 200/80 mg in the 5-10 kg weight band in the ongoing trial, AI424451, and submit data from the completed trial in a future submission. Thus, for the current submission, Reyataz oral powder dosing for pediatric patients weighing 5-10 kg is not under consideration, although AI 424397 data from that weight band was submitted.

3. CMC/Biopharmaceutics

- General product quality considerations
  Each packet (b) (4) of Reyataz powder contains atazanavir, (50 mg/1.5 g powder), aspartame, sucrose and orange-vanilla flavor. One issue regarding the presence of two container-related impurities in the bulk powder ((b) (4)) arose during the review. These impurities were found to be leachables from (b) (4) but Pharmacology/Toxicology reviewers did not consider the levels of (b) (4) to pose a substantial risk (see section 4 below for further details). The proposed acceptance criteria (levels of the 2 leachables < (b) (4) % after 6 months storage) were considered acceptable.

In the ONDQA review, Drs. Yichun Sun and Steve Miller have concluded that the identity, strength, purity and quality of the drug product are acceptable. The container closure systems (b) (4) are child-resistant, and are considered acceptable. A recommendation on approval is pending final labeling negotiations. See ONDQA review for full details.

Biopharmaceutics reviewers found that the proposed dissolution method was not acceptable and the Applicant agreed to institute interim acceptance criterion of Q = (b) (4)% at 15 min for the dissolution test and update the specification table by May 15, 2014. The applicant agreed to a postmarketing commitment (PMC) to develop a more sensitive dissolution method and to test a certain number of batches using the new method. These PMCs are outlined below in section 13.

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- Facilities review/inspection:
  Reyataz powder is manufactured at two facilities, (b) (4) . Drug substance manufacturing sites are Swords Laboratories, and Bristol Myers Squibb-Cruiserath, both in Ireland. The Office of Compliance found all facilities inspections "acceptable."

- Other notable issues (resolved or outstanding):
  The ONDQA has requested that the applicant revise the name (b) (4) to "atazanavir" (omitting the name of the (b) (4)) based on the "Monograph naming policy for salt drug substances in drug products and compounded preparations". ONDQA is aware that the USP has balloted and approved "Reyataz Capsules" as a monograph title on January 14, 2014.

  An additional issue arose regarding the appropriate naming of the dosage form for the Reyataz powder formulation. The applicant proposed the term, (b) (4) However, the ONDQA Precedence meeting on May 7, 2014 recommended that Reyataz Oral Powder would be the most appropriate name for this product because it is intended to be mixed with food or liquid. An additional recommendation from the committee was to assess whether there would be any hazard if the product were ingested directly without mixing in food or liquid. If there were a significant risk, then additional information should be added to Reyataz labeling including carton/container. DMEPA has been consulted on this issue, and has recommended that the following language be added to the Reyataz Oral Powder carton and container labeling "Mix with food or beverage before taking this medicine. See mixing instructions."

4. Nonclinical Pharmacology/Toxicology

All non-clinical pharmacology/toxicology information is cross-referenced to NDA 21567. The only pharmacology/toxicology issue that arose during this review was the potential risk of 2 impurities found in the bulk Reyataz powder product. These impurities, (b) (4)

and [redacted], were present at levels less than [redacted]% in the final product due to leaching from [redacted] Chronic exposure to these chemicals has been associated with [redacted] in mice. Compared to adults, [redacted] may be of greater concern for infants and children. Rodent studies have not found a clear link to carcinogenicity for these entities. However, based on overall risk assessments from the EPA and ATSDR, as well as internal assessment, the Pharmacology/Toxicology reviewers, Drs. Kuei-Meng Wu, Mark Powley and Hanan Ghantous found that the proposed level of the impurities did not present a substantial safety concern.

5. Clinical Pharmacology

The pharmacokinetics of atazanavir and atazanavir/ritonavir in adults and pediatric patients ≥ 6 years old has been described previously in reviews of NDA and sNDA submissions for Reyataz capsules. The proposed atazanavir/ritonavir dose using Reyataz oral powder in combination with ritonavir oral solution in pediatric patients weighing 10 to < 25 kg was evaluated in two pediatric trials, AI424397 and AI424451. The objectives of these two studies were to evaluate safety and antiviral activity, as well as to evaluated pharmacokinetics to determine whether the PK with the proposed doses are similar to those observed in adults administered ATV capsules in combination with RTV. In the two trials, 18 pediatric subjects weighed 10 to < 15 kg and 31 pediatric subjects weighed 15 to 25 kg. No clinically significant difference was noted in the PK parameters in comparison to that reported previously in HIV-infected adults who received Reyataz capsules with ritonavir (300/100 mg daily) as shown in the following table.

Table 1. Pharmacokinetics of Atazanavir given as Reyataz oral powder with Ritonavir oral solution in Pediatric patients weighing 10 to < 25 kg and Reyataz capsules with Ritonavir in Adults.

PK Parameter	10 to < 15 kg ATV/RTV 200/80 mg QD (N=18)	15 to < 25 kg ATV/RTV 250/80 mg QD (N=31)	HIV-infected Adults ATV/RTV 300/100 mg QD (N=10)
Cmax (ng/mL)	5197 (53)	5386 (47)	4422 (58)
AUC (ng.h/mL)	50305 (67)	55525 (46)	46073 (66)
Cmin (ng/mL)	572 (111)	678 (69)	636 (97)

The proposed dosing of Reyataz oral powder for pediatric patients weighing 10 to < 25 kg is shown in the following table.

Table 2. Proposed Dosing for Reyataz Powder with Ritonavir oral solution in Pediatric Patients ≥ 3 months old weighing 10 to < 25 kg.

Body weight	ATV dose	RTV dose
10 kg to less than 15 kg	200 mg (4 packets)	80 mg
15 kg to less than 25 kg	250 mg (5 packets)	80 mg

Clinical Pharmacology reviewers, Dr. Jenny Zheng and Shirley Seo concluded that the proposed dosing of Reyataz oral powder with ritonavir oral solution in pediatric patients weighing 10 to < 25 kg was acceptable.

Previous review of preliminary PK data in pediatric subjects weighing 5 to < 10 kg revealed lower than expected atazanavir exposures for the Reyataz powder dose used initially in AI424397, and DAVP recommended that a higher dose be used in that weight band in the ongoing trial, AI424451. The applicant agreed to evaluate a higher dose of Reyataz powder with ritonavir in the 5-<10 kg weight band, and that data will be submitted as a supplemental NDA with the final study report. Thus, Reyataz oral powder dosing for pediatric patients weighing 5 to 10 kg has not been proposed or further evaluated at this time.

Based on a relative bioavailability study (AI424025) which was conducted in healthy adults comparing the Reyataz capsule to the powder formulation, the bioavailability of the Reyataz powder formulation relative to the capsule was similar based on atazanavir AUC_{INF} when the powder was administered with applesauce or water. See Clinical Pharmacology review by Drs. Zheng and Seo for full details.

The applicant proposed dosing of the Reyataz powder only for patients (b) (4), and was asked by the Division to propose dosing for older pediatric patients and adults who are unable to swallow a capsule. However, because Reyataz powder dosing is currently being evaluated in older children in AI424451, the applicant preferred to wait for final data from that trial before proposing dosing in patients (b) (4) weighing > (b) (4) to < (b) (4) kg. Although Reyataz powder dosing for adults and pediatric patients (b) (4) weighing > (b) (4) kg would be supported by the BA study in adults with the assumption of similar metabolism in adults and adolescents, DAVP agreed to wait to determine whether powder dosing for pediatric patients weighing (b) (4) kg can be supported in the ongoing trial before labeling Reyataz powder for use in adults and older pediatric patients who cannot swallow capsules. Because of the large number of Reyataz powder (b) (4) that are needed for older (b) (4) pediatric patients or adults, capsule dosing is preferred because the likelihood of adherence to the dosing regimen may be higher.

Inspection of bioanalytical laboratories used for determining atazanavir concentrations in plasma samples is pending at this time.

6. Clinical Microbiology

Clinical Virology assessments focused on resistance analysis of viral isolates obtained from subjects who had virologic failure, defined as incomplete virologic response or viral rebound. In AI424397, 9/56 subjects who met these criteria had paired genotypic data available (i.e. from baseline and from time near failure) for comparison. In AI424452, 13/78 subjects met these criteria and had paired genotypic data available for comparison.

See Clinical Virology review by Drs. Eric Donaldson and Jules O'Rear for full details. No treatment-emergent atazanavir-associated substitutions as defined in the approved Reyataz labeling were detected among 9 treatment failures in AI424397, but 4 known protease

inhibitor resistance-associated substitutions were identified in one subject each (L19I/R, M36M/I, H69K/R, and I72I/V). None of these subjects acquired phenotypic resistance as assessed by Monogram Phenosense GT test to atazanavir or atazanavir/ritonavir, or to any NRTI or NNRTI. In AI424451, atazanavir resistance-associated substitutions arose in one subject, including M46M/V, V82V/I, I84I/V, and L90L/M; however, there was no phenotypic resistance to atazanavir or atazanavir/ritonavir. Additional protease inhibitor resistance-associated substitutions arose in 9 other subjects, and 3 subjects developed the M184V substitution with associated phenotypic resistance to lamivudine and emtricitabine.

Overall, resistance patterns were consistent with those observed in previous clinical trials of atazanavir and atazanavir/ritonavir. No novel resistance findings were identified from these two pediatric trials.

7. Clinical/Statistical- Efficacy

Two pediatric clinical trials evaluating Reyataz oral powder were reviewed for this NDA, as shown in the following table.

Table 3. Pediatric Clinical Trials of Reyataz Oral Powder for Treatment of HIV

Trial	Pediatric Population	Age Range	Weight Range	Number (N) of Treated Subjects
AI424397 (PRINCE I)	Treatment-naïve and Treatment-experienced	≥ 3 months to < 5 years/6 months	5 to <25 kg	Total N=56 5 to < 10 kg:21 10 to <15 kg:19 15 to <25 kg: 16
AI424451 (PRINCE II)	Treatment-naïve and Treatment-experienced	≥ 3 months to < 11 years	5 to <35 kg	Total N=78 5 to < 10 kg: 23 10 to <15 kg:20 15 to < 25 kg:34 25 to < 35 kg:1

Both AI424397 and AI424451 were prospective, single-arm, open-label, international multicenter trials. As noted, because AI424451 is ongoing and a higher dose of Reyataz oral powder is being used in that trial in 5 to < 10 kg subjects, this review focuses on antiviral activity in the 10 to < 25 kg weight group. Only one subject in the 25 to < 35 kg weight group had completed 48 weeks in that trial up to the time of the data lock.

See Dr. Shapiro's review for full details on patient demographics and disposition. Virologic success, measured as HIV RNA < 50 copies/mL and < 400 copies/mL, was determined at week 48. Because AI424451 is ongoing and only interim data representing only about 53% of the planned sample size were provided, virologic success at week 48 was assessed for each trial separately.

Virologic response in all subjects (treatment-naïve and –experienced), using the FDA snapshot analysis, is shown in the following table. These results are generally consistent with those seen with other antiretroviral agents, including Reyataz capsules, in other pediatric trials.

Table 4. Virologic Response at week 48 in Pediatric Subjects weighing 10 to < 25 kg who received Reyataz oral powder in AI414397 and AI424451

	AI424397		AI424451	
Baseline weight	10 to < 15 kg	15 to < 25 kg	10 to < 15 kg	15 to < 25 kg
Subjects who received Reyataz oral powder (N)	19	14	13	19
Virologic success (HIV RNA < 50 copies/ml)	13 (68%)	10 (71%)	4 (31%)*	14 (74%)
Virologic success (HIV RNA < 400 copies/ml)	14 (74%)	12 (86%)	8 (62%)	15 (79%)

*Low response rate noted for this group was due to a transient viral "blip," with HIV RNA <400 copies/mL, during the analysis window in 1 subject.

See Dr. Shapiro's clinical review and the statistical review of Drs. Karen Qi and Fraser Smith for further details regarding virologic response and analyses of secondary endpoints. Both Dr. Shapiro and Dr. Qi were able to replicate the applicant's results in their analyses, and no statistical issues were identified.

8. Safety

Safety data from the two pediatric trials which included Reyataz oral powder dosing, AI424397 and AI424451, was submitted or review. This review focused on safety from patients weighing 10 to < 25 kg in these trials because of the lower than expected atazanavir exposures in the 5 to < 10 kg weight group. A total of 89 subjects weighing 10 to < 25 kg received Reyataz oral powder in these two trials, and 65 of these subjects received Reyataz oral powder for 48 weeks. There were no deaths reported in these trials. The following table summarizes adverse events reported through week 48 in 10 to < 25 kg subjects who received Reyataz oral powder in these trials.

Table 5. Summary of Adverse Events reported up to week 48 in Pediatric Subjects weighing 10 to < 25 Kg and receiving Reyataz Oral Powder in AI424397 and AI424451

Adverse Events (AEs)	AI424397 N=35	AI424451 N=54
	n (%)	n (%)
Any AE	33 (94%)	49 (91%)
Death	0	0
Serious AE (nonfatal)	6 (17)	12 (22)
Grade 3 or 4 AE	6 (17)	7 (13)
Discontinuation due to AE	1 (3)	4 (7)

In the pooled pediatric trials of Reyataz oral powder, the most common adverse events (Grade 2-4) reported in these two trials were gastroenteritis (8%), otitis media (7%), and allergic rhinitis (6%). Grade 3-4 adverse events that were reported in more than 1 subject included

hyperbilirubinemia (5 subjects), neutropenia (2 subjects), increased ALT (2 subjects) and increased lipase (2 subjects). The most common Grade 3-4 laboratory abnormalities were increased amylase (13%), increased bilirubin (12%), and decreased neutrophils (11%). None of the adverse events or laboratory abnormalities were considered unexpected in this HIV-infected pediatric population taking Reyataz and NRTIs, including zidovudine. See Dr. Alan Shapiro's review for details regarding the adverse events, including SAEs reported in these trials.

Two of the SAEs were reported as "overdose". In one case, a 6 year old subject received twice daily Reyataz oral powder dosing rather than once daily for 14 days. This patient was asymptomatic and the correct dosage was instituted as soon as the error was discovered. Similarly, in the second case, the subject received twice daily rather than once daily dosing of Reyataz oral powder for 7 days. Again, when the error was discovered, the correct dosage was instituted. However, this patient developed jaundice, hyperbilirubinemia and first degree AV block on ECG. These events resolved over time with continuation of Reyataz. The proposed prescribing and patient information for Reyataz is currently under review to ensure that information that Reyataz should be given once daily is emphasized.

One subject discontinued due to "QT prolongation" on ECG. In this case, the corrected QTc was 477 msec in comparison to baseline QTc which was 382 msec. Reyataz was discontinued and on the same day, the QT prolongation resolved, making a relationship to Reyataz unlikely, as the subject still had HIV viral load suppression and presumably had therapeutic levels of atazanavir at the time of discontinuation. The patient was not on any concomitant medications known to be associated with QT prolongation. Of note, QT prolongation was not observed with Reyataz in a thorough QT study which evaluated therapeutic and supratherapeutic doses in adults. Other adverse events resulting in Reyataz discontinuation were vomiting and ALT/AST elevation. No subjects met Hy's law criteria for hepatic toxicity.

Overall, no new or unexpected safety signals were identified in Dr. Shapiro's review, and the safety profile for Reyataz was similar to that reported with Reyataz capsules in adults and in pediatric subjects in clinical trials or in postmarketing.

9. Advisory Committee Meeting

Not applicable.

10. Pediatrics

Reyataz capsules are currently approved for pediatric patients 6 to 18 years of age. Evaluation of Reyataz in patients at least 3 months old to (b) (4) has been deferred, and in patients less than 3 months old has been waived due to the potential risk of kernicterus. The current PREA PMR dated March 25, 2008 states:

> "Deferred pediatric study or studies under PREA for treatment of HIV-1 infection in pediatric patients ages greater than or equal to 3 months to 18 years to obtain a

> minimum of 100 patients followed for safety for a minimum of 24 weeks at the recommended dose or any higher doses studied during pediatric development."

Note that specific pediatric weight bands were not specified in the original PMR. Based on the total number of pediatric patients who have been studied at the appropriate dose and duration of Reyataz to date in clinical trials (n=123), this post-marketing commitment is considered fulfilled. However, a new PMR will be issued at the time of approval of the current NDA to obtain appropriate dosing of Reyataz oral powder in patients 3 months to (b) (4) weighing 5 to < 10 kg. The Pediatric Review Committee (PeRC) agreed to this plan. The applicant has agreed to the following wording for this new PMR:

> "Deferred pediatric study under PREA to evaluate (b) (4) powder pharmacokinetics, safety and treatment response in HIV-1 infected pediatric patients 3 months and older who weigh 5 kg to less than 10 kg."

A Pediatric Written Request for a clinical trial in pediatric patients from 3 months to 18 years is currently outstanding, and the timeframe has been extended until January 15, 2016 to allow completion of AI424451 to determine appropriate dosing of the Reyataz powder formulation in the youngest patients weighing 5-10 kg.

11. Other Relevant Regulatory Issues

There are no additional relevant regulatory issues with this application.

12. Labeling

The applicant proposed the name (b) (4) for the powder formulation; however, based on naming conventions ONDQA has recommended the name, "Reyataz Oral Powder" instead. In addition, ONDQA has recommended that (b) (4) be removed from (b) (4) based on the "Monograph naming policy for salt drug substances in Drug Products and Compounded Preparations" and on USP unofficial approval of "atazanavir capsules" as monograph title. Acceptance of the recommended change in the established name and for the powder formulation by the applicant is pending.

The Study Endpoint and Labeling Team (SEALD) made extensive recommendations for changes to the Reyataz package insert. The review team decided to make the recommended changes according to the most recent labeling guidances and current best practices to the Indications and Usage section and to the Dosage and Administration section at this time. In the Indications and Usage section, we removed the information from (b) (4) upon which the approval was based and changed (b) (4) to "Limitations of Use."

Although extensive changes were proposed to section 2, I have highlighted the following section for pediatric dosing of Reyataz powder, including instructions for mixing in the appropriate food and administration:

2.4 Dosage and Administration of REYATAZ Oral Powder in Pediatric Patients

"REYATAZ oral powder is for use in treatment naïve or treatment experienced pediatric patients who are at least 3 months and [redacted] weighing at least 10 kg and less than 25 kg. REYATAZ oral powder must be mixed with food or beverage for administration and ritonavir [redacted] must be given immediately afterwards. Table 3 displays the recommended dosages of REYATAZ oral powder and ritonavir [redacted].

Table 3. Recommended Dosages of REYATAZ Oral Powder and Ritonavir in Pediatric Patients at least 3 months [redacted] weighing 10 to < 25 kg[2]

Body Weight	Daily Dosage of REYATAZ Oral Powder	Daily Dosage of Ritonavir Oral Solution
10 kg to less than 15 kg	200 mg (4 packets)[1]	80 mg
15 kg to less than 25 kg	250 mg (5 packets)[1]	80 mg

1 Each package contains 50 mg of REYATAZ

2 [redacted] See [redacted] 7 for instructions concerning co-administration of acid reduct[redacted] medications [e.g. [redacted] (H2RA) or [redacted] (PPIs)] and other antiretroviral drugs (e.g., efavirenz, tenofovir, and didanosine).

Instructions for Mixing REYATAZ Oral Powder (see [redacted] *Instructions for Use*)*

- Determine the number of packets (4, or 5packets) that are needed.
- Prior to mixing, tap the packet to settle the powder.
  Use a clean pair of scissors to cut each packet along the dotted line.
- Mixing with Food: Using a spoon, mix the recommended number of REYATAZ oral powder packets with one Tablespoon of food (such as applesauce or yogurt) [redacted] feed the mixture to infant or young child.
- Mixing with Liquid Infant Formula Using an Oral Dosing Syringe and a Small Medicine Cup: [redacted]
- Mixing with Milk or Water in an [redacted] Drinking Cup: [redacted]

- Administer ritonavir (b) (4) immediately following REYATAZ powder administration.
- Administer the entire dosage of REYATAZ oral powder (mixed in the food or beverage) within one hour of preparation (may leave the mixture at room temperature during this one hour period). Ensure that the patient eats or drinks all the food or beverage that contains the powder. Additional food may be given after consumption of the entire mixture.

*It is preferable to mix REYATAZ with food such as applesauce and yogurt (b) (4)

Infants who (b) (4) drink from a cup or eat solid food, REYATAZ should be mixed with infant formula (b) (4) using an oral dosing syringe. Administration of REYATAZ infant formula (b) (4) using an infant bottle is not recommended because full dose may not be delivered".

Other major labeling changes related to the Reyataz oral powder included addition of safety data with Reyataz oral powder in section 6, and clinical trial data with Reyataz oral powder in section 14.

The proposed changes to the Reyataz PI are currently under negotiation with the Applicant and review of the Patient Package Information (PPI) by the Patient Labeling Team (OMP) is pending. DMEPA has recommended that a statement be included on the carton and container labeling to ensure that Reyataz powder is mixed with food or beverage before administration: "Mix with food or beverage before taking this medicine. See mixing instructions."

13. Recommendations/Risk Benefit Assessment

- **Recommended Regulatory Action: Approval with labeling changes**

- **Risk Benefit Assessment:** Reyataz capsules were initially approved for treatment HIV-1 in adults in 2002, and in pediatric patients older than 6 years of age in 2008; and the efficacy and safety profile of Reyataz is well established. Review of this NDA supplement for Reyataz oral powder in patients at least 3 months old, weighing 10 to < 25 kg revealed antiviral activity (suppression of HIV RNA) similar to that observed in adults and in pediatric subjects in clinical trials of Reyataz capsules, as reviewed previously. Efficacy of Reyataz in pediatric patients can be extrapolated from adults and the pharmacokinetics of the proposed dosing of Reyataz oral powder in this age/weight group for the proposed dosing is sufficiently similar to that in adults to make the efficacy extrapolation. In addition, no new safety issues were identified with Reyataz oral powder in this age group. Thus, the benefit/risk assessment is favorable and supports our recommendation for approval.

- Recommendation for Postmarketing Risk Evaluation and Management Strategies

  REMS is not necessary for this product.

- Recommendation for other Postmarketing Requirements and Commitments:

  1. Pediatric Postmarketing Requirement under PREA:

     Deferred pediatric study under PREA to evaluate (b) (4) powder pharmacokinetics, safety and treatment response in HIV-1 infected pediatric patients 3 months and older who weigh 5 kg to less than 10 kg.

  2. Postmarketing Commitment:

     Development of a new, more sensitive dissolution method, dissolution acceptance criterion proposal, and data supporting the newly proposed dissolution method and acceptance limit.

- Recommended Comments to Applicant

  No additional comments will be conveyed to the applicant in the regulatory action letter. However, the applicant will be asked to update the Reyataz package insert, particularly section 6 Adverse Reactions and section 14 Clinical Studies, based on recommendations from the SEALD team. Specific request will be sent to the Applicant after the action has been taken on this supplement.

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/s/

MARY E SINGER
05/16/2014