

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

206352Orig1s000

021567Orig1s035

PHARMACOLOGY REVIEW(S)

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

PHARMACOLOGY/TOXICOLOGY NDA REVIEW AND EVALUATION

Application number: 206-352

Supporting document/s: NDA 21-567 S-35 (Pediatric supplement)

Applicant's letter date: 12/2/2013

CDER stamp date: 12/2/2013

Product: Atazanavir (Reyataz)

Indication: Treatment of HIV-1 Infection (Extend the indication to pediatric patients who are 10 to < 25 kg using a new (b) (4) Powder for Oral Use formulation in adults)

Applicant: Bristol Myers Squibb

Review Division: Division of Antiviral Products

Reviewer: Kuei-Meng Wu, Ph.D.

Supervisor/Team Leader: Hanan Ghantous, Ph.D., DABT

Division Director: Debra Birnkrant, M.D.

Project Manager: Sammie Beam, Pharm.D.

1 EXECUTIVE SUMMARY

1.1 INTRODUCTION

This is a pediatric supplement of atazanavir proposed to extend the drug's indication for treating HIV-1 infection in pediatric patients who are 10 to < 25 kg. All non-clinical pharmacology/toxicology information is cross-referenced to NDA 21-567 and there is no change in pharmacology/toxicology portion of the labeling. There is no pharmacology/toxicology concern and no nonclinical comments are needed for this pediatric supplemental NDA.

1.2 BRIEF DISCUSSION OF NONCLINICAL FINDINGS

Please refer to NDA 21567 for nonclinical findings.

1.3 RECOMMENDATIONS

1.3.1 Approvability

It is recommended that atazanavir be approved for the proposed indication.

1.3.2 Additional Non-Clinical Recommendations

No additional nonclinical studies are recommended. However there were CMC issues on impurities leached from [REDACTED]^{(b) (4)} for the bulk drug product. The impurities of concerns are [REDACTED]^{(b) (4)}. The risk assessment of these two leachables has been reviewed by Dr. Mark Powley, who concluded that both impurities do not post substantial risks to patients at levels described by the sponsor. More details of the analysis are provided in Dr. Powley's review at the end of this document (see APPENDIX).

1.3.3 Labeling

There is no change in pharmacology/toxicology portion of the drug's labeling.

APPENDIX

MEMORANDUM

Date: May 1, 2014

NDA#: 206,352/SD#4

Drug: Reyataz (Atazanavir) Dry Powder

Sponsor: Bristol-Myers Squibb (BMS)

To: Yichun Sun, Ph.D.
Chemist
CDER/OPS/ONQA/DNDQAI/BRIV

Cc: Kuei-Meng Wu, Ph.D.
Pharmacologist
CDER/OND/OAP/DAVP

Stephen Miller, Ph.D.
Chemist
CDER/OPS/ONDQA/DNDQAI

From: Mark W. Powley, Ph.D.
Pharmacologist
CDER/OND/OAP/DAVP

Concurrence: Hanan Ghantous, Ph.D., DABT
Supervisory Pharmacologist
CDER/OND/OAP/DAVP

Subject: Risk Assessment for Impurities in Atazanavir Dry Powder

Background

This review focuses on the safety of (b) (4).
(b) (4) These chemicals were detected as leachables from the bulk powder packaging used with atazanavir dry powder for oral use in pediatric patients. Based on bulk sample stability testing at 9 months, levels of these 2 impurities were below (b) (4)%. Table 1 summarizes the maximum potential daily exposures to (b) (4) in the final pouch dose form.

Table 1. Leachable exposures^a in atazanavir dry powder

	Clinical Doses	
	200 mg (10 to <15 kg)	250 mg (15 to < 25 kg)
(b) (4)	≤ (b) (4) mg/kg/day	≤ (b) (4) mg/kg/day
(b) (4)	≤ (b) (4) mg/kg/day	≤ (b) (4) mg/kg/day

^a based on (b) (4) in proposed clinical doses of atazanavir

Safety Evaluation

Both (b) (4) have been reported to be negative in the standard bacterial reverse mutation assay (b) (4) as well as chromosomal aberration assays in human lymphocytes (b) (4). General toxicology data for (b) (4) comes from dietary studies in (b) (4). The primary concern noted for both chemicals was (b) (4) following 81 weeks of administration. Although the incidence was not dose-dependent, this effect was observed in males and females at all doses tested. Based on the (b) (4) lesion, the LOAEL for (b) (4) were (b) (4) (b) (4) respectively. The effect was not detected in 13-week range-finding studies. An increased incidence of (b) (4) was also noted in the 81-week studies; however, the effect lacked dose-dependence and was limited to males. Therefore, the studies were considered insufficient to definitively characterize the carcinogenic potential of (b) (4) (b) (4). Note that it is not possible to rule out volatility of test article as a confounding factor in the dietary studies (b) (4).

The 81-week dietary studies served as the basis of formal risk assessments performed by the Agency for Toxic Substances and Disease Registry (b) (4) and the US Environmental Protection Agency (b) (4). The ATSDR derived chronic minimal risk levels (MRL; estimate of human exposure likely to be without appreciable risk of adverse non-cancer effects) of (b) (4) mg/kg/day for (b) (4) and (b) (4) mg/kg/day for (b) (4). The EPA calculated a non-cancer/oral reference dose (RfD; estimate of human exposure likely to without appreciable risk, including sensitive subgroups, of deleterious non-cancer effects during a lifetime) of (b) (4) mg/kg/day for (b) (4). It is noteworthy that the EPA assessment described (b) (4) as a more severe disease infants and children vs. adults. (b) (4)

Using the risk assessment principles described for residual solvents in ICH Q3C(R5), permissible daily exposures (PDE) for (b) (4) were determined to be (b) (4) mg/kg/day and (b) (4) mg/kg/day, respectively. Calculations are shown in the Appendix.

Conclusions

The primary concern with (b) (4) is (b) (4) toxicity, a potentially significant concern for certain subgroups of the intended atazanavir oral powder treatment population (e.g., children ≤ 5 years of age). Maximum levels of both leachables appear acceptable per the (b) (4) risk assessment. In contrast, levels of (b) (4) exceed the limits determined by the FDA and/or EPA risk assessments by (b) (4) fold. Based on the totality of information, (b) (4) do not pose a substantial risk at the levels described.

References

(b) (4)



Appendix

Permissible Daily Exposure = LOAEL/ (F1 x F2 x F3 x F4 x F5)

Based on occurrence of pulmonary alveolar proteinosis in the 81-week dietary studies in mice:

- F1 = 12 (extrapolation from mice to humans)
- F2 = 10 (account for variability between individuals)
- F3 = 1 (study ≥ 1 year in mice)
- F4 = 10 (severe toxicity)
- F5 = 10 (LOAEL used instead of NOAEL)

$$\begin{aligned} \text{PDE} &= \frac{(b) (4) \text{ mg/kg/day}}{(b) (4)} / (12 \times 10 \times 1 \times 10 \times 10) \\ &= (b) (4) \text{ mg/kg/day} \end{aligned}$$

$$\begin{aligned} \text{PDE} &= \frac{(b) (4) \text{ mg/kg/day}}{(b) (4)} / (12 \times 10 \times 1 \times 10 \times 10) \\ &= (b) (4) \text{ mg/kg/day} \end{aligned}$$

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/s/

KUEI MENG WU
05/08/2014

HANAN N GHANTOUS
05/08/2014

PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR NDA/BLA or Supplement

NDA/BLA Number: 206352 Applicant: Bristol Myers Squibb Stamp Date: 12/2/2013

Drug Name: Reyataz NDA/BLA Type: NDA21567 S-35 (Pediatric supplement)

On **initial** overview of the NDA/BLA application for filing:

	Content Parameter	Yes	No	Comment
1	Is the pharmacology/toxicology section organized in accord with current regulations and guidelines for format and content in a manner to allow substantive review to begin?	x		Pharmacology/toxicology section cross-referenced to NDA #21-567, no additional pharmacology/toxicology information included.
2	Is the pharmacology/toxicology section indexed and paginated in a manner allowing substantive review to begin?	x		See above.
3	Is the pharmacology/toxicology section legible so that substantive review can begin?	x		See above.
4	Are all required (*) and requested IND studies (in accord with 505 b1 and b2 including referenced literature) completed and submitted (carcinogenicity, mutagenicity, teratogenicity, effects on fertility, juvenile studies, acute and repeat dose adult animal studies, animal ADME studies, safety pharmacology, etc)?	x		See above.
5	If the formulation to be marketed is different from the formulation used in the toxicology studies, have studies by the appropriate route been conducted with appropriate formulations? (For other than the oral route, some studies may be by routes different from the clinical route intentionally and by desire of the FDA).	x		See above.
6	Does the route of administration used in the animal studies appear to be the same as the intended human exposure route? If not, has the applicant <u>submitted</u> a rationale to justify the alternative route?	x		See above.
7	Has the applicant <u>submitted</u> a statement(s) that all of the pivotal pharm/tox studies have been performed in accordance with the GLP regulations (21 CFR 58) <u>or</u> an explanation for any significant deviations?	x		Studies cross-referenced to NDA #21-567
8	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?	x		Studies cross-referenced to NDA #21-567

File name: 5_Pharmacology_Toxicology Filing Checklist for NDA_BLA or Supplement
010908

**PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR
NDA/BLA or Supplement**

	Content Parameter	Yes	No	Comment
9	Are the proposed labeling sections relative to pharmacology/toxicology appropriate (including human dose multiples expressed in either mg/m2 or comparative serum/plasma levels) and in accordance with 201.57?	x		No changes proposed in the pharmacology/toxicology section of the labeling.
10	Have any impurity – etc. issues been addressed? (New toxicity studies may not be needed.)	x		See above.
11	Has the applicant addressed any abuse potential issues in the submission?	x		Cross-referenced to NDA #21-567, no apparent abuse potential.
12	If this NDA/BLA is to support a Rx to OTC switch, have all relevant studies been submitted?		x	

IS THE PHARMACOLOGY/TOXICOLOGY SECTION OF THE APPLICATION FILEABLE? ____ Yes ____

If the NDA/BLA is not fileable from the pharmacology/toxicology perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

Reviewing Pharmacologist Date

Team Leader/Supervisor Date

File name: 5_Pharmacology_Toxicology Filing Checklist for NDA_BLA or Supplement
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/s/

KUEI MENG WU
01/15/2014

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01/15/2014