

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

206352Orig1s000

021567Orig1s035

OTHER REVIEW(S)

Division of Antiviral Products

REGULATORY PROJECT MANAGER LABELING REVIEW

Application: NDA 206352 and NDA 21567/S-035

Name of Drug: REYATAZ® (atazanavir) capsules, oral powder

Applicant: Bristol-Myers Squibb Company

Labeling Reviewed

Submission Date: December 2, 2013

Receipt Date: December 2, 2013

Labeling Reviewed Date: June 2, 2014

Last Approved Label Date: August 15, 2013 (NDA 21567/S-032 and S-033)

Background and Summary Description:

Atazanavir is currently indicated for use in combination with other antiretroviral agents for the treatment of HIV-1 infection in patients ≥ 6 years. BMS submitted NDA 206352 for Reyataz (atazanavir) oral powder to expand the patient population to pediatric patients 3 months to (b) (4) and 10 to < 25 kg. A companion efficacy supplement was also submitted to NDA 21567 (S-035) for atazanavir capsules as the two NDAs share labeling. These submissions also propose to fulfill post-marketing commitment #1 and partially fulfill the written request for exclusivity. The submission includes new carton and container labels for the powder for oral use, as well as a new "Instructions for Use" document that is proposed as part of the patient labeling.

Review

GENERAL

The term (b) (4) was removed from the established name throughout the labeling. Also minor edits in capitalization and punctuation were made.

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/s/

SAMMIE G BEAM
06/03/2014

ELIZABETH G THOMPSON
06/03/2014

MEMORANDUM

**DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH**

DATE: May 23, 2014

TO: Debra B. Birnkrant, M.D.,
Director,
Division of Antiviral Products (DAVP)

FROM: Xingfang Li, MD. RAC
Division of Bioequivalence and GLP Compliance
Office of Scientific Investigations
and
Arindam Dasgupta, Ph.D.
Division of Bioequivalence and GLP Compliance
Office of Scientific Investigations

THROUGH: Sam H. Haidar, R.Ph., Ph.D.
Chief, Bioequivalence Branch
Division of Bioequivalence and GLP Compliance
Office of Scientific Investigations
and
William H. Taylor, Ph.D.
Director
Division of Bioequivalence and GLP Compliance
Office of Scientific Investigations

SUBJECT: Review of EIR Covering NDA 206-352, REYATAZ
(atazanavir) (b)(4) powder boosted with ritonavir
(RTV) liquid, sponsored by Bristol-Myers Squibb
Company

At the request of the Division of Antiviral Products (DAVP), the Division of Bioequivalence and GLP Compliance (DBGLPC) arranged for the inspection of the clinical and analytical portions of the following safety, efficacy and pharmacokinetic studies:

Study Number: AI424397

Study Title: "A prospective single arm, open-label, international, multicenter study to evaluate the safety, efficacy and pharmacokinetics of atazanavir (ATV) powder boosted with ritonavir (RTV) liquid with an optimized NRTI background therapy, in HIV infected pediatric patients greater than or equal

Page 2 -NDA 206-352, Atazanavir (ATV) powder boosted with Ritonavir (RTV) liquid, sponsored by Bristol-Myers Squibb Company

to 3 Months to less than 6 Years (Pediatric Atazanavir International Clinical Evaluation: the PRINCE I study)"

Study Number: AI424451

Study Title: "A prospective single arm, open-label, international, multicenter study to evaluate the safety, efficacy and pharmacokinetics of atazanavir (ATV) powder boosted with ritonavir (RTV) with an optimized NRTI background therapy, in HIV infected, antiretroviral, naïve and experienced pediatric subjects from 3 months to less than 11 Years (Pediatric Atazanavir International Clinical Evaluation:The PRINCE II study)"

DAVP requested inspections for three clinical sites and one analytical site. The clinical portions were audited at Tygerberg Children's Hospital, Western Cape, South Africa (**Site# 1**) by ORA Investigator Lori Gioia between 05/5/2014-05/09/2014; Chris Hani Baragwanath Hospital, Gauteng South Africa (**Site# 2**) by ORA investigator Yvette M. LaCour-Davis between 05/5/2014-05/09/2014; and University of Free State, Bloemfontein, South Africa (**Site# 3**) by Anthony Keller between 03/31/2014-04/04/2014.

The analytical portion of the studies was audited at (b) (4), by ORA Investigator Michael Serrano and OSI/DBGLPC scientist Xingfang Li between (b) (4).

Following the inspections of clinical site #1 and the analytical site, there were no significant findings, and no Form FDA 483 was issued. The ORA investigator did verify and confirm the 24 and 48 week viral load data for all subjects whose viral loads were reported as <50 copies/mL. The viral load assays being used were Roche Amplify and Abbott RealTime and for both studies, results were based on runs from laboratories that met local requirements.

Following the inspections of clinical site #2 and Site #3, form FDA-483s were issued at each site (**attachments 1 and 2**). We received response to form FDA-483 dated 4/15/2014 from Site #3 and response to form FDA-483 dated 5/23/2014 from site #2 (**attachment 3 and 4**).

Please note that the EIRs have not been received by DBGLPC for any of the clinical site inspections. This review is based on

email correspondences or draft EIR text (not endorsed and with no supporting exhibits) received from the ORA investigators who conducted the inspections at the clinical sites. Once the EIRs are received and reviewed, we will update DAVP and DCP IV if our recommendation changes.

The Form FDA 483 observations for studies AI424397 and AI424451, clinical sites response, and our evaluation follow:

Clinical Site 2: Chris Hani Baragwanath Hospital, Gauteng South Africa

Observation #1

An investigation was not conducted in accordance with the signed statement of investigator and investigational plan.

Specifically, the revised protocol #AI424451, dated 14 Apr 2011, Section 5.5.1.1, titled: "Data Collection (Intensive PK-only for subjects weighing ≥ 25 - <35 kg and/or aged ≥ 6 to <8 years)," states: PK data is viable only if the time elapsed between the dose taken prior to the sampling (taken on the day before the sampling (the 0-hr blood draw) is between 20-28 hours."

The following was observed:

Subject #00009 (b) (6) enrolled in the study on 14 Dec 2011 (Day 1/Baseline). The subject's Week 2 Visit source document indicates subject was dosed with Atazanavir and Ritonavir on 27 Dec 2011 @ "13h15" (1315 hours).

The Week 2 PK Intensive Pharmacokinetic Assessment lab requisition #10020329714859 for the 0 hour PK Time point Sample Collection was drawn on 28 Dec 2011 at 07:55 (00:00 - 23:59) approximately 1 hour 40 minutes prior to the 20-28 hour window as specified in the protocol.

In Dr. Liberty's written responses to Form FDA-483, Dr. Liberty acknowledged the finding above. Dr. Liberty made correction that the 0 hour blood draw took place one hour and twenty minutes too soon for the window period allow instead of 1 hour 40 minutes which has been cited on form FDA 483. He submitted signed protocol deviation (**attachment 5**) which has been created by the

sponsor site monitor and has been submitted to the local regulatory authorities. The protocol deviation stated BMS PK Scientist will exclude Subject #00009 PK sample from the final intensive PK analyses. We defer to the OCP reviewer to evaluate the impact of the sampling time deviation.

Dr. Liberty stated their staff will continue to phone participants before PK days to discuss relevant issues and they are committed to conducting clinical research in compliance with Good Clinical Practice and with all regulatory requirements.

During the inspection, for both studies (**AI424397 and AI424451**) the viral loads were verified by ORA investigator for the following subjects (Please see TABLE 1 and 2).

TABLE 1 (Study AI424397, enrolled 10 subjects)

Subject #	Week 24 Viral Load Verified at < 50 copies	Week 48 Viral Load Verified at < 50 copies
#00016	yes	yes
#00019	Yes	yes
#00026	Yes	Yes
#00027	Yes	No (951 copies)
#00030	Yes	Yes
#00042	Yes	Yes
#00087	No (2,490 copies)	No (79,100 copies)

There is a discrepancy in subject 27 between the source data (collected at the clinical site) and the line listings submitted to the agency for week 48 viral load. We defer to OCP IV to evaluate the impact of the data discrepancy.

TABLE 2 (Study #AI424451, enrolled 12 subjects)

Subject #	Week 24 Viral Load Verified at < 50 copies	Week 48 Viral Load Verified at < 50 copies
#00009	yes	yes
#00028	yes	yes
#00033	yes	yes
#00106	yes	No (146 copies)
#00092	No (3,690 copies)	No (142 copies)
#00096	No (3,620)	Virological failure
#00112	No (24,000 copies)	Virological failure
#00058	Yes	Lost to f/u
#00013	Yes	Yes

In study #AI424451, there are discrepancies in subjects 106, 92, 112, 92 and 90 between the source data (collected at the clinical site) and the line listings submitted to the agency. We defer to OCP IV to evaluate the impact of the data discrepancy.

The ORA investigator confirmed that the viral load assay used was HIV-1 RNA PCR/Cobas Ultra (58) for both studies. Results were based on runs from laboratories that met local requirements.

Clinical Site 3: University of Free State, Bloemfontein, South Africa

Observation 1

Failure to prepare or maintain adequate and accurate case histories with respect to observations and data pertinent to the investigation and informed consent

Observation 1(a): For five of the 16 consented patients in study AI424451, the patients' parents signed one of the three versions of the consent form in a different language than the other two versions. There is no documentation that the signatory is bilingual or has a preferred language:

In Dr. R. van Zyl's written responses to Form FDA-483, Dr. R. van Zyl acknowledged the finding above. He submitted signed affidavits (**attachment 6**) from the parents of the enrolled subjects to provide evidence that the parents were bilingual (**English and Afrikaans**) and understood the informed consent form. He also stated that for future studies, the informed consent process would be administered in the parents' preferred language.

In our opinion, observation 1(a) does not have significant impact on subject safety and outcomes of the study.

Observation 1(b-h): multiple data in the adverse event(AE) log and medical records were inconsistent with those in the case reports. Please see details in attachment 2:

In Dr. R. van Zyl's written responses to Form FDA-483, Dr. R. van Zyl acknowledged the findings above. As corrective action, the investigator team with the full knowledge and support of the sponsor (BMS), verified all data in question in the source

Page 6 -NDA 206-352, Atazanavir (ATV) powder boosted with Ritonavir (RTV) liquid, sponsored by Bristol-Myers Squibb Company

documents and corrected the electronic case report forms (e-CRF's) accordingly.

Dr. R. van Zyl stated that extreme care will be taken in the future to ensure that data are accurately captured in source notes as well as e-CRF's.

In our opinion, observations 1(b-h) do not have a significant impact on the outcome of the study.

Conclusions:

Following review and evaluation of the Form FDA-483 observations and responses from the inspected sites, in our opinion, clinical and analytical data generated for studies AI424397 and #AI424451 were not affected by the cited deficiencies.

However, the clinical reviewer should evaluate the impact of the protocol deviation on the data from subject 0009 (clinical site #2) in study AI424451.

We recommend that the clinical and analytical data for studies AI424397 and AI424451 be accepted for further agency review.

Xingfang Li, M.D., RAC

And

Arindam Dasgupta, Ph.D.
Division of Bioequivalence and GLP compliance
Office of Scientific Investigations

Page 7 -NDA 206-352, Atazanavir (ATV) powder boosted with Ritonavir (RTV) liquid, sponsored by Bristol-Myers Squibb Company

Final Classifications:

Clinical

NAI: Tygerberg Children's Hospital, Western Cape, South Africa
FEI: 3008374644

VAI: Chris Hani Baragwanath Hospital, Gauteng South Africa

VAI: University of Free State, Bloemfontein, South Africa

Analytical

NAI: [REDACTED] (b) (4)
FEI: [REDACTED] (b) (4)

CC:

CDER OSI PM TRACK
OSI/DBGLPC/Taylor/Haidar/Bonapace/Skelly/Choi/Dasgupta/Li
OSI/DBGLPC/Dejernett
CDER/OAP/DAVP/Birnkrant/Shapiro/Beam
OCP/DCP IV/Lazor/Zheng
ORA/SW-FO/KAN-DO/Bromley/Gioia
ORA/CE-FO/CIN-DO/Miser/Lacour-Davis
ORA/OO/OMPTO/DMPTI/DIB/Keller

Draft: XFL 5/20/2014

Edit: AD 5/23/2014; SHH 5/27/2014

BE File # 6663; O:\BE\EIRCOVER\

ECMS: Cabinets/CDER_OC/OSI/Division of Bioequivalence & Good Laboratory Practice Compliance/INSPECTIONS/BE Program/CLINICAL SITES/[REDACTED] (b) (4)

FACTS: **8743584**

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/s/

XINGFANG LI
05/27/2014

ARINDAM DASGUPTA
05/27/2014

MICHAEL F SKELLY
05/27/2014

SAM H HAIDAR
05/28/2014

WILLIAM H TAYLOR
05/29/2014

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy**

PATIENT LABELING REVIEW

Date: May 28, 2014

To: Debra Birnkrant, MD
Director
Division of Antiviral Products (DAVP)

Through: LaShawn Griffiths, MSHS-PH, BSN, RN
Associate Director for Patient Labeling
Division of Medical Policy Programs (DMPP)

Barbara Fuller, RN, MSN, CWOCN
Team Leader, Patient Labeling
Division of Medical Policy Programs (DMPP)

From: Karen Dowdy, RN, BSN
Patient Labeling Reviewer
Division of Medical Policy Programs (DMPP)

Jessica Fox, PharmD, RAC
Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Subject: Review of Patient Labeling: Patient Package Insert (PPI) and
Instructions for Use (IFU)

Drug Name (established name), Dosage Form and Route, Application Type/Number, Supplement Number REYATAZ (atazanavir) capsules, for oral use
NDA 21-567/S-035

REYATAZ (atazanavir) oral powder
NDA 206352

Applicant: Bristol-Myers Squibb Company

1 INTRODUCTION

On December 2, 2013, Bristol-Myers Squibb Company submitted for the Agency's review an original New Drug Application (NDA) for 206352 for REYATAZ (atazanavir) oral powder. This NDA proposes for the treatment of HIV infection in pediatric patients who are 10 to < 25 kg, based on data from two clinical trials (AI424397 and AI424451) using atazanavir powder and supported by clinical trials PACTG 1020A. This submission also seeks to fulfill post-marketing commitment #1, and to partially fulfill the Written Request for Exclusivity. In addition, the Applicant submitted a Prior Approval Supplement to their approved NDA 21-567/S-035 for REYATAZ (atazanavir) capsules for labeling consistency. REYATAZ (atazanavir) capsules and REYATAZ (atazanavir) oral powder will share Prescribing Information and a Patient Package Insert. REYATAZ capsules was originally approved on June 20, 2003 and is indicated for use in combination with other antiretroviral agents for the treatment of HIV-1 infection.

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to the requests by the Division of Antiviral Products (DAVP) on December 18, 2013 for DMPP and OPDP to review the Applicant's proposed Patient Package Insert (PPI) and Instructions for Use (IFU) for REYATAZ (atazanavir) capsules and oral powder.

DMPP conferred with the Division of Medication Error, Prevention, and Analysis (DMEPA) and a separate DMEPA review of the IFU was completed on April 28, 2014.

2 MATERIAL REVIEWED

- Draft REYATAZ (atazanavir) capsules and oral powder Patient Package Insert (PPI) received on December 2, 2013, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on May 19, 2014.
- Draft REYATAZ (atazanavir) oral powder Instructions for Use (IFU) received on December 2, 2013, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on May 19, 2014.
- Draft REYATAZ (atazanavir) capsules and oral powder Prescribing Information (PI) received on December 2, 2013, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on May 19, 2014.
- Division of Medication Error, Prevention, and Analysis (DMEPA) Label and Labeling Review for REYATAZ (atazanavir) capsules and oral powder dated April 28, 2014.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of

60% corresponds to an 8th grade reading level. In our review of the PPI and IFU the target reading levels are at or below an 8th grade level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APFont to make medical information more accessible for patients with vision loss. We have reformatted the PPI and IFU documents using the Verdana font, size 11.

In our collaborative review of the PPI and IFU we have:

- simplified wording and clarified concepts where possible
- ensured that the PPI and IFU are consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information
- ensured that the PPI and IFU are free of promotional language or suggested revisions to ensure that they are free of promotional language
- ensured that the PPI and IFU meet the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)
- The enclosed IFU review comments are collaborative DMPP and DMEPA.

4 CONCLUSION

The PPI and IFU are acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the PPI and IFU are appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the PPI or IFU.

Please let us know if you have any questions.

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/s/

KAREN M DOWDY
05/28/2014

JESSICA M FOX
05/28/2014

BARBARA A FULLER
05/28/2014

LASHAWN M GRIFFITHS
05/28/2014

PMR/PMC Development Template: Product Quality (CMC)

This template should be completed by the review chemist (ONDQA) or biologist (OBP) and included for *each* type of CMC PMR/PMC in the Action Package. See #4 for a list of CMC PMR/PMC types

NDA/BLA # NDA 206352
Product Name: Atazanavir Oral Powder, 50 mg

PMC #1 Description: Development of a new, more sensitive dissolution method, dissolution acceptance criterion proposal, and data supporting the newly proposed dissolution method and acceptance limit.

PMC Schedule Milestones: Final Report Submission: Sept 2, 2015

- **ADD MORE AS NEEDED USING THE SAME TABULAR FORMAT FOR EACH PMC.**
- **INCLUDE DESCRIPTIONS AND MILESTONES IN THE TABLE ABOVE FOR ALL CMC/OBP NON-REPORTABLE PMCS *FOR WHICH THE FOLLOWING ANSWERS WILL BE IDENTICAL.* USE A SEPARATE TEMPLATE FOR EACH PMR/PMC FOR WHICH THE ANSWERS TO THE FOLLOWING QUESTIONS DIFFER.**
- ***DO NOT USE THIS FORM* IF ANY STUDIES WILL BE REQUIRED UNDER FDAAA OR WILL BE PUBLICALLY REPORTABLE**

1. During application review, explain why this issue is appropriate for a PMC instead of a pre-approval requirement. Check reason below and describe.

- Need for drug (unmet need/life-threatening condition)
- Long-term data needed (e.g., stability data)
- Only feasible to conduct post-approval
- Improvements to methods
- Theoretical concern
- Manufacturing process analysis
- Other

The development of a new (more sensitive) dissolution method and the collection of dissolution profile data using the new method on a sufficient number of batches to support a proposed dissolution acceptance criterion cannot be completed within the current review cycle.

2. Describe the particular review issue and the goal of the study.

The current dissolution method is not discriminating; it is insensitive to potential aberrant batches of the proposed product as more than $\frac{(b)}{(4)}$ % atazanavir is released in $\frac{(b)}{(4)}$ min. The goal of the PMC is to develop a more sensitive dissolution method.

3. [OMIT – for PMRs only]
4. What type of study is agreed upon (describe and check type below)?

Select only one. Fill out a new sheet for each type of PMR/PMC study.

- Dissolution testing
 Assay
 Sterility
 Potency
 Product delivery
 Drug substance characterization
 Intermediates characterization
 Impurity characterization
 Reformulation
 Manufacturing process issues
 Other

Describe the agreed-upon study:

1. Develop a more sensitive dissolution method for Atazanavir Powder for Oral Use that will demonstrate adequate discriminating power.
2. As part of the new dissolution method development, conduct experiments to investigate the discriminating power of the method. In general, the testing conducted to demonstrate the discriminating ability of the selected dissolution method should compare the dissolution profiles of the target formulation and the variant formulations that are intentionally manufactured with meaningful variations for the most relevant critical manufacturing variables (i.e., \pm (b) (4) % change to the specification-ranges of these variables)
3. Propose a dissolution acceptance criterion that is adequate for the product based on adequate number of commercial batches. The in-vitro dissolution profile (e.g., 10, 15, 20, 30, 45, 60 min) should encompass the timeframe over which at least (b) (4) % of the drug is dissolved or where the plateau of drug dissolved is reached, if incomplete dissolution is occurring. The selection of the specification time point should be where $Q =$ (b) (4) % dissolution occurs.
4. If all experimental conditions produce results that are similar to the current method, discuss the overall findings to support Applicant's original proposal that dissolution testing is not appropriate for the product.
5. The applicant will submit a data package including a dissolution development report detailing experimental efforts to develop a more discriminating method. Based upon the results, the applicant will either a) recommend a new method including the associated acceptance criteria or b) recommend deletion of the interim dissolution method. If a new method is recommended, the acceptance criteria would be based on the results from 10 batches: 1 commercial launch batch, 7 experimental commercial scale batches prepared at the commercial manufacturing and (b) (4) filling sites and 2 clinical batches at 2X commercial batch size manufactured at the clinical manufacturing site and filled at the commercial (b) (4) filling site. If the results of the investigation do not result in a more sensitive dissolution method, the applicant will submit the results of the investigation and recommend that the dissolution test be removed from the specifications. The applicant will submit the data package with the recommendation as part of a Type C meeting request by December 2, 2014. The purpose of the Type C meeting request will be to discuss the results of the investigation and gain concurrence with the Agency on the path forward.
6. Depending on the outcome of the Type C meeting, BMS will then submit a PAS to either modify the dissolution method, or to eliminate the test. Taking into consideration the time to schedule and complete the Type C meeting (approximately three months), BMS commits to submit the above referenced PAS no later than September 2, 2015.

5. To be completed by ONDQA/OBP Manager:

- Does the study meet criteria for PMCs?
- Are the objectives clear from the description of the PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

- This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

(Signature line for BLAs only)

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/s/

SAMMIE G BEAM
05/27/2014

PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for ***each*** PMR/PMC in the Action Package.

NDA/BLA # NDA 206352
Product Name: Reyataz (atazanavir)

PMR/PMC Description: Deferred pediatric study or studies 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.

PMR/PMC Schedule Milestones:	Final Protocol Submission:	Previously submitted
	Study/Trial Completion:	October 2014
	Final Report Submission:	June 2015
	Other:	

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

See #2

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

The goal of the proposed PMR trial is to evaluate pharmacokinetics, safety and antiviral activity of Reyataz powder formulation for dosing infants that are at least 3 months old and weigh 5 to < 10 kg. Reyataz powder formulation has already been evaluated in pediatric patients that are older than 3 months and weigh 10 to < 25 kg. These data are currently under review for NDA 206352. Previously submitted pharmacokinetic data for the 5 to < 10 kg weight cohort revealed lower than expected atazanavir exposures, and higher doses of the Reyataz powder formulation are currently being evaluated in this weight group in the ongoing pediatric trial AI424451.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

If not a PMR, skip to 4.

– **Which regulation?**

- Accelerated Approval (subpart H/E)
- Animal Efficacy Rule
- Pediatric Research Equity Act
- FDAAA required safety study/clinical trial

– **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
- Assess signals of serious risk related to the use of the drug?
- Identify an unexpected serious risk when available data indicate the potential for a serious risk?

– **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

Analysis of spontaneous postmarketing adverse events?

Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

Analysis using pharmacovigilance system?

Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?

Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

Study AI424451 is an ongoing single-arm open label trial in pediatric patients ages 3 months to less than 11 years of age. The sponsor has agreed to evaluate higher doses of Reyataz powder formulation in the subgroup of infants \geq 3 months and weighing between 5 to < 10 kg in this ongoing trial.

Required

- Observational pharmacoepidemiologic study
- Registry studies
- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
- Pharmacokinetic studies or clinical trials
- Drug interaction or bioavailability studies or clinical trials
- Dosing trials

Continuation of Question 4

- Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)
-
- Meta-analysis or pooled analysis of previous studies/clinical trials
 - Immunogenicity as a marker of safety
 - Other (provide explanation)
-

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
- Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
- Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
- Dose-response study or clinical trial performed for effectiveness
- Nonclinical study, not safety-related (specify)

- Other
-

5. Is the PMR/PMC clear, feasible, and appropriate?

- Does the study/clinical trial meet criteria for PMRs or PMCs?
- Are the objectives clear from the description of the PMR/PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

- Check if this form describes a FDAAA PMR that is a randomized controlled clinical trial

If so, does the clinical trial meet the following criteria?

- There is a significant question about the public health risks of an approved drug
- There is not enough existing information to assess these risks
- Information cannot be gained through a different kind of investigation
- The trial will be appropriately designed to answer question about a drug's efficacy and safety, and
- The trial will emphasize risk minimization for participants as the protocol is developed

PMR/PMC Development Coordinator:

This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.

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/s/

ALAN M SHAPIRO
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Center for Drug Evaluation and Research
Office of Prescription Drug Promotion**

*****Pre-decisional Agency Information*****

Memorandum

Date: May 21, 2014

To: Sammie Beam, Regulatory Project Manager
Division of Antiviral Products

From: Jessica Fox, PharmD, RAC, Regulatory Review Officer
Office of Prescription Drug Promotion

Subject: NDA 021567/S-35 – REYATAZ (atazanavir) capsules
NDA 2063525 – REYATAZ (atazanavir) oral powder

As requested in the Division of Antiviral Products' (DAVP) consult dated December 17, 2013, the Office of Prescription Drug Promotion (OPDP) has reviewed the REYATAZ prescribing information, patient labeling, and carton and container labeling.

OPDP's comments on the prescribing information are provided below in the proposed substantially complete version of the labeling received via email from DAVP on May 19, 2014.

OPDP reviewed the carton and container labeling received via email from DAVP on May 16, 2014, and has no comments at this time.

The Division of Medical Policy Programs and OPDP will provide a single, consolidated review of the patient labeling under separate cover.

Thank you for your consult. OPDP appreciates the opportunity to provide comments. If you have any questions, please contact Jessica Fox at (301) 796-5329 or at Jessica.Fox@fda.hhs.gov.

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/s/

JESSICA M FOX
05/21/2014

LABEL AND LABELING REVIEW MEMORANDUM

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

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Date of This Review: May 21, 2014

Requesting Office or Division: Division of Anti-Viral Products (DAVP)

Application Type and Number: NDA 206352 and NDA 021567/S-035

Product Name and Strength: Reyataz (atazanavir) (b) (4) Powder for Oral Use
50 mg per packet

Product Type: Single Ingredient Product

Rx or OTC: Rx

Sponsor Name: Bristol Meyers Squibb

Submission Date: December 2, 2013

OSE RCM #: 2013-2743-2

DMEPA Primary Reviewer: James Schlick, RPh, MBA

DMEPA Associate Director: Irene Z. Chan, PharmD, BCPS

1 REASON FOR REVIEW

This review evaluates the revised container labels, carton labeling, prescribing information, and instructions for use for confusion that could lead to medication errors. DMEPA previously reviewed these materials in OSE Review 2013-2743 dated April 28, 2014 and 2013-2743-1 dated May 9, 2014 under NDA 206352 and NDA 021567/S-035.

2 MATERIALS REVIEWED

We considered the revised container labels, carton labeling, prescribing information, and instructions for use submitted via email on May 16, 2014. Appendix A includes the revised materials.

3 OVERALL ASSESSMENT AND CONCLUSION

The Sponsor has incorporated the recommended changes into the revised container labels, carton labeling, prescribing information, and instructions for use. We conclude that the revised labeling are acceptable and have no additional comments at this time.

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/s/

JAMES H SCHLICK
05/21/2014

IRENE Z CHAN
05/21/2014

LABEL AND LABELING REVIEW MEMORANDUM

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

***** This document contains proprietary information that cannot be released to the public*****

Date of This Review: May 09, 2014

Requesting Office or Division: Division of Anti-Viral Products (DAVP)

Application Type and Number: NDA 206352 and NDA 021567/S-035

Product Name and Strength: Reyataz (atazanavir) (b) (4) Powder for Oral Use
50 mg per packet

Product Type: Single Ingredient Product

Rx or OTC: Rx

Sponsor Name: Bristol Meyers Squibb

Submission Date: December 2, 2013

OSE RCM #: 2013-2743-1

DMEPA Primary Reviewer: James Schlick, RPh, MBA

DMEPA Associate Director: Irene Z. Chan, PharmD, BCPS

1 REASON FOR REVIEW

The Division of Antiviral Products (DAVP) requested that we assess the risk for direct ingestion of Reyataz powder without mixing with food or beverage. DMEPA previously reviewed proposed container labels and carton labeling for Reyataz powder in OSE Review 2013-2743 dated April 28, 2014 under NDA 206352 and NDA 021567/S-035.

2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this memorandum. The Appendices provide the methods and results for each material reviewed.

Table 1. Materials Considered for this Label and Labeling Review	
Material Reviewed	Appendix Section (for Methods and Results)
Institute for Safe Medication Practices (ISMP) Newsletters	A
Labels and Labeling	B

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

Our review of the ISMP newsletters confirmed that the risk for administering the powder directly does exist. We identified three post marketing cases where oral powder was ingested without reconstituting the product first. In two of the three cases, the volume of powder administered was equal to the prescribed volume of suspension, which led to an overdose. The products involved in these cases were multiple dose bottles, unlike Reyataz powder, which is in unit dose packets. Therefore, we believe the proposed packaging helps to minimize the risk for overdose associated with direct powder ingestion. Additionally, Reyataz powder will likely be prescribed in packets or milligrams, thus also decreasing the risk for overdose.

Our review of the labels and labeling determined that the information in the patient package insert is clear with regards to mixing with food or beverage before administering. However, we recommend adding a statement on the container label and carton labeling to promote proper administration since we have concerns about whether absorption differences will arise if Reyataz powder is not mixed with food or beverage. Given the patient population and disease state, proper absorption and adequate drug levels are important.

4 CONCLUSION

We have determined there is a risk for direct ingestion of Reyataz powder without mixing with food or beverage. Therefore, a statement should be added to the container labels and carton labeling to promote proper administration. We make this recommendation in Section 4.1.

4.1 RECOMMENDATIONS FOR THE SPONSOR

A. Carton Labeling and Container Label

1. To ensure that Reyataz powder is mixed with food or beverage before administration, we recommend adding the following statement to the principal display panel (PDP):

“Mix with food or beverage before taking this medicine. See mixing instructions.”

To accommodate this on the container label, consider moving the “Each packet contains...” and “Keep out of reach...” statements to the back panel.

APPENDIX A. ISMP NEWSLETTERS

A.1 Methods

We searched the Institute for Safe Medication Practices (ISMP) newsletters on May 8, 2014 using the criteria below, and then individually reviewed each newsletter. We limited our analysis to newsletters that described medication errors or actions possibly associated with the label and labeling.

ISMP Newsletters Search Strategy	
Date Searched	May 8, 2014
ISMP Newsletter Search Strategy	Select one of the following: Match Exact word or phrase
ISMP Newsletter Searched	ISMP Community Edition
Search Terms	Powder

A.2 Results

The search yielded an article discussing the direct ingestion of oral powder without proper reconstitution.

The article contained three distinct cases. The first two cases involved pediatric patients that received amoxicillin powder equal to the volume of liquid prescribed. Each case resulted in overdose. In one case the patient was taken to the hospital to be treated. The outcome of the treatment was not reported in the other case. The third case involved Tamiflu that was dispensed in powder form. The parents knew from past experience that the powder should have been reconstituted. They sought clarification, reconstituted the drug, and gave the correct dose.

Article Reference: ISMP Medication Safety Alert – Community Care Edition. Volume 12, Issue 2, February 2013.

APPENDIX B. LABELS AND LABELING

B.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,¹ along with postmarket medication error data, we reviewed the following Reyataz labels and labeling submitted by Bristol Meyers Squibb on December 2, 2013.

- Container label
- Carton labeling

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¹ Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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/s/

JAMES H SCHLICK
05/09/2014

IRENE Z CHAN
05/09/2014

LABEL AND LABELING REVIEW

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

***** This document contains proprietary information that cannot be released to the public*****

Date of This Review: April 28, 2014

Requesting Office or Division: Division of Anti-Viral Products (DAVP)

Application Type and Number: NDA 206352 and NDA 021567/S-035

Product Name and Strength: Reyataz (atazanavir) (b) (4) Powder for Oral Use
50 mg per packet
Reyataz (atazanavir) Capsules
150 mg, 200 mg, and 300 mg

Product Type: Single Ingredient Product

Rx or OTC: Rx

Sponsor Name: Bristol Meyers Squibb

Submission Date: December 2, 2013

OSE RCM #: 2013-2743

DMEPA Primary Reviewer: James Schlick, RPh, MBA

DMEPA Team Leader: Irene Z. Chan, PharmD, BCPS

1 REASON FOR REVIEW

This review evaluates the proposed container labels, carton and insert labeling, and instructions for use for Reyataz (atazanavir) Pediatric Powder for Oral Suspension, 50 mg, for areas of vulnerability that could lead to medication errors. The Sponsor plans to have the proposed (b) (4) powder for oral (b) (4) and currently marketed Reyataz capsules share one package insert.

2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
FDA Adverse Event Reporting System (FAERS)	B
Previous DMEPA Reviews	C
Human Factors Study	D N/A
ISMP Newsletters	E
Labels and Labeling	F

N/A=not applicable for this review

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

We determined the use of (b) (4) in the dosage form, (b) (4) may lead to medication errors. For the powder, the proposed indication is for a subset of pediatric patients- children greater than 3 months old who weigh between 10 kg to less than 25 kg. The term (b) (4) generally refers to infants, children, and adolescents ranging in age from 0 to 17 years with a wide range in weight. The use of (b) (4) in the dosage form may cause health care practitioners to accidentally prescribe the powder to patients outside the proposed age and weight ranges.

The Division of Antiviral Products (DAVP) previously asked the Applicant whether it's possible to administer Reyataz (b) (4) Powder through a syringe, as we believe it is more likely that the full dose will be consumed by the child if administered through a syringe rather than through a bottle. The Sponsor, in their February 19, 2014 submission, stated that it is possible to deliver the dose using an oral syringe and infant formula. Using an oral syringe will help ensure the caregiver can deliver the full dose to the patient. The bottle method may lead to an under dose

if residual infant formula is left in the bottle or if the baby does not finish the contents due to larger volume. To decrease the risk of error, DMEPA recommends replacing instructions for the baby bottle with instructions to prepare and administer the dose in an oral syringe to ensure the whole dose is given to younger patients who cannot eat food.

We are concerned that the proposed instructions may be lacking with regards to accurately measuring volumes of food or beverage used in preparation of the dose. Therefore, we provide recommendations in section 4 to include this information.

After reviewing the *Dosage and Administration* section in the insert labeling and *Instructions for Use*, we determined additional instructions should be added on the proper washing of the containers used to prepare the dose to prevent inadvertent exposure to drug of other household members. We provide recommendations in section 4.

The Sponsor states in the *Dosage and Administration* section that the powder formulation must not be used in adults. However, the Reyataz review team notes that although the capsules are not bioequivalent to the oral powder, they are clinically interchangeable in pediatric and adult patients. The review team will make specific edits to the prescribing information to reflect this.

There is color similarity between the 150 mg capsule and 50 mg powder presentations on the carton and container labels. Also, there is no statement on the carton and container labels that states the minimum age and weight requirement for the powder. We provide recommendations in section 4 to choose a color other than the colors used to differentiate the capsule strengths and to add a statement about the minimum age and weight requirement.

4 CONCLUSION

We conclude that the use of (b) (4) in the dosage form may lead to medication error. Additionally, there are areas of vulnerability in the labels and labeling that can be improved to minimize the risk for confusion that can lead to medication errors. We provide recommendations in Sections 4.1 and 4.2 below to address our concerns, and we advise these are implemented prior to approval of this application.

4.1 RECOMMENDATIONS FOR THE SPONSOR

A. Container Labels and Carton Labeling

1. Add the statement “For patients who are at least 3 months of age and weigh at least 10 kg” to the principal display panel. Consider moving the “Each packet contains...” statement and/or “Keep out of the reach of children” statement on the container label to the back panel to make room for this statement.

2. The 150 mg capsule and 50 mg powder strength presentations use similar colors (b) (4) on the carton and container labels. Choose a different color for the 150 mg powder strength presentation and color banner at the top of the principal display panels that is not similar to the colors used to differentiate the capsule strengths.

4.2 RECOMMENDATIONS FOR THE DIVISION

The following recommendations pertain to the *Prescribing Information* and *Instructions for Use* in NDA 206352 and NDA 021567/S-035.

A. Comment on the Established Name

1. We determined the use of the term (b) (4) in the presentation of the dosage form, (b) (4) may lead to medication errors. (b) (4)
(b) (4)
(b) (4) We defer to DAVP and ONDQA regarding the appropriate final finished dosage form.

B. Comments to Replace (b) (4) with an Oral Syringe to Administer the Dose in Patients Who Cannot Eat Semisolid or Solid Food.

1. Section 2.2, *Instructions for Mixing Reyataz (b) (4) Powder*

Replace (b) (4) with “or oral syringe” in the following statement:

(b) (4)
(b) (4)

2. Instructions for Use (IFU)

- a. See comment 1 above. Update Step 3 accordingly. Additionally, Figure B should also be updated to replace the (b) (4) with oral syringe.
- b. To ensure that a full dose is given for those patients who cannot eat semisolid or solid food and are on baby formula, add specific instructions detailing the use of an oral syringe to deliver the dose.
- c. Add specific instructions on how to deliver the residual drug left in the cup or oral syringe after giving the dose.
- d. Replace the statement (b) (4) with the minimum amount or exact amount of food, beverage, or infant formula that is required to prepare and deliver the dose.

- e. Include additional instructions in the Instructions for Use (IFU) section to address proper washing and rinsing of containers, cups, or oral syringes after administration to prevent accidental exposure to drug.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Reyataz that Bristol Myers Squibb submitted on December 2, 2013.

Table 2. Relevant Product Information for Reyataz (atazanavir) Pediatric Powder for Oral Use			
Active Ingredient	Atazanavir		
Indication	Indicated in combination with other antiretroviral agents for the treatment of HIV-1 infection.		
Route of Administration	Orally		
Dosage Form	Powder for Oral Use		
Strength	50 mg		
Dose and Frequency	Patients (10 kg to less than 25 kg) for REYATAZ Pediatric Powder with Ritonavir		
	Body weight	REYATAZ dose	ritonavir^b 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
Reyataz should only be administered to pediatric patients that are at least 3 months of age.			
How Supplied/Container Closure	REYATAZ (b) (4) Powder is an orange-vanilla flavored powder, packed in child-resistant packets containing 50 mg of atazanavir as atazanavir sulfate in 1.5 g of powder. REYATAZ (b) (4) Powder for oral use is supplied in cartons (NDC 0003-3638-10) of 30 packets each.		
Storage	Store at or below 30°C (86°F).		

APPENDIX B. FDA ADVERSE EVENT REPORTING SYSTEM (FAERS)

B.1 Methods

We searched the FDA Adverse Event Reporting System (FAERS) on February 10, 2014 using the criteria in Table 3, and then individually reviewed each case. We limited our analysis to cases that described errors possibly associated with the label and labeling. We used the NCC MERP Taxonomy of Medication Errors to code the type and factors contributing to the errors when sufficient information was provided by the reporter¹

Table 3: FAERS Search Strategy	
Date Range	September 16, 2011 (Date of last search) to February 10, 2014
Drug Names	Atazanavir [active ingredient] Reyataz [product name]
MedDRA Search Strategy	Medication Errors [HLGT] Product Packaging Issues [HLT] Product Label Issues [HLT] Product Quality Issues (NEC)[HLT]

B.2 Results

Our search identified 46 cases, of which 20 described errors possibly associated with the current labels and labeling for Reyataz. We excluded 26 cases because they described:

- Adverse event not related to Reyataz
- Intentional overdose
- Medication error not related to Reyataz
- No medication error identified in the case
- Duplicate cases

Dose Omission (n=3)

Three cases described instances where the dose was omitted. One case involved a patient reporting she missed 2 doses in a 6 month period. A patient in the second case missed doses because the medication she received in the mail did not contain powder in the capsules; instead the powder was on the bottom of the bottle. A lot number was provided and we will forward it to DQRS for follow-up. A patient in the third case missed 5 doses due to kidney stones.

¹ The National Coordinating Council for Medication Error Reporting and Prevention (NCC MERP) Taxonomy of Medication Errors. Website <http://www.nccmerp.org/pdf/taxo2001-07-31.pdf>.

The insert labeling is clear with regards to proper dosage instructions. Therefore, we do not recommend any changes related to this issue at this time.

Drug Interaction (n=1)

One case described a drug interaction between atazanavir and lamotrigine where a patient developed status epilepticus and was hospitalized for treatment. The reporting physician stated a possible cause was the increase in metabolism of the lamotrigine by atazanavir and ritonavir. The lamotrigine and atazanavir interaction is listed in the prescribing and patient information. Therefore, we do not recommend any changes to the insert regarding this issue.

Incorrect Administration (n=5)

Five cases involved patients opening the capsules and sprinkling the contents in applesauce, placing the contents in water to dissolve, or administering the contents of the capsule via a PEG tube. Three of the 5 cases stated the age of the patients (17, 45, and 47). Three cases reported no adverse outcome and 2 cases did not report outcome.

The approved insert labeling includes clear instructions to not open the capsule. Therefore, we do not recommend any changes to the insert regarding this issue.

Incorrect Frequency of Administration (n=3)

One case involved a patient taking the correct daily dose of 400 mg, but splitting the daily dose into a 200 mg twice daily regimen. The second case included a report where the patient was prescribed a dose of 300 mg once daily, but was taking 300 mg twice daily. The third case reported a physician mistakenly renewed a once daily therapy as three times daily. The patient took this regimen for 14 months before the error was realized when he was hospitalized for renal insufficiency and proteinuria. The physician stated that the kidney issues may have been related to atazanavir along with other HIV medications taken by the patient. No root cause was identified.

The insert labeling is clear with regards to frequency of administration. Therefore, we do not recommend any changes to the insert regarding this issue.

Incorrect Storage (n=3)

Three cases identified the improper storage of Reyataz. The first case reported that a dispensing facility had placed the medication in the freezer. It was not reported if patients received the medication and the outcome was not reported. The second case contained a report of a mail order medication package left at 4°F for 10 to 12 hours. In the third case, a health care practitioner recommended placing the medication in in the refrigerator to a patient. The patient took 10 doses before realizing the package must be stored at room temperature. The outcome of the case was not reported.

The insert labeling and carton labeling is clear regarding storage. Therefore, we do not recommend any changes to the insert or carton regarding this issue.

Improper Dose (n=3)

One case described a patient taking 600 mg once daily, and a second case involved a patient taking 200 mg once daily instead of the prescribed 400 mg once daily regimen. The outcome was not reported and a root cause was not identified in both cases.

In the third case, a patient was taking 300 mg daily for one year rather than 200 mg once daily. The patient was accidentally prescribed 300 mg once daily when the medication was ordered through the patient assistance program. The report stated that the patient did not have any adverse outcomes. The root cause was not identified.

Wrong Strength(n=1)

One case involved a patient who took 100 mg once daily instead of 300 mg once daily. It was identified that the patient received 100 mg capsules rather than 300 mg capsules in his bottle. A pharmacist estimated that the patient took about 25 doses of the 100 mg capsules before the error was identified. The report stated the patient did not experience any adverse reactions from the error.

The 100 mg capsule was discontinued on April 1, 2013 per Red Book, and the current insert labeling accessed at Daily Med² website on February 11, 2014 does not include the 100 mg strength. Therefore, potential confusion with the container labels and capsule appearance has been mitigated by the removal of the 100 mg capsule.

Wrong Patient Error (n=1)

A patient mistakenly took atazanavir for 14 days when he was not supposed to take it. A root cause was not identified and the outcome was not reported.

B.3 List of FAERS Case Numbers

Below is a list of the FAERS case number and manufacturer control numbers for the cases relevant for this review.

FAERS Case Number	Version	Mfr. Control Number
<u>8189057</u>	1	US-BRISTOL-MYERS SQUIBB COMPANY-16156374
<u>8699380</u>	1	US-BRISTOL-MYERS SQUIBB COMPANY-16686735
<u>8699382</u>	1	US-BRISTOL-MYERS SQUIBB COMPANY-15844517

² <http://dailymed.nlm.nih.gov/dailymed>

<u>8699390</u>	1	US-BRISTOL-MYERS SQUIBB COMPANY-15920978
<u>8699397</u>	1	US-BRISTOL-MYERS SQUIBB COMPANY-15961881
<u>8699422</u>	1	US-BRISTOL-MYERS SQUIBB COMPANY-16231656
<u>8699430</u>	1	US-BRISTOL-MYERS SQUIBB COMPANY-16310989
<u>8699432</u>	1	US-BRISTOL-MYERS SQUIBB COMPANY-16341463
<u>8699434</u>	1	US-BRISTOL-MYERS SQUIBB COMPANY-16349458
<u>8699437</u>	1	US-BRISTOL-MYERS SQUIBB COMPANY-16372476
<u>8699442</u>	1	US-BRISTOL-MYERS SQUIBB COMPANY-16402935
<u>8699452</u>	2	US-BRISTOL-MYERS SQUIBB COMPANY-16471419
<u>8699454</u>	2	US-BRISTOL-MYERS SQUIBB COMPANY-16481574
<u>8699462</u>	1	US-BRISTOL-MYERS SQUIBB COMPANY-16530560
(b) (4)	3	(b) (4)
<u>9259080</u>	2	FR-BRISTOL-MYERS SQUIBB COMPANY-18802470
<u>9312619</u>	1	PT-BRISTOL-MYERS SQUIBB COMPANY-18920959
<u>9447847</u>	1	US-BRISTOL-MYERS SQUIBB COMPANY-19149384
<u>9469602</u>	1	US-BRISTOL-MYERS SQUIBB COMPANY-19199900
<u>9506821</u>	1	

B.4 Description of FAERS

The FDA Adverse Event Reporting System (FAERS) is a database that contains information on adverse event and medication error reports submitted to FDA. The database is designed to

support the FDA's postmarket safety surveillance program for drug and therapeutic biologic products. The informatic structure of the FAERS database adheres to the international safety reporting guidance issued by the International Conference on Harmonisation. Adverse events and medication errors are coded to terms in the Medical Dictionary for Regulatory Activities (MedDRA) terminology. Product names are coded using the FAERS Product Dictionary. More information about FAERS can be found at:

<http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Surveillance/AdverseDrugEffects/default.htm>.

APPENDIX C. PREVIOUS DMEPA REVIEWS

C.1 Methods

We searched the L Drive:\MED ERROR CONSULTS COMPLETED on February 10, 2014 using the terms, 'Reyataz' or 'Atazanavir' to identify reviews previously performed by DMEPA.

C.2 Results

The search yielded the following reviews:

2011-333 Reyataz (Atazanavir) Labeling Review, dated 9/27/2011

2010-1833 Reyataz (Atazanavir) Labeling Review, dated 1/31/2011

2001-193-3 Reyataz.Label.Final, dated 2/20/2003

We reviewed them to ensure all of our recommendations were considered or implemented. We also reviewed our previous reviews for any issues that may be relevant to this review. Our evaluation found that all of our previous recommendations were implemented.

APPENDIX E. ISMP NEWSLETTERS

E.1 Methods

We searched the Institute for Safe Medication Practices (ISMP) newsletters on February 10, 2014 using the criteria below, and then individually reviewed each newsletter. We limited our analysis to newsletters that described medication errors or actions possibly associated with the label and labeling.

ISMP Newsletters Search Strategy	
Date Range	February 11, 2014
ISMP Newsletter Search Strategy	Select one of the following: Match Exact word or phrase
Search Terms	Reyataz, atazanavir

E.2 Results

The search did not yield any articles related to Reyataz or atazanavir.

APPENDIX F. LABELS AND LABELING

F.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,³ along with postmarket medication error data, we reviewed the following Reyataz labels and labeling submitted by Bristol Meyers Squibb on December 2, 2013.

- Container label
- Carton labeling
- Prescribing Information (no image)
- Instructions for Use (no image)

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³ Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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/s/

JAMES H SCHLICK
04/28/2014

IRENE Z CHAN
04/28/2014

RPM FILING REVIEW

(Including Memo of Filing Meeting)

To be completed for all new NDAs, BLAs, and Efficacy Supplements [except SE8 (labeling change with clinical data) and SE9 (manufacturing change with clinical data)]

Application Information		
NDA # 206352 21567	NDA Supplement #: S-000 (Original NDA) S-035	Efficacy Supplement Type N/A SE-5
Proprietary Name: Reyataz Established/Proper Name: atazanavir sulfate Dosage Form: NDA 206352: pediatric powder for oral use, 50 mg/packet NDA 21567 S-035: capsules, 100mg, 150mg, 200mg and 300mg Strengths: see above		
Applicant: Bristol-Myers Squibb Company Agent for Applicant (if applicable): N/A		
Date of Application: December 2, 2013 Date of Receipt: December 2, 2013 Date clock started after UN: N/A		
PDUFA Goal Date: June 2, 2014		Action Goal Date (if different):
Filing Date: January 31, 2014		Date of Filing Meeting: January 10, 2014
Chemical Classification: (1,2,3 etc.) (original NDAs only) 3		
Proposed indication(s)/Proposed change(s): Indicated for use in combination with other antiretroviral agents for the treatment of HIV-1 infection/Proposed new dosage form and expansion of patient population include pediatric patients 10 to < 25kg.		
Type of Original NDA: AND (if applicable) Type of NDA Supplement:	<input checked="" type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)	<input checked="" type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)
<i>If 505(b)(2): Draft the "505(b)(2) Assessment" review found at:</i> http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499 . .		
Review Classification:	<input type="checkbox"/> Standard <input checked="" type="checkbox"/> Priority <input type="checkbox"/> Tropical Disease Priority Review Voucher submitted	
<i>If the application includes a complete response to pediatric WR, review classification is Priority.</i> <i>If a tropical disease priority review voucher was submitted, review classification is Priority.</i>		
Resubmission after withdrawal? <input type="checkbox"/>		Resubmission after refuse to file? <input type="checkbox"/>
Part 3 Combination Product? <input type="checkbox"/> <i>If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults</i>	<input type="checkbox"/> Convenience kit/Co-package <input type="checkbox"/> Pre-filled drug delivery device/system (syringe, patch, etc.) <input type="checkbox"/> Pre-filled biologic delivery device/system (syringe, patch, etc.) <input type="checkbox"/> Device coated/impregnated/combined with drug <input type="checkbox"/> Device coated/impregnated/combined with biologic <input type="checkbox"/> Separate products requiring cross-labeling <input type="checkbox"/> Drug/Biologic	

	<input type="checkbox"/> Possible combination based on cross-labeling of separate products <input type="checkbox"/> Other (drug/device/biological product)
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<input type="checkbox"/> Fast Track Designation <input type="checkbox"/> Breakthrough Therapy Designation <input type="checkbox"/> Rolling Review <input type="checkbox"/> Orphan Designation <input type="checkbox"/> Rx-to-OTC switch, Full <input type="checkbox"/> Rx-to-OTC switch, Partial <input type="checkbox"/> Direct-to-OTC Other:	<input type="checkbox"/> PMC response <input checked="" type="checkbox"/> PMR response: <input type="checkbox"/> FDAAA [505(o)] <input checked="" type="checkbox"/> PREA deferred pediatric studies [21 CFR 314.55(b)/21 CFR 601.27(b)] <input type="checkbox"/> Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) <input type="checkbox"/> Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)			
Collaborative Review Division (<i>if OTC product</i>):				
List referenced IND Number(s): 60,878; 56897				
Goal Dates/Product Names/Classification Properties	YES	NO	NA	Comment
PDUFA and Action Goal dates correct in tracking system? <i>If no, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
Are the proprietary, established/proper, and applicant names correct in tracking system? <i>If no, ask the document room staff to make the corrections. Also, ask the document room staff to add the established/proper name to the supporting IND(s) if not already entered into tracking system.</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
Is the review priority (S or P) and all appropriate classifications/properties entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug)? <i>For NDAs/NDA supplements, check the New Application and New Supplement Notification Checklists for a list of all classifications/properties at: http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163969.htm</i> <i>If no, ask the document room staff to make the appropriate entries.</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Application Integrity Policy	YES	NO	NA	Comment
Is the application affected by the Application Integrity Policy (AIP)? <i>Check the AIP list at: http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm</i>	<input type="checkbox"/>	<input checked="" type="checkbox"/>		
<i>If yes, explain in comment column.</i>				
<i>If affected by AIP, has OC/OMPQ been notified of the submission? If yes, date notified:</i>	<input type="checkbox"/>	<input type="checkbox"/>		
User Fees	YES	NO	NA	Comment
Is Form 3397 (User Fee Cover Sheet) included with authorized signature?	<input checked="" type="checkbox"/>	<input type="checkbox"/>		

<u>User Fee Status</u> <i>If a user fee is required and it has not been paid (and it is not exempted or waived), the application is unacceptable for filing following a 5-day grace period. Review stops. Send Unacceptable for Filing (UN) letter and contact user fee staff.</i>	Payment for this application: <input checked="" type="checkbox"/> Paid* <input type="checkbox"/> Exempt (orphan, government) <input type="checkbox"/> Waived (e.g., small business, public health) <input type="checkbox"/> Not required			
<i>If the firm is in arrears for other fees (regardless of whether a user fee has been paid for this application), the application is unacceptable for filing (5-day grace period does not apply). Review stops. Send UN letter and contact the user fee staff.</i>	Payment of other user fees: <input checked="" type="checkbox"/> Not in arrears <input type="checkbox"/> In arrears *Payment not required for efficacy supplements, data is included by reference to NDA 206352			
505(b)(2) (NDAs/NDA Efficacy Supplements only)	YES	NO	NA	Comment
Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action is less than that of the reference listed drug (RLD)? [see 21 CFR 314.54(b)(1)].	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug [see 21 CFR 314.54(b)(2)]? <i>If you answered yes to any of the above questions, the application may be refused for filing under 21 CFR 314.101(d)(9). Contact the 505(b)(2) review staff in the Immediate Office of New Drugs</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Is there unexpired exclusivity on any drug product containing the active moiety (e.g., 5-year, 3-year, orphan, or pediatric exclusivity)? <i>Check the Electronic Orange Book at: http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm</i> If yes, please list below:	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration	
<i>If there is unexpired, 5-year exclusivity remaining on the active moiety for the proposed drug product, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity will extend both of the timeframes in this provision by 6 months. 21 CFR 314.108(b)(2). Unexpired, 3-year exclusivity may block the approval but not the submission of a 505(b)(2) application.</i>				
Exclusivity	YES	NO	NA	Comment
Does another product (same active moiety) have orphan exclusivity for the same indication? <i>Check the Orphan Drug</i>	<input type="checkbox"/>	<input checked="" type="checkbox"/>		

Designations and Approvals list at: http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm				
If another product has orphan exclusivity , is the product considered to be the same product according to the orphan drug definition of sameness [see 21 CFR 316.3(b)(13)]? <i>If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? (<i>NDAs/NDA efficacy supplements only</i>) If yes, # years requested: three <i>Note: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use (<i>NDAs only</i>)?	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
If yes , did the applicant: (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b): request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)? <i>If yes, contact Mary Ann Holovac, Director of Drug Information, OGD/DLPS/LRB.</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	

Format and Content				
<i>Do not check mixed submission if the only electronic component is the content of labeling (COL).</i>	<input type="checkbox"/> All paper (except for COL) <input checked="" type="checkbox"/> All electronic <input type="checkbox"/> Mixed (paper/electronic) <input checked="" type="checkbox"/> CTD <input type="checkbox"/> Non-CTD <input type="checkbox"/> Mixed (CTD/non-CTD)			
If mixed (paper/electronic) submission , which parts of the application are submitted in electronic format?				
Overall Format/Content	YES	NO	NA	Comment
If electronic submission , does it follow the eCTD guidance? ¹ If not , explain (e.g., waiver granted).	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Index: Does the submission contain an accurate comprehensive index?	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
Is the submission complete as required under 21 CFR 314.50 (<i>NDAs/NDA efficacy supplements</i>) or under 21 CFR 601.2 (<i>BLAs/BLA efficacy supplements</i>) including:	<input checked="" type="checkbox"/>	<input type="checkbox"/>		

1

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072349.pdf>

<input checked="" type="checkbox"/> legible <input checked="" type="checkbox"/> English (or translated into English) <input checked="" type="checkbox"/> pagination <input checked="" type="checkbox"/> navigable hyperlinks (electronic submissions only)				
If no, explain.				
BLAs only: Companion application received if a shared or divided manufacturing arrangement?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
If yes, BLA #				
Forms and Certifications				
<i>Electronic forms and certifications with electronic signatures (scanned, digital, or electronic – similar to DARRTS, e.g., /s/) are acceptable. Otherwise, paper forms and certifications with hand-written signatures must be included. Forms include: user fee cover sheet (3397), application form (356h), patent information (3542a), financial disclosure (3454/3455), and clinical trials (3674); Certifications include: debarment certification, patent certification(s), field copy certification, and pediatric certification.</i>				
Application Form	YES	NO	NA	Comment
Is form FDA 356h included with authorized signature per 21 CFR 314.50(a)?	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
<i>If foreign applicant, a U.S. agent must sign the form [see 21 CFR 314.50(a)(5)].</i>				
Are all establishments and their registration numbers listed on the form/attached to the form?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Patent Information (NDAs/NDA efficacy supplements only)	YES	NO	NA	Comment
Is patent information submitted on form FDA 3542a per 21 CFR 314.53(c)?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Financial Disclosure	YES	NO	NA	Comment
Are financial disclosure forms FDA 3454 and/or 3455 included with authorized signature per 21 CFR 54.4(a)(1) and (3)?	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
<i>Forms must be signed by the APPLICANT, not an Agent [see 21 CFR 54.2(g)].</i>				
<i>Note: Financial disclosure is required for bioequivalence studies that are the basis for approval.</i>				
Clinical Trials Database	YES	NO	NA	Comment
Is form FDA 3674 included with authorized signature?	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
<i>If yes, ensure that the application is also coded with the supporting document category, "Form 3674."</i>				

<i>If no, ensure that language requesting submission of the form is included in the acknowledgement letter sent to the applicant</i>				
Debarment Certification	YES	NO	NA	Comment
Is a correctly worded Debarment Certification included with authorized signature? <i>Certification is not required for supplements if submitted in the original application; If foreign applicant, both the applicant and the U.S. Agent must sign the certification [per Guidance for Industry: Submitting Debarment Certifications].</i> <i>Note: Debarment Certification should use wording in FD&C Act Section 306(k)(1) i.e., “[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application.” Applicant may not use wording such as, “To the best of my knowledge...”</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Field Copy Certification (NDAs/NDA efficacy supplements only)	YES	NO	NA	Comment
For paper submissions only: Is a Field Copy Certification (that it is a true copy of the CMC technical section) included? <i>Field Copy Certification is not needed if there is no CMC technical section or if this is an electronic submission (the Field Office has access to the EDR)</i> <i>If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
Controlled Substance/Product with Abuse Potential	YES	NO	NA	Comment
<u>For NMEs:</u> Is an Abuse Liability Assessment, including a proposal for scheduling, submitted per 21 CFR 314.50(d)(5)(vii)? <i>If yes, date consult sent to the Controlled Substance Staff:</i> <u>For non-NMEs:</u> <i>Date of consult sent to Controlled Substance Staff:</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
Pediatrics	YES	NO	NA	Comment
<u>PREA</u> Does the application trigger PREA? <i>If yes, notify PeRC RPM (PeRC meeting is required)²</i> <i>Note: NDAs/BLAs/efficacy supplements for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver & deferral requests, pediatric plans, and pediatric assessment studies must be</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		PeRC Meeting April 2, 2014

² <http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027829.htm>

<i>reviewed by PeRC prior to approval of the application/supplement.</i>				
If the application triggers PREA , are the required pediatric assessment studies or a full waiver of pediatric studies included?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
If studies or full waiver not included , is a request for full waiver of pediatric studies OR a request for partial waiver and/or deferral with a pediatric plan included? <i>If no, request in 74-day letter</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
If a request for full waiver/partial waiver/deferral is included , does the application contain the certification(s) required by FDCA Section 505B(a)(3) and (4)? <i>If no, request in 74-day letter</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	Previously granted partial deferral until January 15, 2016.
BPCA (NDAs/NDA efficacy supplements only): Is this submission a complete response to a pediatric Written Request? <i>If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required)³</i>	<input type="checkbox"/>	<input checked="" type="checkbox"/>		
Proprietary Name	YES	NO	NA	Comment
Is a proposed proprietary name submitted? <i>If yes, ensure that the application is also coded with the supporting document category, "Proprietary Name/Request for Review."</i>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	Reyataz is already approved for capsules
REMS	YES	NO	NA	Comment
Is a REMS submitted? <i>If yes, send consult to OSE/DRISK and notify OC/OSI/DSC/PMSB via the CDER OSI RMP mailbox</i>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
Prescription Labeling	<input type="checkbox"/> Not applicable			
Check all types of labeling submitted.	<input checked="" type="checkbox"/> Package Insert (PI) <input checked="" type="checkbox"/> Patient Package Insert (PPI) <input checked="" type="checkbox"/> Instructions for Use (IFU) <input type="checkbox"/> Medication Guide (MedGuide) <input checked="" type="checkbox"/> Carton labels <input checked="" type="checkbox"/> Immediate container labels <input type="checkbox"/> Diluent <input type="checkbox"/> Other (specify)			
	YES	NO	NA	Comment
Is Electronic Content of Labeling (COL) submitted in SPL	<input checked="" type="checkbox"/>	<input type="checkbox"/>		

³ <http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027837.htm>

format?				
<i>If no, request applicant to submit SPL before the filing date.</i>				
Is the PI submitted in PLR format? ⁴	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
If PI not submitted in PLR format , was a waiver or deferral requested before the application was received or in the submission? If requested before application was submitted , what is the status of the request?	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
<i>If no waiver or deferral, request applicant to submit labeling in PLR format before the filing date.</i>				
All labeling (PI, PPI, MedGuide, IFU, carton and immediate container labels) consulted to OPDP?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
MedGuide, PPI, IFU (plus PI) consulted to OSE/DRISK? (send WORD version if available)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Carton and immediate container labels, PI, PPI sent to OSE/DMEPA and appropriate CMC review office (OBP or ONDQA)?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
OTC Labeling	<input checked="" type="checkbox"/> Not Applicable			
Check all types of labeling submitted.	<input type="checkbox"/> Outer carton label <input type="checkbox"/> Immediate container label <input type="checkbox"/> Blister card <input type="checkbox"/> Blister backing label <input type="checkbox"/> Consumer Information Leaflet (CIL) <input type="checkbox"/> Physician sample <input type="checkbox"/> Consumer sample <input type="checkbox"/> Other (specify)			
	YES	NO	NA	Comment
Is electronic content of labeling (COL) submitted?	<input type="checkbox"/>	<input type="checkbox"/>		
<i>If no, request in 74-day letter.</i>				
Are annotated specifications submitted for all stock keeping units (SKUs)?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<i>If no, request in 74-day letter.</i>				
If representative labeling is submitted, are all represented SKUs defined?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<i>If no, request in 74-day letter.</i>				
All labeling/packaging, and current approved Rx PI (if switch) sent to OSE/DMEPA?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Other Consults	YES	NO	NA	Comment
Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team)	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	

4

<http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/StudyEndpointsandLabelingDevelopmentTeam/ucm025576.htm>

<i>If yes, specify consult(s) and date(s) sent:</i>				
Meeting Minutes/SPAs	YES	NO	NA	Comment
End-of Phase 2 meeting(s)? Date(s):	<input type="checkbox"/>	<input checked="" type="checkbox"/>		
<i>If yes, distribute minutes before filing meeting</i>				
Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? Date(s): NDA 206352: November 19, 2012	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
<i>If yes, distribute minutes before filing meeting</i>				
Any Special Protocol Assessments (SPAs)? Date(s):	<input type="checkbox"/>	<input checked="" type="checkbox"/>		
<i>If yes, distribute letter and/or relevant minutes before filing meeting</i>				

ATTACHMENT

MEMO OF FILING MEETING

DATE: January 10, 2014

BLA/NDA/Supp #: NDA 206352, NDA 21567 S-035

PROPRIETARY NAME: Reyataz®

ESTABLISHED/PROPER NAME: atazanavir sulfate

DOSAGE FORM/STRENGTH: NDA 206352: pediatric powder for oral use, 50 mg/packet;
NDA 21567 S-035: capsules, 100mg, 150mg, 200mg and 300mg

APPLICANT: Bristol-Myers Squibb

PROPOSED INDICATION(S)/PROPOSED CHANGE(S): Indicated for use in combination with other antiretroviral agents for the treatment of HIV-1 infection/Proposed new dosage form and expansion of patient population include pediatric patients 10 to < 25kg.

BACKGROUND: BMS has submitted NDA 206352 for Reyataz (atazanavir sulfate) powder for oral use to expand the patient population to pediatric patients 10 to < 25kg. A companion efficacy supplement was also submitted to NDA 21567 (S-035) for atazanavir capsules as the two NDAs share labeling. These submissions also propose to fulfill post-marketing commitment #1 and partially fulfill the written request for exclusivity.

The submission includes new carton and container labels for the powder for oral use, as well as a new "Instructions for Use" document that is proposed as part of the patient labeling.

REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Sammie Beam	Y
	CPMS/TL:	Elizabeth Thompson	Y
Cross-Discipline Team Leader (CDTL)	Mary Singer		Y
Clinical	Reviewer:	Alan Shapiro	Y
	TL:	Mary Singer	Y
Social Scientist Review (<i>for OTC products</i>)	Reviewer:		
	TL:		

OTC Labeling Review (<i>for OTC products</i>)	Reviewer:		
	TL:		
Clinical Microbiology (<i>for antimicrobial products</i>)	Reviewer:	Eric Donaldson	Y
	TL:	Julian O'Rear	Y

Clinical Pharmacology	Reviewer:	Jenny Zheng	Y
	TL:	Shirley Seo	Y
Biostatistics	Reviewer:	Karen Qi	Y
	TL:	Fraser Smith	N
Nonclinical (Pharmacology/Toxicology)	Reviewer:	Kuei Meng Wu	Y
	TL:	Hanan Ghantous	Y
Statistics (carcinogenicity)	Reviewer:		
	TL:		
Immunogenicity (assay/assay validation) (<i>for BLAs/BLA efficacy supplements</i>)	Reviewer:		
	TL:		
Product Quality (CMC)	Reviewer:	Yichun Sun Steve Miller	Y-Miller
	TL:	Rapti Madurawe	
Quality Microbiology (<i>for sterile products</i>)	Reviewer:		
	TL:		
CMC Labeling Review	Reviewer:		
	TL:		
Facility Review/Inspection	Reviewer:		
	TL:		
OSE/DMEPA (proprietary name)	Reviewer:	James Schlick	Y
	TL:		
OSE/DRISK (REMS)	Reviewer:	Nyedra Booker	Y
	TL:		
OC/OSI/DSC/PMSB (REMS)	Reviewer:		
	TL:		

Bioresearch Monitoring (OSI)	Reviewer:		
	TL:		
Controlled Substance Staff (CSS)	Reviewer:		
	TL:		
Other reviewers	Karen Dowdy, PLT; Jessica Fox, OPDP		Y
Other attendees	Danyal Chaudhry, OSE		Y

FILING MEETING DISCUSSION:

GENERAL	
<ul style="list-style-type: none"> • 505(b)(2) filing issues: <ul style="list-style-type: none"> ○ Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA? ○ Did the applicant provide a scientific “bridge” demonstrating the relationship between the proposed product and the referenced product(s)/published literature? <p>Describe the scientific bridge (e.g., BA/BE studies):</p> 	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> • Per reviewers, are all parts in English or English translation? <p>If no, explain:</p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> • Electronic Submission comments <p>List comments:</p>	<input checked="" type="checkbox"/> Not Applicable
CLINICAL	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter— Comments were sent earlier per request
<ul style="list-style-type: none"> • Clinical study site(s) inspections(s) needed? <p>If no, explain: Reyataz (atazanavir) has previously been</p>	<input type="checkbox"/> YES <input checked="" type="checkbox"/> NO

<p>studied in pediatric subjects < 6 years of age with a powder formulation and pediatric subjects > 6 years of age with a capsule formulation in Study AI424020 (PACTG 1020) which was submitted for review in NDA Supplement 21-567 S15 in 2007. There was a clinical inspection of multiple sites as part of NDA 21-567 S15 review. The current supplement NDA206352 / NDA21567 consist of two additional pharmacokinetic (PK), safety, and antiviral activity studies which examine an increased dose of the powder formulation in pediatric subjects mostly under the age of six years. The primary focus of these two studies is to validate the PK of the increased dose of the atazanavir powder formulation so no additional clinical inspections are required.</p>	
<p>• Advisory Committee Meeting needed?</p> <p>Comments:</p> <p><i>If no, for an NME NDA or original BLA , include the reason. For example:</i></p> <ul style="list-style-type: none"> ○ <i>this drug/biologic is not the first in its class</i> ○ <i>the clinical study design was acceptable</i> ○ <i>the application did not raise significant safety or efficacy issues</i> ○ <i>the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease</i> 	<p><input type="checkbox"/> YES Date if known:</p> <p><input type="checkbox"/> NO</p> <p><input checked="" type="checkbox"/> To be determined</p> <p>Reason:</p>
<p>• Abuse Liability/Potential</p> <p>Comments:</p>	<p><input checked="" type="checkbox"/> Not Applicable</p> <p><input type="checkbox"/> FILE</p> <p><input type="checkbox"/> REFUSE TO FILE</p> <p><input type="checkbox"/> Review issues for 74-day letter</p>
<p>• If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance?</p> <p>Comments:</p>	<p><input checked="" type="checkbox"/> Not Applicable</p> <p><input type="checkbox"/> YES</p> <p><input type="checkbox"/> NO</p>
<p>CLINICAL MICROBIOLOGY</p> <p>Comments:</p>	<p><input type="checkbox"/> Not Applicable</p> <p><input checked="" type="checkbox"/> FILE</p> <p><input type="checkbox"/> REFUSE TO FILE</p> <p><input type="checkbox"/> Review issues for 74-day letter</p>

CLINICAL PHARMACOLOGY Comments:	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> • Clinical pharmacology study site(s) inspections(s) needed? 	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
BIOSTATISTICS Comments:	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
NONCLINICAL (PHARMACOLOGY/TOXICOLOGY) Comments:	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
IMMUNOGENICITY (BLAs/BLA efficacy supplements only) Comments:	<input type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
PRODUCT QUALITY (CMC) Comments:	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<u>Environmental Assessment</u> <ul style="list-style-type: none"> • Categorical exclusion for environmental assessment (EA) requested? If no, was a complete EA submitted? If EA submitted, consulted to EA officer (OPS)? Comments:	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO
<u>Quality Microbiology (for sterile products)</u>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES

<ul style="list-style-type: none"> Was the Microbiology Team consulted for validation of sterilization? (NDAs/NDA supplements only) <p>Comments:</p>	<input type="checkbox"/> NO
<p><u>Facility Inspection</u></p> <ul style="list-style-type: none"> Establishment(s) ready for inspection? Establishment Evaluation Request (EER/TBP-EER) submitted to OMPQ? <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> YES <input checked="" type="checkbox"/> NO
<p><u>Facility/Microbiology Review (BLAs only)</u></p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p><u>CMC Labeling Review</u></p> <p>Comments:</p>	<input type="checkbox"/> Review issues for 74-day letter
<p>APPLICATIONS IN THE PROGRAM (PDUFA V) (NME NDAs/Original BLAs)</p> <ul style="list-style-type: none"> Were there agreements made at the application's pre-submission meeting (and documented in the minutes) regarding certain late submission components that could be submitted within 30 days after receipt of the original application? If so, were the late submission components all submitted within 30 days? 	<input checked="" type="checkbox"/> N/A <input type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> What late submission components, if any, arrived after 30 days? 	

<ul style="list-style-type: none"> Was the application otherwise complete upon submission, including those applications where there were no agreements regarding late submission components? 	<input type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> Is a comprehensive and readily located list of all clinical sites included or referenced in the application? 	<input type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> Is a comprehensive and readily located list of all manufacturing facilities included or referenced in the application? 	<input type="checkbox"/> YES <input type="checkbox"/> NO

REGULATORY PROJECT MANAGEMENT

Signatory Authority: Jeff Murray

Date of Mid-Cycle Meeting (for NME NDAs/BLAs in “the Program” PDUFA V):

21st Century Review Milestones (see attached) (listing review milestones in this document is optional):

Comments:

REGULATORY CONCLUSIONS/DEFICIENCIES

<input type="checkbox"/>	The application is unsuitable for filing. Explain why:
<input checked="" type="checkbox"/>	<p>The application, on its face, appears to be suitable for filing.</p> <p><u>Review Issues:</u></p> <p><input type="checkbox"/> No review issues have been identified for the 74-day letter.</p> <p><input checked="" type="checkbox"/> Review issues have been identified for the 74-day letter. List (optional):</p> <p><u>Review Classification:</u></p> <p><input type="checkbox"/> Standard Review</p> <p><input checked="" type="checkbox"/> Priority Review</p>

ACTIONS ITEMS

<input type="checkbox"/>	Ensure that any updates to the review priority (S or P) and classifications/properties are entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug).
<input type="checkbox"/>	If RTF, notify everybody who already received a consult request, OSE PM, and Product

	Quality PM (to cancel EER/TBP-EER).
<input type="checkbox"/>	If filed, and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
<input type="checkbox"/>	BLA/BLA supplements: If filed, send 60-day filing letter
<input checked="" type="checkbox"/>	If priority review: <ul style="list-style-type: none"> • notify sponsor in writing by day 60 (For BLAs/BLA supplements: include in 60-day filing letter; For NDAs/NDA supplements: see CST for choices) • notify OMPQ (so facility inspections can be scheduled earlier)
<input checked="" type="checkbox"/>	Send review issues/no review issues by day 74
<input checked="" type="checkbox"/>	Conduct a PLR format labeling review and include labeling issues in the 74-day letter— PLR labeling issues were sent before 74 days, but not in 74-day letter.
<input type="checkbox"/>	Update the PDUFA V DARRTS page (for NME NDAs in the Program)
<input type="checkbox"/>	BLA/BLA supplements: Send the Product Information Sheet to the product reviewer and the Facility Information Sheet to the facility reviewer for completion. Ensure that the completed forms are forwarded to the CDER RMS-BLA Superuser for data entry into RMS-BLA one month prior to taking an action [These sheets may be found in the CST eRoom at: http://eroom.fda.gov/eRoom/CDER2/CDERStandardLettersCommittee/0_1685f]
<input type="checkbox"/>	Other

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

SAMMIE G BEAM
02/20/2014

ELIZABETH G THOMPSON
02/24/2014

**REGULATORY PROJECT MANAGER
PHYSICIAN'S LABELING RULE (PLR) FORMAT REVIEW
OF THE PRESCRIBING INFORMATION**

Complete for all new NDAs, BLAs, Efficacy Supplements, and PLR Conversion Labeling Supplements

Application: NDA 206352
NDA 21567/S-035

Application Type: New NDA and Efficacy Supplement

Name of Drug/Dosage Form: Reyataz ® atazanavir sulfate
NDA powder for oral use, 50mg per packet
sNDA capsules, 100, 150, 200 and 300mg

Applicant: Bristol-Myers-Squibb

Receipt Date: December 2, 2013

Goal Date: June 2, 2013

1. Regulatory History and Applicant's Main Proposals

BMS submitted NDA 206352 for Reyataz (atazanavir sulfate) powder for oral use to expand the patient population to pediatric patients 10 to < 25kg. A companion efficacy supplement was also submitted to NDA 21567 (S-035) for atazanavir capsules as the two NDAs share labeling. These submissions also propose to fulfill post-marketing commitment #1 and partially fulfill the written request for exclusivity.

2. Review of the Prescribing Information

This review is based on the applicant's submitted Word format of the prescribing information (PI). The applicant's proposed PI was reviewed in accordance with the labeling format requirements listed in the "Selected Requirements for Prescribing Information (SRPI)" checklist (see the Appendix).

3. Conclusions/Recommendations

SRPI format deficiencies were identified in the review of this PI. For a list of these deficiencies see the Appendix.

All SRPI format deficiencies of the PI will be conveyed to the applicant in an advice letter. The applicant will be asked to correct these deficiencies and resubmit the PI in Word format by February 27, 2014. The resubmitted PI will be used for further labeling review.

Selected Requirements of Prescribing Information

Appendix

The Selected Requirement of Prescribing Information (SRPI) is a 42-item, drop-down checklist of important format elements of the prescribing information (PI) based on labeling regulations (21 CFR 201.56 and 201.57) and guidances.

Highlights

See Appendix A for a sample tool illustrating the format for the Highlights.

HIGHLIGHTS GENERAL FORMAT and HORIZONTAL LINES IN THE PI

- NO** 1. Highlights (HL) must be in a minimum of 8-point font and should be in two-column format, with ½ inch margins on all sides and between columns.

Comment: *There is less than a 1/2 inch between columns.*

- YES** 2. The length of HL must be one-half page or less (the HL Boxed Warning does not count against the one-half page requirement) unless a waiver has been granted in a previous submission (e.g., the application being reviewed is an efficacy supplement).

Instructions to complete this item: If the length of the HL is one-half page or less, then select “YES” in the drop-down menu because this item meets the requirement. However, if HL is longer than one-half page:

➤ **For the Filing Period:**

- *For efficacy supplements:* If a waiver was previously granted, select “YES” in the drop-down menu because this item meets the requirement.
- *For NDAs/BLAs and PLR conversions:* Select “NO” because this item does not meet the requirement (deficiency). The RPM notifies the Cross-Discipline Team Leader (CDTL) of the excessive HL length and the CDTL determines if this deficiency is included in the 74-day or advice letter to the applicant.

➤ **For the End-of-Cycle Period:**

- Select “YES” in the drop down menu if a waiver has been previously (or will be) granted by the review division in the approval letter and document that waiver was (or will be) granted.

Comment: *Waiver was granted March 25, 2008.*

- YES** 3. A horizontal line must separate HL from the Table of Contents (TOC). A horizontal line must separate the TOC from the FPI.

Comment:

- YES** 4. All headings in HL must be **bolded** and presented in the center of a horizontal line (each horizontal line should extend over the entire width of the column as shown in Appendix A). The headings should be in UPPER CASE letters.

Comment:

Selected Requirements of Prescribing Information

- YES** 5. White space should be present before each major heading in HL. There must be no white space between the HL Heading and HL Limitation Statement. There must be no white space between the product title and Initial U.S. Approval. See Appendix A for a sample tool illustrating white space in HL.

Comment:

- YES** 6. Each summarized statement or topic in HL must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contain more detailed information. The preferred format is the numerical identifier in parenthesis [e.g., (1.1)] at the end of each summarized statement or topic.

Comment:

- YES** 7. Section headings must be presented in the following order in HL:

Section	Required/Optional
• Highlights Heading	Required
• Highlights Limitation Statement	Required
• Product Title	Required
• Initial U.S. Approval	Required
• Boxed Warning	Required if a BOXED WARNING is in the FPI
• Recent Major Changes	Required for only certain changes to PI*
• Indications and Usage	Required
• Dosage and Administration	Required
• Dosage Forms and Strengths	Required
• Contraindications	Required (if no contraindications must state "None.")
• Warnings and Precautions	Not required by regulation, but should be present
• Adverse Reactions	Required
• Drug Interactions	Optional
• Use in Specific Populations	Optional
• Patient Counseling Information Statement	Required
• Revision Date	Required

* RMC only applies to the BOXED WARNING, INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS AND PRECAUTIONS sections.

Comment:

HIGHLIGHTS DETAILS

Highlights Heading

- YES** 8. At the beginning of HL, the following heading must be **bolded** and should appear in all UPPER CASE letters: "**HIGHLIGHTS OF PRESCRIBING INFORMATION**".

Comment:

Highlights Limitation Statement

- YES** 9. The **bolded** HL Limitation Statement must include the following verbatim statement: "**These highlights do not include all the information needed to use (insert name of drug product) safely and effectively. See full prescribing information for (insert name of drug product).**" The name of drug product should appear in UPPER CASE letters.

Comment:

Product Title in Highlights

Selected Requirements of Prescribing Information

- YES** 10. Product title must be **bolded**.
Comment: *The title needs to change to lowercase (capsules, powder).*

Initial U.S. Approval in Highlights

- YES** 11. Initial U.S. Approval in HL must be **bolded**, and include the verbatim statement “**Initial U.S. Approval:**” followed by the **4-digit year**.
Comment:

Boxed Warning (BW) in Highlights

- N/A** 12. All text in the BW must be **bolded**.
Comment:

- N/A** 13. The BW must have a heading in UPPER CASE, containing the word “**WARNING**” (even if more than one warning, the term, “**WARNING**” and not “**WARNINGS**” should be used) and other words to identify the subject of the warning (e.g., “**WARNING: SERIOUS INFECTIONS and ACUTE HEPATIC FAILURE**”). The BW heading should be centered.
Comment:

- N/A** 14. The BW must always have the verbatim statement “*See full prescribing information for complete boxed warning.*” This statement should be centered immediately beneath the heading and appear in *italics*.
Comment:

- N/A** 15. The BW must be limited in length to 20 lines (this includes white space but does not include the BW heading and the statement “*See full prescribing information for complete boxed warning.*”).
Comment:

Recent Major Changes (RMC) in Highlights

- YES** 16. RMC pertains to only the following five sections of the FPI: BOXED WARNING, INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS AND PRECAUTIONS. RMC must be listed in the same order in HL as the modified text appears in FPI.
Comment:

- YES** 17. The RMC must include the section heading(s) and, if appropriate, subsection heading(s) affected by the recent major change, together with each section’s identifying number and date (month/year format) on which the change was incorporated in the PI (supplement approval date). For example, “Warnings and Precautions, Acute Liver Failure (5.1) --- 9/2013”.
Comment:

- YES** 18. The RMC must list changes for at least one year after the supplement is approved and must be removed at the first printing subsequent to one year (e.g., no listing should be one year older than revision date).
Comment:

Indications and Usage in Highlights

YES

Selected Requirements of Prescribing Information

19. If a product belongs to an established pharmacologic class, the following statement is required under the Indications and Usage heading in HL: “(Product) is a (name of established pharmacologic class) indicated for (indication)”.

Comment:

Dosage Forms and Strengths in Highlights

- YES** 20. For a product that has several dosage forms (e.g., capsules, tablets, and injection), bulleted subheadings or tabular presentations of information should be used under the Dosage Forms and Strengths heading.

Comment:

Contraindications in Highlights

- YES** 21. All contraindications listed in the FPI must also be listed in HL or must include the statement “None” if no contraindications are known. Each contraindication should be bulleted when there is more than one contraindication.

Comment:

Adverse Reactions in Highlights

- YES** 22. For drug products other than vaccines, the verbatim **bolded** statement must be present: “**To report SUSPECTED ADVERSE REACTIONS, contact (insert name of manufacturer) at (insert manufacturer’s U.S. phone number) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch**”.

Comment:

Patient Counseling Information Statement in Highlights

- YES** 23. The Patient Counseling Information statement must include one of the following three **bolded** verbatim statements that is most applicable:

If a product **does not** have FDA-approved patient labeling:

- “**See 17 for PATIENT COUNSELING INFORMATION**”

If a product **has** FDA-approved patient labeling:

- “**See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling**”
- “**See 17 for PATIENT COUNSELING INFORMATION and Medication Guide**”

Comment:

Revision Date in Highlights

- YES** 24. The revision date must be at the end of HL, and should be **bolded** and right justified (e.g., “**Revised: 9/2013**”).

Comment: *Date will be added on approval of labeling.*

Selected Requirements of Prescribing Information

Contents: Table of Contents (TOC)

See Appendix A for a sample tool illustrating the format for the Table of Contents.

- YES** 25. The TOC should be in a two-column format.
Comment:
- YES** 26. The following heading must appear at the beginning of the TOC: “**FULL PRESCRIBING INFORMATION: CONTENTS**”. This heading should be in all UPPER CASE letters and **bolded**.
Comment:
- N/A** 27. The same heading for the BW that appears in HL and the FPI must also appear at the beginning of the TOC in UPPER CASE letters and **bolded**.
Comment:
- YES** 28. In the TOC, all section headings must be **bolded** and should be in UPPER CASE.
Comment:
- YES** 29. In the TOC, all subsection headings must be indented and not bolded. The headings should be in title case [first letter of all words are capitalized except first letter of prepositions (through), articles (a, an, and the), or conjunctions (for, and)].
Comment:
- YES** 30. The section and subsection headings in the TOC must match the section and subsection headings in the FPI.
Comment: Section 17 will have subsections removed.
- YES** 31. In the TOC, when a section or subsection is omitted, the numbering must not change. If a section or subsection from 201.56(d)(1) is omitted from the FPI and TOC, the heading “FULL PRESCRIBING INFORMATION: CONTENTS” must be followed by an asterisk and the following statement must appear at the end of TOC: “*Sections or subsections omitted from the full prescribing information are not listed.”
Comment:

Selected Requirements of Prescribing Information

Full Prescribing Information (FPI)

FULL PRESCRIBING INFORMATION: GENERAL FORMAT

- YES** 32. The **bolded** section and subsection headings in the FPI must be named and numbered in accordance with 21 CFR 201.56(d)(1) as noted below (section and subsection headings should be in UPPER CASE and title case, respectively). If a section/subsection required by regulation is omitted, the numbering must not change. Additional subsection headings (i.e., those not named by regulation) must also be **bolded** and numbered.

BOXED WARNING
1 INDICATIONS AND USAGE
2 DOSAGE AND ADMINISTRATION
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
6 ADVERSE REACTIONS
7 DRUG INTERACTIONS
8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
8.2 Labor and Delivery
8.3 Nursing Mothers
8.4 Pediatric Use
8.5 Geriatric Use
9 DRUG ABUSE AND DEPENDENCE
9.1 Controlled Substance
9.2 Abuse
9.3 Dependence
10 OVERDOSAGE
11 DESCRIPTION
12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
12.2 Pharmacodynamics
12.3 Pharmacokinetics
12.4 Microbiology (by guidance)
12.5 Pharmacogenomics (by guidance)
13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
13.2 Animal Toxicology and/or Pharmacology
14 CLINICAL STUDIES
15 REFERENCES
16 HOW SUPPLIED/STORAGE AND HANDLING
17 PATIENT COUNSELING INFORMATION

Comment:

- NO** 33. The preferred presentation for cross-references in the FPI is the section (not subsection) heading followed by the numerical identifier. The entire cross-reference should be in *italics* and enclosed within brackets. For example, “[*see Warnings and Precautions (5.2)*]” or “[*see Warnings and Precautions (5.2)*]”.

Comment: *The entire reference should be italicized.*

Selected Requirements of Prescribing Information

- YES** 34. If RMCs are listed in HL, the corresponding new or modified text in the FPI sections or subsections must be marked with a vertical line on the left edge.

Comment:

FULL PRESCRIBING INFORMATION DETAILS

FPI Heading

- YES** 35. The following heading must be **bolded** and appear at the beginning of the FPI: “**FULL PRESCRIBING INFORMATION**”. This heading should be in UPPER CASE.

Comment:

BOXED WARNING Section in the FPI

- N/A** 36. In the BW, all text should be **bolded**.

Comment:

- N/A** 37. The BW must have a heading in UPPER CASE, containing the word “**WARNING**” (even if more than one Warning, the term, “**WARNING**” and not “**WARNINGS**” should be used) and other words to identify the subject of the Warning (e.g., “**WARNING: SERIOUS INFECTIONS and ACUTE HEPATIC FAILURE**”).

Comment:

CONTRAINDICATIONS Section in the FPI

- N/A** 38. If no Contraindications are known, this section must state “None.”

Comment:

ADVERSE REACTIONS Section in the FPI

- YES** 39. When clinical trials adverse reactions data are included (typically in the “Clinical Trials Experience” subsection of ADVERSE REACTIONS), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

“Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.”

Comment:

- YES** 40. When postmarketing adverse reaction data are included (typically in the “Postmarketing Experience” subsection of ADVERSE REACTIONS), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

“The following adverse reactions have been identified during post-approval use of (insert drug name). Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.”

Comment:

PATIENT COUNSELING INFORMATION Section in the FPI

- NO** 41. Must reference any FDA-approved patient labeling in Section 17 (PATIENT COUNSELING INFORMATION section). The reference should appear at the beginning of Section 17 and

Selected Requirements of Prescribing Information

include the type(s) of FDA-approved patient labeling (e.g., Patient Information, Medication Guide, Instructions for Use).

Comment: *Needs to reference "Instructions for Use."*

- YES** 42. FDA-approved patient labeling (e.g., Medication Guide, Patient Information, or Instructions for Use) must not be included as a subsection under section 17 (PATIENT COUNSELING INFORMATION). All FDA-approved patient labeling must appear at the end of the PI upon approval.

Comment:

Selected Requirements of Prescribing Information

Appendix A: Format of the Highlights and Table of Contents

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use [DRUG NAME] safely and effectively. See full prescribing information for [DRUG NAME].

[DRUG NAME (nonproprietary name) dosage form, route of administration, controlled substance symbol]
Initial U.S. Approval: [year]

WARNING: [SUBJECT OF WARNING]

See full prescribing information for complete boxed warning.

- [text]
- [text]

RECENT MAJOR CHANGES

[section (X.X)] [m/year]
[section (X.X)] [m/year]

INDICATIONS AND USAGE

[DRUG NAME] is a [name of pharmacologic class] indicated for:

- [text]
- [text]

DOSAGE AND ADMINISTRATION

- [text]
- [text]

DOSAGE FORMS AND STRENGTHS

- [text]

CONTRAINDICATIONS

- [text]
- [text]

WARNINGS AND PRECAUTIONS

- [text]
- [text]

ADVERSE REACTIONS

Most common adverse reactions (incidence > x%) are [text].

To report SUSPECTED ADVERSE REACTIONS, contact [name of manufacturer] at [phone #] or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

- [text]
- [text]

USE IN SPECIFIC POPULATIONS

- [text]
- [text]

See 17 for PATIENT COUNSELING INFORMATION [and FDA-approved patient labeling OR and Medication Guide].

Revised: [m/year]

FULL PRESCRIBING INFORMATION: CONTENTS*

WARNING: [SUBJECT OF WARNING]

1 INDICATIONS AND USAGE

- 1.1 [text]
- 1.2 [text]

2 DOSAGE AND ADMINISTRATION

- 2.1 [text]
- 2.2 [text]

3 DOSAGE FORMS AND STRENGTHS

4 CONTRAINDICATIONS

5 WARNINGS AND PRECAUTIONS

- 5.1 [text]
- 5.2 [text]

6 ADVERSE REACTIONS

- 6.1 [text]
- 6.2 [text]

7 DRUG INTERACTIONS

- 7.1 [text]
- 7.2 [text]

8 USE IN SPECIFIC POPULATIONS

- 8.1 Pregnancy
- 8.2 Labor and Delivery
- 8.3 Nursing Mothers
- 8.4 Pediatric Use
- 8.5 Geriatric Use

9 DRUG ABUSE AND DEPENDENCE

- 9.1 Controlled Substance
- 9.2 Abuse
- 9.3 Dependence

10 OVERDOSAGE

11 DESCRIPTION

12 CLINICAL PHARMACOLOGY

- 12.1 Mechanism of Action
- 12.2 Pharmacodynamics
- 12.3 Pharmacokinetics
- 12.4 Microbiology
- 12.5 Pharmacogenomics

13 NONCLINICAL TOXICOLOGY

- 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
- 13.2 Animal Toxicology and/or Pharmacology

14 CLINICAL STUDIES

- 14.1 [text]
- 14.2 [text]

15 REFERENCES

16 HOW SUPPLIED/STORAGE AND HANDLING

17 PATIENT COUNSELING INFORMATION

*Sections or subsections omitted from the full prescribing information are not listed.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

SAMMIE G BEAM
02/05/2014

ELIZABETH G THOMPSON
02/06/2014