CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

21-567/S025

Trade Name: REYATAZ® Capsules

Generic Name: Atazanavir Sulphate

Sponsor: Bristol-Myers Squibb

Approval Date: 02/04/2011

Indication: REYATAZ is a protease inhibitor indicated for use in combination with other antiretroviral agents for the treatment of HIV-1 infection.

CENTER FOR DRUG EVALUATION AND RESEARCH

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

NDA 21-567S-025

SUPPLEMENT APPROVAL

Bristol Myers Squibb Company
Attention: Hwei-Gene Wang, PhD
Associate Director, US Liaison
5 Research Parkway
Wallingford, CT 06492

Dear Dr. Wang:

Please refer to your Supplemental New Drug Application (sNDA) dated and received August 6, 2010, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Reyataz® atazanavir sulfate 100 mg, 150 mg, 200 mg and 300 mg capsules.

We acknowledge receipt of your amendments dated September 28, 2010, October 20, 2010, October 26, 2010, October 27, 2010, November 4, 2010, November 11, 2010, December 20, 2010, December 22, 2010, January 6, 2011, January 11, 2011, January 21, 2011, January 25, 2011, January 26, 2011, February 1, 2011 and February 3, 2011.

This Prior Approval supplemental new drug application was submitted to provide dosing recommendations for treatment of HIV-1 infection during pregnancy based on data from Study AI424-182, a study of atazanavir/ritonavir in combination with zidovudine/lamivudine in HIV-infected pregnant women.

We have completed our review of this supplemental application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed, agreed-upon labeling text.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit, using the FDA automated drug registration and listing system (eLIST), the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format, as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm, that is identical to the enclosed labeling (text for the package insert and text for the patient package insert) and include the labeling changes proposed in any pending "Changes Being Effected" (CBE) supplements and any annual reportable changes not included in the enclosed labeling. Information on submitting SPL files using eLIST may be found in the guidance for industry titled "SPL Standard for Content of Labeling Technical Qs and As" at http://www.fda.gov/downloads/DrugsGuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf.

The SPL will be accessible from publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications for this NDA, including CBE supplements for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 314.50(l)(1)(i)] in MS Word format that includes the changes approved in this supplemental application.

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit the following, in triplicate, (1) a cover letter requesting advisory comments, (2) the proposed materials in draft or mock-up form with annotated references, and (3) the package insert(s) to:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications
5901-B Ammendale Road
Beltsville, MD 20705-1266

You must submit final promotional materials and package insert(s), accompanied by a Form FDA 2253, at the time of initial dissemination or publication [21 CFR 314.81(b)(3)(i)]. Form FDA 2253 is available at http://www.fda.gov/opacom/morechoices/fdaforms/cder.html; instructions are provided on page 2 of the form. For more information about submission of promotional materials to the Division of Drug Marketing, Advertising, and Communications (DDMAC), see http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm.

LETTERS TO HEALTH CARE PROFESSIONALS

If you decide to issue a letter communicating important safety-related information about this drug product (i.e., a "Dear Health Care Professional" letter), we request that you submit, at least 24 hours prior to issuing the letter, an electronic copy of the letter to this NDA to the following address:

MedWatch Program
Office of Special Health Issues
Food and Drug Administration
10903 New Hampshire Ave
Building 32, Mail Stop 5353
Silver Spring, MD 20993

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, please contact Venessa M Perry, MPH, Regulatory Project Manager, at 301.796.4891.

Sincerely,

{See appended electronic signature page}

Debra Birnkrant, M.D.
Director
Division of Antiviral Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

ENCLOSURE(S):
Content of Labeling

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

/s/

VENESSA M PERRY
02/04/2011

JEFFREY S MURRAY
02/04/2011

CENTER FOR DRUG EVALUATION AND RESEARCH

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LABELING

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use REYATAZ safely and effectively. See full prescribing information for REYATAZ.

REYATAZ® (atazanavir sulfate) Capsules
Initial U.S. Approval: 2003

----------RECENT MAJOR CHANGES----------
Contraindications (4) 04/2010
Dosage and Administration (2.3) 02/2011

----------INDICATIONS AND USAGE----------
REYATAZ is a protease inhibitor indicated for use in combination with other antiretroviral agents for the treatment of HIV-1 infection. (1)

----------DOSAGE AND ADMINISTRATION----------
- *Treatment-naive patients* REYATAZ 300 mg with ritonavir 100 mg once daily with food or REYATAZ 400 mg once daily with food. When coadministered with tenofovir, the recommended dose is REYATAZ 300 mg with ritonavir 100 mg. (2.1)
- *Treatment-experienced patients* REYATAZ 300 mg with ritonavir 100 mg once daily with food. (2.1)
- *Pediatric patients (6 to less than 18 years of age)* Dosage is based on body weight not to exceed the adult dose. (2.2)
- *Pregnancy* REYATAZ 300 mg with ritonavir 100 mg once daily with food, with dosing modifications for some concomitant medications. (2.3)
- *Concomitant therapy* Dosing modifications may be required. (2.1, 7)
- *Renal impairment* Dosing modifications may be required. (2.4)
- *Hepatic impairment* Dosing modifications may be required. (2.5)

----------DOSAGE FORMS AND STRENGTHS----------
- Capsules: 100 mg, 150 mg, 200 mg, 300 mg. (3, 16)

----------CONTRAINDICATIONS----------
- REYATAZ is contraindicated in patients with previously demonstrated hypersensitivity (eg, Stevens-Johnson syndrome, erythema multiforme, or toxic skin eruptions) to any of the components of this product. (4)
- Coadministration with alfuzosin, triazolam, orally administered midazolam, ergot derivatives, rifampin, irinotecan, lovastatin, simvastatin, indinavir, cisapride, pimozide, St. John's wort, and sildenafil when dosed as REVATIO®. (4)

----------WARNINGS AND PRECAUTIONS----------
- *Cardiac conduction abnormalities* PR interval prolongation may occur in some patients. Use with caution in patients with preexisting conduction system disease or when administered with other drugs that may prolong the PR interval. (5.2, 6.4, 7.3, 12.2, 17.3)
- *Rash* Discontinue if severe rash develops. (5.3, 6.4, 17.4)
- *Hyperbilirubinemia* Most patients experience asymptomatic increases in indirect bilirubin, which is reversible upon discontinuation. Do not dose reduce. If a concomitant transaminase increase occurs, evaluate for alternative etiologies. (5.4, 6.2)
- *Hepatotoxicity* Patients with hepatitis B or C are at risk of increased transaminases or hepatic decompensation. Monitor liver function tests prior to therapy and during treatment. (2.5, 5.5, 6.3, 6.4, 8.8)
- *Nephrolithiasis* has been reported. Consider temporary interruption or discontinuation. (5.6, 6.4)
- Patients receiving REYATAZ may develop new onset or exacerbations of diabetes mellitus/hyperglycemia (5.7, 6.4), immune reconstitution syndrome (5.8), and redistribution/accumulation of body fat. (5.9)
- *Hemophilia* Spontaneous bleeding may occur and additional factor VIII may be required. (5.10)

----------ADVERSE REACTIONS----------
Most common adverse reactions (≥2%) are nausea, jaundice/scleral icterus, rash, headache, abdominal pain, vomiting, insomnia, peripheral neurologic symptoms, dizziness, myalgia, diarrhea, depression, and fever. (6.1, 6.2)

To report SUSPECTED ADVERSE REACTIONS, contact Bristol-Myers Squibb at 1-800-721-5072 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch

----------DRUG INTERACTIONS----------
Coadministration of REYATAZ can alter the concentration of other drugs and other drugs may alter the concentration of atazanavir. The potential drug-drug interactions must be considered prior to and during therapy. (4, 5.1, 7, 12.3)

----------USE IN SPECIFIC POPULATIONS----------
- *Pregnancy* Use only if the potential benefit justifies the potential risk. Physicians are encouraged to register patients in the Antiretroviral Pregnancy Registry. (8 1)
- *Nursing mothers* should be instructed not to breast-feed due to the potential for postnatal HIV transmission. (8.3)
- *Hepatitis B or C co-infection* Monitor liver enzymes. (5.5, 6.3)
- *Renal impairment* Do not use in treatment-experienced patients with end stage renal disease managed with hemodialysis. (2.4, 8.7)
- *Hepatic impairment* Do not use REYATAZ in patients with severe hepatic impairment. REYATAZ/ritonavir is not recommended. (2.5, 8.8)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling

Revised: 02/2011

FULL PRESCRIBING INFORMATION: CONTENTS*

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

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

REYATAZ® (atazanavir sulfate) is indicated in combination with other antiretroviral agents for the treatment of HIV-1 infection. This indication is based on analyses of plasma HIV-1 RNA levels and CD4+ cell counts from controlled studies of 96 weeks duration in antiretroviral-naive and 48 weeks duration in antiretroviral-treatment-experienced adult and pediatric patients at least 6 years of age.

The following points should be considered when initiating therapy with REYATAZ:

- In Study AI424-045, REYATAZ/ritonavir and lopinavir/ritonavir were similar for the primary efficacy outcome measure of time-averaged difference in change from baseline in HIV RNA level. This study was not large enough to reach a definitive conclusion that REYATAZ/ritonavir and lopinavir/ritonavir are equivalent on the secondary efficacy outcome measure of proportions below the HIV RNA lower limit of detection [see *Clinical Studies (14.2)*].
- The number of baseline primary protease inhibitor mutations affects the virologic response to REYATAZ/ritonavir [see *Clinical Pharmacology (12.4)*].

2 DOSAGE AND ADMINISTRATION

General Dosing Recommendations:

- REYATAZ Capsules must be taken with food.
- The recommended oral dosage of REYATAZ depends on the treatment history of the patient and the use of other coadministered drugs. When coadministered with H_2-receptor antagonists or proton-pump inhibitors, dose separation may be required [see *Dosage and Administration (2.1)*].
- When coadministered with didanosine buffered or enteric-coated formulations, REYATAZ should be given (with food) 2 hours before or 1 hour after didanosine.
- REYATAZ without ritonavir is not recommended for treatment-experienced patients with prior virologic failure [see *Clinical Studies (14)*].
- Efficacy and safety of REYATAZ with ritonavir in doses greater than 100 mg once daily have not been established. The use of higher ritonavir doses might alter the safety profile

of atazanavir (cardiac effects, hyperbilirubinemia) and, therefore, is not recommended. Prescribers should consult the complete prescribing information for NORVIR® (ritonavir) when using this agent.

2.1 Recommended Adult Dosage

Table 1 summarizes the recommended REYATAZ dosing regimen in adults. All REYATAZ dosing regimens are to be administered as a single dose with food.

Table 1: REYATAZ Dosing Regimens

Treatment-Naive Patients	**REYATAZ 300 mg with ritonavir 100 mg once daily**
If unable to tolerate ritonavir	**REYATAZ 400 mg once daily**
When combined with any of the following: Tenofovir H_2-receptor antagonist Proton-pump inhibitor • The H_2-receptor antagonist dose should not exceed a dose comparable to famotidine 40 mg twice daily. Administer REYATAZ and ritonavir simultaneously with, and/or at least 10 hours after the H_2-receptor antagonist. • If unable to tolerate ritonavir, administer REYATAZ 400 mg once daily at least 2 hours before and at least 10 hours after the H_2-receptor antagonist. No single dose of the H_2-receptor antagonist should exceed a dose comparable to famotidine 20 mg and the total daily dose should not exceed a dose comparable to famotidine 40 mg. • The proton-pump inhibitor dose should not exceed a dose comparable to omeprazole 20 mg daily and must be taken approximately 12 hours prior to REYATAZ and ritonavir.	**REYATAZ 300 mg with ritonavir 100 mg once daily**
When combined with efavirenz • Efavirenz should be administered on an empty stomach, preferably at bedtime.	**REYATAZ 400 mg with ritonavir 100 mg once daily**
Treatment-Experienced Patients	**REYATAZ 300 mg with ritonavir 100 mg once daily**
Do not coadminister with proton-pump inhibitors or efavirenz in treatment-experienced patients.	
When given with an H_2-receptor antagonist • The H_2-receptor antagonist dose should not exceed a dose comparable to famotidine 20 mg twice daily. Administer REYATAZ and ritonavir simultaneously with, and/or at least 10 hours after the H_2-receptor antagonist.	**REYATAZ 300 mg with ritonavir 100 mg once daily**
When given with both tenofovir *and* an H_2-receptor antagonist • The H_2-receptor antagonist dose should not exceed a dose comparable to famotidine 20 mg twice daily. Administer REYATAZ and ritonavir simultaneously with, and/or at least 10 hours after the H_2-receptor antagonist.	**REYATAZ 400 mg with ritonavir 100 mg once daily**

[For these drugs and other antiretroviral agents for which dosing modification may be appropriate, see *Drug Interactions (7)*.]

2.2 Recommended Pediatric Dosage

The recommended dosage of REYATAZ for pediatric patients (6 to less than 18 years of age) is based on body weight and should not exceed the recommended adult dosage. REYATAZ Capsules must be taken with food. The data are insufficient to recommend dosing of REYATAZ for any of the following: (1) patients less than 6 years of age, (2) without ritonavir in patients less than 13 years of age, and (3) treatment-experienced pediatric patients with body weight less than 25 kg.

Treatment-Naive Pediatric Patients

The recommended dosage of REYATAZ with ritonavir in treatment-naive patients at least 6 years of age is shown in Table 2.

For treatment-naive patients at least 13 years of age and at least 39 kg, who are unable to tolerate ritonavir, the recommended dose is REYATAZ 400 mg (without ritonavir) once daily with food.

Table 2: Dosage for Treatment-Naive Pediatric Patients (6 to less than 18 years of age) for REYATAZ Capsules with ritonavir

Body Weight (kg)	Body Weight (lbs)	REYATAZ dose[a,b] (mg)	ritonavir dose[b] (mg)
15 to less than 25	33 to less than 55	150	80[c]
25 to less than 32	55 to less than 70	200	100[d]
32 to less than 39	70 to less than 86	250	100[d]
at least 39	at least 86	300	100[d]

[a] The recommended dosage of REYATAZ can be achieved using a combination of commercially available capsule strengths.

[b] The dosage of REYATAZ and ritonavir was calculated as follows:

- 15 kg to less than 20 kg: REYATAZ 8.5 mg/kg with ritonavir 4 mg/kg once daily with food.
- at least 20 kg: REYATAZ 7 mg/kg with ritonavir 4 mg/kg once daily with food not to exceed REYATAZ 300 mg and ritonavir 100 mg.

[c] Ritonavir liquid.

[d] Ritonavir capsule or liquid.

Treatment-Experienced Pediatric Patients

The recommended dosage of REYATAZ with ritonavir in treatment-experienced patients at least 6 years of age is shown in Table 3.

Table 3: Dosage for Treatment-Experienced Pediatric Patients (6 to less than 18 years of age) for REYATAZ Capsules with ritonavir

Body Weight (kg)	Body Weight (lbs)	REYATAZ dose[a,b] (mg)	ritonavir dose[b] (mg)
25 to less than 32	55 to less than 70	200	100[c]
32 to less than 39	70 to less than 86	250	100[c]
at least 39	at least 86	300	100[c]

[a] The recommended dosage of REYATAZ can be achieved using a combination of commercially available capsule strengths.

[b] The dosage was calculated as REYATAZ 7 mg/kg with ritonavir 4 mg/kg once daily with food not to exceed REYATAZ 300 mg and ritonavir 100 mg.

[c] Ritonavir capsule or liquid.

2.3 Pregnancy

Dosing During Pregnancy and the Postpartum Period:

- REYATAZ should not be administered without ritonavir.
- REYATAZ should only be administered to pregnant women with HIV-1 strains susceptible to atazanavir.
- For pregnant patients, no dose adjustment is required for REYATAZ with the following exceptions:
  - For treatment-experienced pregnant women during the second or third trimester, when REYATAZ is coadministered with either an H_2-receptor antagonist **or** tenofovir, REYATAZ 400 mg with ritonavir 100 mg once daily is recommended. There are insufficient data to recommend a REYATAZ dose for use with both an H_2-receptor antagonist *and* tenofovir in treatment-experienced pregnant women.
- No dose adjustment is required for postpartum patients. However, patients should be closely monitored for adverse events because atazanavir exposures could be higher during the first 2

months after delivery. [See *Use in Specific Populations (8.1)* and *Clinical Pharmacology (12.3)*.]

2.4 Renal Impairment

For patients with renal impairment, including those with severe renal impairment who are not managed with hemodialysis, no dose adjustment is required for REYATAZ. Treatment-naive patients with end stage renal disease managed with hemodialysis should receive REYATAZ 300 mg with ritonavir 100 mg. REYATAZ should not be administered to HIV-treatment-experienced patients with end stage renal disease managed with hemodialysis. [See *Use in Specific Populations (8.7)*.]

2.5 Hepatic Impairment

REYATAZ should be used with caution in patients with mild-to-moderate hepatic impairment. For patients with moderate hepatic impairment (Child-Pugh Class B) who have not experienced prior virologic failure, a dose reduction to 300 mg once daily should be considered. REYATAZ should not be used in patients with severe hepatic impairment (Child-Pugh Class C). REYATAZ/ritonavir has not been studied in subjects with hepatic impairment and is not recommended. [See *Warnings and Precautions (5.5)* and *Use in Specific Populations (8.8)*.]

3 DOSAGE FORMS AND STRENGTHS

- 100 mg capsule with blue cap and white body, printed with white ink “BMS 100 mg” on the cap and with blue ink “3623” on the body.
- 150 mg capsule with blue cap and powder blue body, printed with white ink “BMS 150 mg” on the cap and with blue ink “3624” on the body.
- 200 mg capsule with blue cap and blue body, printed with white ink “BMS 200 mg” on the cap and with white ink “3631” on the body.
- 300 mg capsule with red cap and blue body, printed with white ink “BMS 300 mg” on the cap and with white ink “3622” on the body.

4 CONTRAINDICATIONS

REYATAZ (atazanavir sulfate) is contraindicated:

- in patients with previously demonstrated clinically significant hypersensitivity (eg, Stevens-Johnson syndrome, erythema multiforme, or toxic skin eruptions) to any of the components of this product.

- when coadministered with drugs that are highly dependent on CYP3A or UGT1A1 for clearance, and for which elevated plasma concentrations are associated with serious and/or life-threatening events. These and other contraindicated drugs are listed in Table 4.

Table 4: Drugs That Are Contraindicated with REYATAZ (atazanavir) (Information in the table applies to REYATAZ with or without ritonavir, unless otherwise indicated)

Drug Class	Drugs within class that are contraindicated with REYATAZ	Clinical Comment
Alpha 1-Adrenoreceptor Antagonist	Alfuzosin	Potential for increased alfuzosin concentrations, which can result in hypotension.
Antimycobacterials	Rifampin	Rifampin substantially decreases plasma concentrations of atazanavir, which may result in loss of therapeutic effect and development of resistance.
Antineoplastics	Irinotecan	Atazanavir inhibits UGT1A1 and may interfere with the metabolism of irinotecan, resulting in increased irinotecan toxicities.
Benzodiazepines	Triazolam, orally administered midazolam[a]	Triazolam and orally administered midazolam are extensively metabolized by CYP3A4. Coadministration of triazolam or orally administered midazolam with REYATAZ may cause large increases in the concentration of these benzodiazepines. Potential for serious and/or life-threatening events such as prolonged or increased sedation or respiratory depression.
Ergot Derivatives	Dihydroergotamine, ergotamine, ergonovine, methylergonovine	Potential for serious and/or life-threatening events such as acute ergot toxicity characterized by peripheral vasospasm and ischemia of the extremities and other tissues.
GI Motility Agent	Cisapride	Potential for serious and/or life-threatening reactions such as cardiac arrhythmias.
Herbal Products	St. John's wort (*Hypericum perforatum*)	Patients taking REYATAZ should not use products containing St. John's wort because coadministration may be expected to reduce plasma concentrations of atazanavir. This may result in loss of therapeutic effect and development of resistance.
HMG-CoA Reductase Inhibitors	Lovastatin, simvastatin	Potential for serious reactions such as myopathy including rhabdomyolysis.
Neuroleptic	Pimozide	Potential for serious and/or life-threatening reactions such as cardiac arrhythmias.

Table 4: Drugs That Are Contraindicated with REYATAZ (atazanavir) (Information in the table applies to REYATAZ with or without ritonavir, unless otherwise indicated)

Drug Class	Drugs within class that are contraindicated with REYATAZ	Clinical Comment
PDE5 Inhibitor	Sildenafil[b] when dosed as REVATIO® for the treatment of pulmonary arterial hypertension	A safe and effective dose in combination with REYATAZ has not been established for sildenafil (REVATIO®) when used for the treatment of pulmonary hypertension. There is increased potential for sildenafil-associated adverse events (which include visual disturbances, hypotension, priapism, and syncope).
Protease Inhibitors	Indinavir	Both REYATAZ and indinavir are associated with indirect (unconjugated) hyperbilirubinemia.

[a] See *Drug Interactions, Table 14 (7)* for parenterally administered midazolam.

[b] See *Drug Interactions, Table 14 (7)* for sildenafil when dosed as VIAGRA® for erectile dysfunction.

5 WARNINGS AND PRECAUTIONS

5.1 Drug Interactions

See Table 4 for a listing of drugs that are contraindicated for use with REYATAZ due to potentially life-threatening adverse events, significant drug interactions, or loss of virologic activity. [See *Contraindications (4).*] Please refer to Table 14 for established and other potentially significant drug interactions [see *Drug Interactions (7.3)*].

5.2 Cardiac Conduction Abnormalities

Atazanavir has been shown to prolong the PR interval of the electrocardiogram in some patients. In healthy volunteers and in patients, abnormalities in atrioventricular (AV) conduction were asymptomatic and generally limited to first-degree AV block. There have been rare reports of second-degree AV block and other conduction abnormalities [see *Adverse Reactions (6.4)* and *Overdosage (10)*]. In clinical trials that included electrocardiograms, asymptomatic first-degree AV block was observed in 5.9% of atazanavir-treated patients (n=920), 5.2% of lopinavir/ritonavir-treated patients (n=252), 10.4% of nelfinavir-treated patients (n=48), and 3.0% of efavirenz-treated patients (n=329). In Study AI424-045, asymptomatic first-degree AV block was observed in 5% (6/118) of atazanavir/ritonavir-treated patients and 5% (6/116) of lopinavir/ritonavir-treated patients who had on-study electrocardiogram measurements. Because of limited clinical experience in patients with preexisting conduction system disease (eg, marked

first-degree AV block or second- or third-degree AV block), atazanavir should be used with caution in these patients. [See *Clinical Pharmacology (12.2)*.]

Atazanavir in combination with diltiazem increased diltiazem plasma concentration by 2-fold with an additive effect on the PR interval. When used in combination with atazanavir, a dose reduction of diltiazem by one-half should be considered and ECG monitoring is recommended. In a pharmacokinetic study between atazanavir 400 mg once daily and atenolol 50 mg once daily, no clinically significant additive effect of atazanavir and atenolol on the PR interval was observed. Dose adjustment of atenolol is not required when used in combination with atazanavir. [See *Drug Interactions (7)* and *Clinical Pharmacology (12.2)*.] Pharmacokinetic studies between atazanavir and other drugs that prolong the PR interval including beta blockers [other than atenolol, see *Drug Interactions (7)*], verapamil, and digoxin have not been performed. An additive effect of atazanavir and these drugs cannot be excluded; therefore, caution should be exercised when atazanavir is given concurrently with these drugs, especially those that are metabolized by CYP3A (eg, verapamil).

5.3 Rash

In controlled clinical trials, rash (all grades, regardless of causality) occurred in approximately 20% of patients treated with REYATAZ. The median time to onset of rash in clinical studies was 7.3 weeks and the median duration of rash was 1.4 weeks. Rashes were generally mild-to-moderate maculopapular skin eruptions. Treatment-emergent adverse reactions of moderate or severe rash (occurring at a rate of ≥2%) are presented for the individual clinical studies [see *Adverse Reactions (6.1)*]. Dosing with REYATAZ was often continued without interruption in patients who developed rash. The discontinuation rate for rash in clinical trials was <1%. REYATAZ should be discontinued if severe rash develops. Cases of Stevens-Johnson syndrome, erythema multiforme, and toxic skin eruptions have been reported in patients receiving REYATAZ. [See *Contraindications (4)*.]

5.4 Hyperbilirubinemia

Most patients taking REYATAZ experience asymptomatic elevations in indirect (unconjugated) bilirubin related to inhibition of UDP-glucuronosyl transferase (UGT). This hyperbilirubinemia is reversible upon discontinuation of REYATAZ. Hepatic transaminase elevations that occur with hyperbilirubinemia should be evaluated for alternative etiologies. No long-term safety data are available for patients experiencing persistent elevations in total bilirubin >5 times ULN. Alternative antiretroviral therapy to REYATAZ may be considered if jaundice or scleral icterus associated with bilirubin elevations presents cosmetic concerns for patients. Dose reduction of

atazanavir is not recommended since long-term efficacy of reduced doses has not been established. [See *Adverse Reactions (6.1, 6.2)*.]

5.5 Hepatotoxicity

Caution should be exercised when administering REYATAZ to patients with hepatic impairment because atazanavir concentrations may be increased. [See *Dosage and Administration (2.5)*.] Patients with underlying hepatitis B or C viral infections or marked elevations in transaminases before treatment may be at increased risk for developing further transaminase elevations or hepatic decompensation. In these patients, appropriate laboratory testing should be conducted prior to initiating therapy with REYATAZ and these patients should be monitored during treatment. [See *Adverse Reactions (6.3)* and *Use in Specific Populations (8.8)*.]

5.6 Nephrolithiasis

Cases of nephrolithiasis were reported during postmarketing surveillance in HIV-infected patients receiving REYATAZ therapy. Because these events were reported voluntarily during clinical practice, estimates of frequency cannot be made. If signs or symptoms of nephrolithiasis occur, temporary interruption or discontinuation of therapy may be considered. [See *Adverse Reactions (6.4)*.]

5.7 Diabetes Mellitus/Hyperglycemia

New-onset diabetes mellitus, exacerbation of preexisting diabetes mellitus, and hyperglycemia have been reported during postmarketing surveillance in HIV-infected patients receiving protease inhibitor therapy. Some patients required either initiation or dose adjustments of insulin or oral hypoglycemic agents for treatment of these events. In some cases, diabetic ketoacidosis has occurred. In those patients who discontinued protease inhibitor therapy, hyperglycemia persisted in some cases. Because these events have been reported voluntarily during clinical practice, estimates of frequency cannot be made and a causal relationship between protease inhibitor therapy and these events has not been established. [See *Adverse Reactions (6.4)*.]

5.8 Immune Reconstitution Syndrome

Immune reconstitution syndrome has been reported in patients treated with combination antiretroviral therapy, including REYATAZ. During the initial phase of combination antiretroviral treatment, patients whose immune system responds may develop an inflammatory response to indolent or residual opportunistic infections (such as *Mycobacterium avium*

infection, cytomegalovirus, *Pneumocystis jiroveci* pneumonia, or tuberculosis), which may necessitate further evaluation and treatment.

5.9 Fat Redistribution

Redistribution/accumulation of body fat including central obesity, dorsocervical fat enlargement (buffalo hump), peripheral wasting, facial wasting, breast enlargement, and "cushingoid appearance" have been observed in patients receiving antiretroviral therapy. The mechanism and long-term consequences of these events are currently unknown. A causal relationship has not been established.

5.10 Hemophilia

There have been reports of increased bleeding, including spontaneous skin hematomas and hemarthrosis, in patients with hemophilia type A and B treated with protease inhibitors. In some patients additional factor VIII was given. In more than half of the reported cases, treatment with protease inhibitors was continued or reintroduced. A causal relationship between protease inhibitor therapy and these events has not been established.

5.11 Resistance/Cross-Resistance

Various degrees of cross-resistance among protease inhibitors have been observed. Resistance to atazanavir may not preclude the subsequent use of other protease inhibitors. [See *Clinical Pharmacology (12.4)*.]

6 ADVERSE REACTIONS

The following adverse reactions are discussed in greater detail in other sections of the labeling:

- cardiac conduction abnormalities [see *Warnings and Precautions (5.2)*]
- rash [see *Warnings and Precautions (5.3)*]
- hyperbilirubinemia [see *Warnings and Precautions (5.4)*]
- nephrolithiasis [see *Warnings and Precautions (5.6)*]

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.

6.1 Clinical Trial Experience in Adults

Treatment-Emergent Adverse Reactions in Treatment-Naive Patients

The safety profile of REYATAZ in treatment-naive adults is based on 1625 HIV-1 infected patients in clinical trials. 536 patients received REYATAZ 300 mg with ritonavir 100 mg and 1089 patients received REYATAZ 400 mg or higher (without ritonavir).

The most common adverse reactions are nausea, jaundice/scleral icterus, and rash.

Selected clinical adverse reactions of moderate or severe intensity reported in ≥2% of treatment-naive patients receiving combination therapy including REYATAZ 300 mg with ritonavir 100 mg and REYATAZ 400 mg (without ritonavir) are presented in Tables 5 and 6, respectively.

Table 5: Selected Treatment-Emergent Adverse Reactions[a] of Moderate or Severe Intensity Reported in ≥2% of Adult Treatment-Naive Patients,[b] Study AI424-138

	96 weeks[c] REYATAZ 300 mg with ritonavir 100 mg (once daily) and tenofovir with emtricitabine[d] (n=441)	96 weeks[c] lopinavir 400 mg with ritonavir 100 mg (twice daily) and tenofovir with emtricitabine[d] (n=437)
Digestive System		
Nausea	4%	8%
Jaundice/scleral icterus	5%	*
Diarrhea	2%	12%
Skin and Appendages		
Rash	3%	2%

* None reported in this treatment arm.

[a] Includes events of possible, probable, certain, or unknown relationship to treatment regimen.

[b] Based on the regimen containing REYATAZ.

[c] Median time on therapy.

[d] As a fixed-dose combination: 300 mg tenofovir, 200 mg emtricitabine once daily.

Table 6: Selected Treatment-Emergent Adverse Reactions[a] of Moderate or Severe Intensity Reported in ≥2% of Adult Treatment-Naive Patients,[b] Studies AI424-034, AI424-007, and AI424-008

	Study AI424-034		Studies AI424-007, -008	
	64 weeks[c] REYATAZ 400 mg once daily + lamivudine + zidovudine[e] (n=404)	64 weeks[c] efavirenz 600 mg once daily + lamivudine + zidovudine[e] (n=401)	120 weeks[c,d] REYATAZ 400 mg once daily + stavudine + lamivudine or didanosine (n=279)	73 weeks[c,d] nelfinavir 750 mg TID or 1250 mg BID + stavudine + lamivudine or didanosine (n=191)
Body as a Whole				
Headache	6%	6%	1%	2%
Digestive System				
Nausea	14%	12%	6%	4%
Jaundice/scleral icterus	7%	*	7%	*
Vomiting	4%	7%	3%	3%
Abdominal pain	4%	4%	4%	2%
Diarrhea	1%	2%	3%	16%
Nervous System				
Insomnia	3%	3%	<1%	*
Dizziness	2%	7%	<1%	*
Peripheral neurologic symptoms	<1%	1%	4%	3%
Skin and Appendages				
Rash	7%	10%	5%	1%

* None reported in this treatment arm.

[a] Includes events of possible, probable, certain, or unknown relationship to treatment regimen.

[b] Based on regimens containing REYATAZ.

[c] Median time on therapy.

[d] Includes long-term follow-up.

[e] As a fixed-dose combination: 150 mg lamivudine, 300 mg zidovudine twice daily.

Treatment-Emergent Adverse Reactions in Treatment-Experienced Patients

The safety profile of REYATAZ in treatment-experienced adults is based on 119 HIV-1 infected patients in clinical trials.

The most common adverse reactions are jaundice/scleral icterus and myalgia.

Selected clinical adverse reactions of moderate or severe intensity reported in ≥2% of treatment-experienced patients receiving REYATAZ/ritonavir are presented in Table 7.

Table 7: Selected Treatment-Emergent Adverse Reactions[a] of Moderate or Severe Intensity Reported in ≥2% of Adult Treatment-Experienced Patients,[b] Study AI424-045

	48 weeks[c] REYATAZ/ritonavir 300/100 mg once daily + tenofovir + NRTI (n=119)	48 weeks[c] lopinavir/ritonavir 400/100 mg twice daily[d] + tenofovir + NRTI (n=118)
Body as a Whole		
Fever	2%	*
Digestive System		
Jaundice/scleral icterus	9%	*
Diarrhea	3%	11%
Nausea	3%	2%
Nervous System		
Depression	2%	<1%
Musculoskeletal System		
Myalgia	4%	*

* None reported in this treatment arm.

[a] Includes events of possible, probable, certain, or unknown relationship to treatment regimen.

[b] Based on the regimen containing REYATAZ.

[c] Median time on therapy.

[d] As a fixed-dose combination.

Laboratory Abnormalities in Treatment-Naive Patients

The percentages of adult treatment-naive patients treated with combination therapy including REYATAZ (atazanavir sulfate) 300 mg with ritonavir 100 mg and REYATAZ 400 mg (without ritonavir) with Grade 3–4 laboratory abnormalities are presented in Tables 8 and 9, respectively.

Table 8: Grade 3–4 Laboratory Abnormalities Reported in ≥2% of Adult Treatment-Naive Patients,[a] Study AI424-138

Variable	Limit[c]	96 weeks[b] REYATAZ 300 mg with ritonavir 100 mg (once daily) and tenofovir with emtricitabine[d] (n=441)	96 weeks[b] lopinavir 400 mg with ritonavir 100 mg (twice daily) and tenofovir with emtricitabine[d] (n=437)
Chemistry	High		
SGOT/AST	≥5.1 x ULN	3%	1%
SGPT/ALT	≥5.1 x ULN	3%	2%
Total Bilirubin	≥2.6 x ULN	44%	<1%
Lipase	≥2.1 x ULN	2%	2%
Creatine Kinase	≥5.1 x ULN	8%	7%
Total Cholesterol	≥240 mg/dL	11%	25%
Hematology	Low		
Neutrophils	<750 cells/mm^3	5%	2%

[a] Based on the regimen containing REYATAZ.
[b] Median time on therapy.
[c] ULN = upper limit of normal.
[d] As a fixed-dose combination: 300 mg tenofovir, 200 mg emtricitabine once daily.

Table 9: Grade 3–4 Laboratory Abnormalities Reported in ≥2% of Adult Treatment-Naive Patients,[a] Studies AI424-034, AI424-007, and AI424-008

		Study AI424-034		Studies AI424-007, -008	
		64 weeks[b] REYATAZ 400 mg once daily + lamivudine + zidovudine[e]	64 weeks[b] efavirenz 600 mg once daily + lamivudine + zidovudine[e]	120 weeks[b,c] REYATAZ 400 mg once daily + stavudine + lamivudine or + stavudine + didanosine	73 weeks[b,c] nelfinavir 750 mg TID or 1250 mg BID + stavudine + lamivudine or + stavudine + didanosine
Variable	**Limit[d]**	**(n=404)**	**(n=401)**	**(n=279)**	**(n=191)**
Chemistry	High				
SGOT/AST	≥5.1 x ULN	2%	2%	7%	5%
SGPT/ALT	≥5.1 x ULN	4%	3%	9%	7%
Total Bilirubin	≥2.6 x ULN	35%	<1%	47%	3%
Amylase	≥2.1 x ULN	*	*	14%	10%
Lipase	≥2.1 x ULN	<1%	1%	4%	5%
Creatine Kinase	≥5.1 x ULN	6%	6%	11%	9%
Total Cholesterol	≥240 mg/dL	6%	24%	19%	48%
Triglycerides	≥751 mg/dL	<1%	3%	4%	2%
Hematology	Low				
Hemoglobin	<8.0 g/dL	5%	3%	<1%	4%
Neutrophils	<750 cells/mm^3	7%	9%	3%	7%

* None reported in this treatment arm.

[a] Based on regimen(s) containing REYATAZ.

[b] Median time on therapy.

[c] Includes long-term follow-up.

[d] ULN = upper limit of normal.

[e] As a fixed-dose combination: 150 mg lamivudine, 300 mg zidovudine twice daily.

Laboratory Abnormalities in Treatment-Experienced Patients

The percentages of adult treatment-experienced patients treated with combination therapy including REYATAZ/ritonavir with Grade 3–4 laboratory abnormalities are presented in Table 10.

Table 10: Grade 3–4 Laboratory Abnormalities Reported in ≥2% of Adult Treatment-Experienced Patients, Study AI424-045[a]

Variable	Limit[c]	48 weeks[b] REYATAZ/ritonavir 300/100 mg once daily + tenofovir + NRTI (n=119)	48 weeks[b] lopinavir/ritonavir 400/100 mg twice daily[d] + tenofovir + NRTI (n=118)
Chemistry	High		
SGOT/AST	≥5.1 x ULN	3%	3%
SGPT/ALT	≥5.1 x ULN	4%	3%
Total Bilirubin	≥2.6 x ULN	49%	<1%
Lipase	≥2.1 x ULN	5%	6%
Creatine Kinase	≥5.1 x ULN	8%	8%
Total Cholesterol	≥240 mg/dL	25%	26%
Triglycerides	≥751 mg/dL	8%	12%
Glucose	≥251 mg/dL	5%	<1%
Hematology	Low		
Platelets	<50,000 cells/mm^3	2%	3%
Neutrophils	<750 cells/mm^3	7%	8%

[a] Based on regimen(s) containing REYATAZ.
[b] Median time on therapy.
[c] ULN = upper limit of normal.
[d] As a fixed-dose combination.

Lipids, Change from Baseline in Treatment-Naive Patients

For Study AI424-138 and Study AI424-034, changes from baseline in LDL-cholesterol, HDL-cholesterol, total cholesterol, and triglycerides are shown in Tables 11 and 12, respectively.

Table 11: Lipid Values, Mean Change from Baseline, Study AI424-138

	REYATAZ/ritonavir[a,b]					lopinavir/ritonavir[b,c]				
	Baseline	Week 48		Week 96		Baseline	Week 48		Week 96	
	mg/dL (n=428[e])	mg/dL (n=372[e])	Change[d] (n=372[e])	mg/dL (n=342[e])	Change[d] (n=342[e])	mg/dL (n=424[e])	mg/dL (n=335[e])	Change[d] (n=335[e])	mg/dL (n=291[e])	Change[d] (n=291[e])
LDL-Cholesterol[f]	92	105	+14%	105	+14%	93	111	+19%	110	+17%
HDL-Cholesterol[f]	37	46	+29%	44	+21%	36	48	+37%	46	+29%
Total Cholesterol[f]	149	169	+13%	169	+13%	150	187	+25%	186	+25%
Triglycerides[f]	126	145	+15%	140	+13%	129	194	+52%	184	+50%

[a] REYATAZ 300 mg with ritonavir 100 mg once daily with the fixed-dose combination: 300 mg tenofovir, 200 mg emtricitabine once daily.

[b] Values obtained after initiation of serum lipid-reducing agents were not included in these analyses. At baseline, serum lipid-reducing agents were used in 1% in the lopinavir/ritonavir treatment arm and 1% in the REYATAZ/ritonavir arm. Through Week 48, serum lipid-reducing agents were used in 8% in the lopinavir/ritonavir treatment arm and 2% in the REYATAZ/ritonavir arm. Through Week 96, serum lipid-reducing agents were used in 10% in the lopinavir/ritonavir treatment arm and 3% in the REYATAZ/ritonavir arm.

[c] Lopinavir 400 mg with ritonavir 100 mg twice daily with the fixed-dose combination 300 mg tenofovir, 200 mg emtricitabine once daily.

[d] The change from baseline is the mean of within-patient changes from baseline for patients with both baseline and Week 48 or Week 96 values and is not a simple difference of the baseline and Week 48 or Week 96 mean values, respectively.

[e] Number of patients with LDL-cholesterol measured.

[f] Fasting.

Table 12: Lipid Values, Mean Change from Baseline, Study AI424-034

	REYATAZ[a,b]			efavirenz[b,c]		
	Baseline mg/dL (n=383[e])	Week 48 mg/dL (n=283[e])	Week 48 Change[d] (n=272[e])	Baseline mg/dL (n=378[e])	Week 48 mg/dL (n=264[e])	Week 48 Change[d] (n=253[e])
LDL-Cholesterol[f]	98	98	+1%	98	114	+18%
HDL-Cholesterol	39	43	+13%	38	46	+24%
Total Cholesterol	164	168	+2%	162	195	+21%
Triglycerides[f]	138	124	-9%	129	168	+23%

[a] REYATAZ 400 mg once daily with the fixed-dose combination: 150 mg lamivudine, 300 mg zidovudine twice daily.

[b] Values obtained after initiation of serum lipid-reducing agents were not included in these analyses. At baseline, serum lipid-reducing agents were used in 0% in the efavirenz treatment arm and <1% in the REYATAZ arm. Through Week 48, serum lipid-reducing agents were used in 3% in the efavirenz treatment arm and 1% in the REYATAZ arm.

[c] Efavirenz 600 mg once daily with the fixed-dose combination: 150 mg lamivudine, 300 mg zidovudine twice daily.

[d] The change from baseline is the mean of within-patient changes from baseline for patients with both baseline and Week 48 values and is not a simple difference of the baseline and Week 48 mean values.

[e] Number of patients with LDL-cholesterol measured.

[f] Fasting.

Lipids, Change from Baseline in Treatment-Experienced Patients

For Study AI424-045, changes from baseline in LDL-cholesterol, HDL-cholesterol, total cholesterol, and triglycerides are shown in Table 13. The observed magnitude of dyslipidemia was less with REYATAZ/ritonavir than with lopinavir/ritonavir. However, the clinical impact of such findings has not been demonstrated.

Table 13: Lipid Values, Mean Change from Baseline, Study AI424-045

	REYATAZ/ritonavir[a,b]			lopinavir/ritonavir[b,c]		
	Baseline mg/dL (n=111[e])	Week 48 mg/dL (n=75[e])	Week 48 Change[d] (n=74[e])	Baseline mg/dL (n=108[e])	Week 48 mg/dL (n=76[e])	Week 48 Change[d] (n=73[e])
LDL-Cholesterol[f]	108	98	−10%	104	103	+1%
HDL-Cholesterol	40	39	−7%	39	41	+2%
Total Cholesterol	188	170	−8%	181	187	+6%
Triglycerides[f]	215	161	−4%	196	224	+30%

[a] REYATAZ 300 mg once daily + ritonavir + tenofovir + 1 NRTI.

[b] Values obtained after initiation of serum lipid-reducing agents were not included in these analyses. At baseline, serum lipid-reducing agents were used in 4% in the lopinavir/ritonavir treatment arm and 4% in the REYATAZ/ritonavir arm. Through Week 48, serum lipid-reducing agents were used in 19% in the lopinavir/ritonavir treatment arm and 8% in the REYATAZ/ritonavir arm.

[c] Lopinavir/ritonavir (400/100 mg) BID + tenofovir + 1 NRTI.

[d] The change from baseline is the mean of within-patient changes from baseline for patients with both baseline and Week 48 values and is not a simple difference of the baseline and Week 48 mean values.

[e] Number of patients with LDL-cholesterol measured.

[f] Fasting.

6.2 Clinical Trial Experience in Pediatric Patients

The safety and tolerability of REYATAZ Capsules with and without ritonavir have been established in pediatric patients at least 6 years of age from the open-label, multicenter clinical trial PACTG 1020A. Use of REYATAZ in pediatric patients less than 6 years of age is under investigation.

The safety profile of REYATAZ in pediatric patients (6 to less than 18 years of age) was comparable to that observed in clinical studies of REYATAZ in adults. The most common Grade 2–4 adverse events (≥5%, regardless of causality) reported in pediatric patients were cough (21%), fever (19%), rash (14%), jaundice/scleral icterus (13%), diarrhea (8%), vomiting (8%), headache (7%), and rhinorrhea (6%). Asymptomatic second-degree atrioventricular block was reported in 2% of patients. The most common Grade 3–4 laboratory abnormality was elevation

of total bilirubin (≥3.2 mg/dL) which occurred in 49% of pediatric patients. All other Grade 3–4 laboratory abnormalities occurred with a frequency of less than 3%.

6.3 Patients Co-infected With Hepatitis B and/or Hepatitis C Virus

Liver function tests should be monitored in patients with a history of hepatitis B or C.

In study AI424-138, 60 patients treated with REYATAZ/ritonavir 300 mg/100 mg once daily, and 51 patients treated with lopinavir/ritonavir 400 mg/100 mg twice daily, each with fixed dose tenofovir-emtricitabine, were seropositive for hepatitis B and/or C at study entry. ALT levels >5 times ULN developed in 10% (6/60) of the REYATAZ/ritonavir-treated patients and 8% (4/50) of the lopinavir/ritonavir-treated patients. AST levels >5 times ULN developed in 10% (6/60) of the REYATAZ/ritonavir-treated patients and none (0/50) of the lopinavir/ritonavir-treated patients.

In study AI424-045, 20 patients treated with REYATAZ/ritonavir 300 mg/100 mg once daily, and 18 patients treated with lopinavir/ritonavir 400 mg/100 mg twice daily, were seropositive for hepatitis B and/or C at study entry. ALT levels >5 times ULN developed in 25% (5/20) of the REYATAZ/ritonavir-treated patients and 6% (1/18) of the lopinavir/ritonavir-treated patients. AST levels >5 times ULN developed in 10% (2/20) of the REYATAZ/ritonavir-treated patients and 6% (1/18) of the lopinavir/ritonavir-treated patients.

In studies AI424-008 and AI424-034, 74 patients treated with 400 mg of REYATAZ (atazanavir sulfate) once daily, 58 who received efavirenz, and 12 who received nelfinavir were seropositive for hepatitis B and/or C at study entry. ALT levels >5 times the upper limit of normal (ULN) developed in 15% of the REYATAZ-treated patients, 14% of the efavirenz-treated patients, and 17% of the nelfinavir-treated patients. AST levels >5 times ULN developed in 9% of the REYATAZ-treated patients, 5% of the efavirenz-treated patients, and 17% of the nelfinavir-treated patients. Within atazanavir and control regimens, no difference in frequency of bilirubin elevations was noted between seropositive and seronegative patients. [See *Warnings and Precautions (5.5)*.]

6.4 Postmarketing Experience

The following events have been identified during postmarketing use of REYATAZ. Because these reactions are reported voluntarily from a population of unknown size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Body as a Whole: edema

Cardiovascular System: second-degree AV block, third-degree AV block, left bundle branch block, QTc prolongation [see *Warnings and Precautions (5.2)*]

Gastrointestinal System: pancreatitis

Hepatic System: hepatic function abnormalities

Hepatobiliary Disorders: cholelithiasis, cholecystitis, cholestasis

Metabolic System and Nutrition Disorders: diabetes mellitus, hyperglycemia [see *Warnings and Precautions (5.7)*]

Musculoskeletal System: arthralgia

Renal System: nephrolithiasis [see *Warnings and Precautions (5.6)*]

Skin and Appendages: alopecia, maculopapular rash [see *Contraindications (4)* and *Warnings and Precautions (5.3)*], pruritus

7 DRUG INTERACTIONS

See also *Contraindications (4)* and *Clinical Pharmacology (12.3).*

7.1 Potential for REYATAZ to Affect Other Drugs

Atazanavir is an inhibitor of CYP3A and UGT1A1. Coadministration of REYATAZ and drugs primarily metabolized by CYP3A or UGT1A1 may result in increased plasma concentrations of the other drug that could increase or prolong its therapeutic and adverse effects.

Atazanavir is a weak inhibitor of CYP2C8. Caution should be used when REYATAZ without ritonavir is coadministered with drugs highly dependent on CYP2C8 with narrow therapeutic indices (eg, paclitaxel, repaglinide). When REYATAZ with ritonavir is coadministered with substrates of CYP2C8, clinically significant interactions are not expected. [See *Clinical Pharmacology, Table 15 (12.3).*]

The magnitude of CYP3A-mediated drug interactions on coadministered drug may change when REYATAZ is coadministered with ritonavir. See the complete prescribing information for NORVIR® (ritonavir) for information on drug interactions with ritonavir.

7.2 Potential for Other Drugs to Affect Atazanavir

Atazanavir is a CYP3A4 substrate; therefore, drugs that induce CYP3A4 may decrease atazanavir plasma concentrations and reduce REYATAZ's therapeutic effect.

Atazanavir solubility decreases as pH increases. Reduced plasma concentrations of atazanavir are expected if proton-pump inhibitors, antacids, buffered medications, or H_2-receptor antagonists are administered with atazanavir.

7.3 Established and Other Potentially Significant Drug Interactions

Table 14 provides dosing recommendations as a result of drug interactions with REYATAZ. These recommendations are based on either drug interaction studies or predicted interactions due to the expected magnitude of interaction and potential for serious events or loss of efficacy.

Table 14: Established and Other Potentially Significant Drug Interactions: Alteration in Dose or Regimen May Be Recommended Based on Drug Interaction Studies[a] or Predicted Interactions (Information in the table applies to REYATAZ with or without ritonavir, unless otherwise indicated)

Concomitant Drug Class: **Specific Drugs**	**Effect on Concentration of Atazanavir or Concomitant Drug**	**Clinical Comment**
HIV Antiviral Agents		
Nucleoside Reverse Transcriptase Inhibitors (NRTIs) didanosine buffered formulations enteric-coated (EC) capsules	↓ atazanavir ↓ didanosine	Coadministration of REYATAZ with didanosine buffered tablets resulted in a marked decrease in atazanavir exposure. It is recommended that REYATAZ be given (with food) 2 h before or 1 h after didanosine buffered formulations. Simultaneous administration of didanosine EC and REYATAZ with food results in a decrease in didanosine exposure. Thus, REYATAZ and didanosine EC should be administered at different times.
Nucleotide Reverse Transcriptase Inhibitors tenofovir disoproxil fumarate	↓ atazanavir ↑ tenofovir	Tenofovir may decrease the AUC and C_{min} of atazanavir. When coadministered with tenofovir, it is recommended that REYATAZ 300 mg be given with ritonavir 100 mg and tenofovir 300 mg (all as a single daily dose with food). **REYATAZ without ritonavir should not be coadministered with tenofovir.** REYATAZ increases tenofovir concentrations. The mechanism of this interaction is unknown. Higher tenofovir concentrations could potentiate tenofovir-associated adverse events, including renal disorders. Patients receiving REYATAZ and tenofovir should be monitored for tenofovir-associated adverse events. For pregnant women taking REYATAZ with ritonavir *and* tenofovir, see *Dosage and Administration (2.3)*.

Table 14: Established and Other Potentially Significant Drug Interactions: Alteration in Dose or Regimen May Be Recommended Based on Drug Interaction Studies[a] or Predicted Interactions (Information in the table applies to REYATAZ with or without ritonavir, unless otherwise indicated)

Concomitant Drug Class: **Specific Drugs**	**Effect on Concentration of Atazanavir or Concomitant Drug**	**Clinical Comment**
Non-nucleoside Reverse Transcriptase Inhibitors (NNRTIs) efavirenz	↓ atazanavir	Efavirenz decreases atazanavir exposure. ***In treatment-naive patients:*** If REYATAZ is combined with efavirenz, REYATAZ 400 mg (two 200-mg capsules) with ritonavir 100 mg should be administered once daily all as a single dose with food, and efavirenz 600 mg should be administered once daily on an empty stomach, preferably at bedtime. ***In treatment-experienced patients:*** Do not coadminister REYATAZ with efavirenz in treatment-experienced patients due to decreased atazanavir exposure.
Non-nucleoside Reverse Transcriptase Inhibitors nevirapine	↓ atazanavir ↑ nevirapine	Do not coadminister REYATAZ with nevirapine because: • Nevirapine substantially decreases atazanavir exposure. • Potential risk for nevirapine associated toxicity due to increased nevirapine exposures.
Protease Inhibitors saquinavir (soft gelatin capsules)	↑ saquinavir	Appropriate dosing recommendations for this combination, with or without ritonavir, with respect to efficacy and safety have not been established. In a clinical study, saquinavir 1200 mg coadministered with REYATAZ 400 mg and tenofovir 300 mg (all given once daily) plus nucleoside analogue reverse transcriptase inhibitors did not provide adequate efficacy [see *Clinical Studies (14.2)*].
Protease Inhibitors ritonavir	↑ atazanavir	If REYATAZ is coadministered with ritonavir, it is recommended that REYATAZ 300 mg once daily be given with ritonavir 100 mg once daily with food. See the complete prescribing information for NORVIR® (ritonavir) for information on drug interactions with ritonavir.
Protease Inhibitors others	↑ other protease inhibitor	***REYATAZ/ritonavir:*** Although not studied, the coadministration of REYATAZ/ritonavir and other protease inhibitors would be expected to increase exposure to the other protease inhibitor. Such coadministration is not recommended.
Other Agents		
Antacids and buffered medications	↓ atazanavir	Reduced plasma concentrations of atazanavir are expected if antacids, including buffered medications, are administered with REYATAZ. REYATAZ should be administered 2 hours before or 1 hour after these medications.
Antiarrhythmics amiodarone, bepridil, lidocaine (systemic), quinidine	↑ amiodarone, bepridil, lidocaine (systemic), quinidine	Coadministration with REYATAZ has the potential to produce serious and/or life-threatening adverse events and has not been studied. Caution is warranted and therapeutic concentration monitoring of these drugs is recommended if they are used concomitantly with REYATAZ (atazanavir sulfate).
Anticoagulants warfarin	↑ warfarin	Coadministration with REYATAZ has the potential to produce serious and/or life-threatening bleeding and has not been studied. It is recommended that INR (International Normalized Ratio) be monitored.
Antidepressants tricyclic antidepressants	↑ tricyclic antidepressants	Coadministration with REYATAZ has the potential to produce serious and/or life-threatening adverse events and has not been studied. Concentration monitoring of these drugs is recommended if they are used concomitantly with REYATAZ.

Table 14: Established and Other Potentially Significant Drug Interactions: Alteration in Dose or Regimen May Be Recommended Based on Drug Interaction Studies[a] or Predicted Interactions (Information in the table applies to REYATAZ with or without ritonavir, unless otherwise indicated)

Concomitant Drug Class: **Specific Drugs**	**Effect on Concentration of Atazanavir or Concomitant Drug**	**Clinical Comment**
trazodone	↑ trazodone	Concomitant use of trazodone and REYATAZ with or without ritonavir may increase plasma concentrations of trazodone. Adverse events of nausea, dizziness, hypotension, and syncope have been observed following coadministration of trazodone and ritonavir. If trazodone is used with a CYP3A4 inhibitor such as REYATAZ, the combination should be used with caution and a lower dose of trazodone should be considered.
Antifungals ketoconazole, itraconazole	***REYATAZ/ ritonavir:*** ↑ ketoconazole ↑ itraconazole	Coadministration of ketoconazole has only been studied with REYATAZ without ritonavir (negligible increase in atazanavir AUC and C_{max}). Due to the effect of ritonavir on ketoconazole, high doses of ketoconazole and itraconazole (>200 mg/day) should be used cautiously with REYATAZ/ritonavir.
Antifungals voriconazole	Effect is unknown	Coadministration of voriconazole with REYATAZ, with or without ritonavir, has not been studied. Administration of voriconazole with ritonavir 100 mg every 12 hours decreased voriconazole steady-state AUC by an average of 39%. Voriconazole should not be administered to patients receiving REYATAZ/ritonavir, unless an assessment of the benefit/risk to the patient justifies the use of voriconazole. Coadministration of voriconazole with REYATAZ (without ritonavir) may increase atazanavir concentrations; however, no data are available.
Antigout colchicine	↑ colchicine	REYATAZ should not be coadministered with colchicine to patients with renal or hepatic impairment. ***Recommended dosage of colchicine when administered with REYATAZ:*** ***Treatment of gout flares:*** 0.6 mg (1 tablet) for 1 dose, followed by 0.3 mg (half tablet) 1 hour later. Not to be repeated before 3 days. ***Prophylaxis of gout flares:*** If the original regimen was 0.6 mg *twice* a day, the regimen should be adjusted to 0.3 mg *once a day*. If the original regimen was 0.6 mg *once* a day, the regimen should be adjusted to 0.3 mg *once every other day*. ***Treatment of familial Mediterranean fever (FMF):*** Maximum daily dose of 0.6 mg (may be given as 0.3 mg twice a day).
Antimycobacterials rifabutin	↑ rifabutin	A rifabutin dose reduction of up to 75% (eg, 150 mg every other day or 3 times per week) is recommended. Increased monitoring for rifabutin-associated adverse reactions including neutropenia is warranted.
Benzodiazepines parenterally administered midazolam[b]	↑ midazolam	Concomitant use of parenteral midazolam with REYATAZ may increase plasma concentrations of midazolam. Coadministration should be done in a setting which ensures close clinical monitoring and appropriate medical management in case of respiratory depression and/or prolonged sedation. Dosage reduction for midazolam should be considered, especially if more than a single dose of midazolam is administered. Coadministration of oral midazolam with REYATAZ is CONTRAINDICATED.
Calcium channel blockers diltiazem	↑ diltiazem and desacetyl-diltiazem	Caution is warranted. A dose reduction of diltiazem by 50% should be considered. ECG monitoring is recommended. Coadministration of REYATAZ/ritonavir with diltiazem has not been studied.
eg, felodipine, nifedipine, nicardipine, and verapamil	↑ calcium channel blocker	Caution is warranted. Dose titration of the calcium channel blocker should be considered. ECG monitoring is recommended.

Table 14: Established and Other Potentially Significant Drug Interactions: Alteration in Dose or Regimen May Be Recommended Based on Drug Interaction Studies[a] or Predicted Interactions (Information in the table applies to REYATAZ with or without ritonavir, unless otherwise indicated)

Concomitant Drug Class: **Specific Drugs**	**Effect on Concentration of Atazanavir or Concomitant Drug**	**Clinical Comment**
Endothelin receptor antagonists bosentan	↓ atazanavir ↑ bosentan	Plasma concentrations of atazanavir may be decreased when bosentan is administered with REYATAZ without ritonavir. Coadministration of bosentan and REYATAZ without ritonavir is not recommended. ***Coadministration of bosentan in patients on REYATAZ/ritonavir:*** For patients who have been receiving REYATAZ/ritonavir for at least 10 days, start bosentan at 62.5 mg once daily or every other day based on individual tolerability. ***Coadministration of REYATAZ/ritonavir in patients on bosentan:*** Discontinue bosentan at least 36 hours before starting REYATAZ/ritonavir. At least 10 days after starting REYATAZ/ritonavir, resume bosentan at 62.5 mg once daily or every other day based on individual tolerability.
HMG-CoA reductase inhibitors atorvastatin, rosuvastatin	↑ atorvastatin ↑ rosuvastatin	Use the lowest possible dose of atorvastatin or rosuvastatin with careful monitoring, or consider other HMG-CoA reductase inhibitors such as pravastatin or fluvastatin in combination with REYATAZ (with or without ritonavir). The risk of myopathy, including rhabdomyolysis, may be increased when HIV protease inhibitors, including REYATAZ, are used in combination with these drugs.

Table 14: Established and Other Potentially Significant Drug Interactions: Alteration in Dose or Regimen May Be Recommended Based on Drug Interaction Studies[a] or Predicted Interactions (Information in the table applies to REYATAZ with or without ritonavir, unless otherwise indicated)

Concomitant Drug Class: **Specific Drugs**	**Effect on Concentration of Atazanavir or Concomitant Drug**	**Clinical Comment**
H_2-Receptor antagonists	↓ atazanavir	Plasma concentrations of atazanavir were substantially decreased when REYATAZ 400 mg once daily was administered simultaneously with famotidine 40 mg twice daily, which may result in loss of therapeutic effect and development of resistance. ***In treatment-naive patients:*** REYATAZ 300 mg with ritonavir 100 mg once daily with food should be administered simultaneously with, and/or at least 10 hours after, a dose of the H_2-receptor antagonist. An H_2-receptor antagonist dose comparable to famotidine 20 mg once daily up to a dose comparable to famotidine 40 mg twice daily can be used with REYATAZ 300 mg with ritonavir 100 mg in treatment-naive patients. OR For patients unable to tolerate ritonavir, REYATAZ 400 mg once daily with food should be administered at least 2 hours before and at least 10 hours after a dose of the H_2-receptor antagonist. No single dose of the H_2-receptor antagonist should exceed a dose comparable to famotidine 20 mg, and the total daily dose should not exceed a dose comparable to famotidine 40 mg. However, REYATAZ should not be used without ritonavir in pregnant women. ***In treatment-experienced patients:*** Whenever an H_2-receptor antagonist is given to a patient receiving REYATAZ with ritonavir, the H_2-receptor antagonist dose should not exceed a dose comparable to famotidine 20 mg twice daily, and the REYATAZ and ritonavir doses should be administered simultaneously with, and/or at least 10 hours after, the dose of the H_2-receptor antagonist. • REYATAZ 300 mg with ritonavir 100 mg once daily (all as a single dose with food) if taken with an H_2-receptor antagonist. For pregnant women taking REYATAZ with ritonavir and an H_2-receptor antagonist, see *Dosage and Administration (2.3)*. • REYATAZ 400 mg with ritonavir 100 mg once daily (all as a single dose with food) if taken with both tenofovir and an H_2-receptor antagonist. For pregnant women taking REYATAZ with ritonavir and both tenofovir and an H_2-receptor antagonist, see *Dosage and Administration (2.3)*.
Hormonal contraceptives ethinyl estradiol and norgestimate or norethindrone	↓ ethinyl estradiol ↑ norgestimate[c]	Use with caution if coadministration of REYATAZ or REYATAZ/ritonavir with oral contraceptives is considered. If an oral contraceptive is administered with REYATAZ plus ritonavir, it is recommended that the oral contraceptive contain at least 35 mcg of ethinyl estradiol. If REYATAZ is administered without ritonavir, the oral contraceptive should contain no more than 30 mcg of ethinyl estradiol.
	↑ ethinyl estradiol ↑ norethindrone[d]	Potential safety risks include substantial increases in progesterone exposure. The long-term effects of increases in concentration of the progestational agent are unknown and could increase the risk of insulin resistance, dyslipidemia, and acne. Coadministration of REYATAZ or REYATAZ/ritonavir with other hormonal contraceptives (eg, contraceptive patch, contraceptive vaginal ring, or injectable contraceptives) or oral contraceptives containing progestagens other than norethindrone or norgestimate, or less than 25 mcg of ethinyl estradiol, has not been studied; therefore, alternative methods of contraception are recommended.

Table 14: Established and Other Potentially Significant Drug Interactions: Alteration in Dose or Regimen May Be Recommended Based on Drug Interaction Studies[a] or Predicted Interactions (Information in the table applies to REYATAZ with or without ritonavir, unless otherwise indicated)

Concomitant Drug Class: **Specific Drugs**	**Effect on Concentration of Atazanavir or Concomitant Drug**	**Clinical Comment**
Immunosuppressants cyclosporin, sirolimus, tacrolimus	↑ immunosuppressants	Therapeutic concentration monitoring is recommended for immunosuppressant agents when coadministered with REYATAZ (atazanavir sulfate).
Inhaled beta agonist salmeterol	↑ salmeterol	Coadministration of salmeterol with REYATAZ is not recommended. Concomitant use of salmeterol and REYATAZ may result in increased risk of cardiovascular adverse events associated with salmeterol, including QT prolongation, palpitations, and sinus tachycardia.
Inhaled/nasal steroid fluticasone	***REYATAZ*** ↑ fluticasone	Concomitant use of fluticasone propionate and REYATAZ (without ritonavir) may increase plasma concentrations of fluticasone propionate. Use with caution. Consider alternatives to fluticasone propionate, particularly for long-term use.
	REYATAZ/ritonavir ↑ fluticasone	Concomitant use of fluticasone propionate and REYATAZ/ritonavir may increase plasma concentrations of fluticasone propionate, resulting in significantly reduced serum cortisol concentrations. Systemic corticosteroid effects, including Cushing's syndrome and adrenal suppression, have been reported during postmarketing use in patients receiving ritonavir and inhaled or intranasally administered fluticasone propionate. Coadministration of fluticasone propionate and REYATAZ/ritonavir is not recommended unless the potential benefit to the patient outweighs the risk of systemic corticosteroid side effects [see *Warnings and Precautions (5.1)*].
Macrolide antibiotics clarithromycin	↑ clarithromycin ↓ 14-OH clarithromycin ↑ atazanavir	Increased concentrations of clarithromycin may cause QTc prolongations; therefore, a dose reduction of clarithromycin by 50% should be considered when it is coadministered with REYATAZ. In addition, concentrations of the active metabolite 14-OH clarithromycin are significantly reduced; consider alternative therapy for indications other than infections due to *Mycobacterium avium* complex. Coadministration of REYATAZ/ritonavir with clarithromycin has not been studied.
Opioids Buprenorphine	↑ buprenorphine ↑ norbuprenorphine	Coadministration of buprenorphine and REYATAZ with or without ritonavir increases the plasma concentration of buprenorphine and norbuprenorphine. Coadministration of REYATAZ plus ritonavir with buprenorphine warrants clinical monitoring for sedation and cognitive effects. A dose reduction of buprenorphine may be considered. Coadministration of buprenorphine and REYATAZ with ritonavir is not expected to decrease atazanavir plasma concentrations. Coadministration of buprenorphine and REYATAZ without ritonavir may decrease atazanavir plasma concentrations. REYATAZ without ritonavir should not be coadministered with buprenorphine.

Table 14: Established and Other Potentially Significant Drug Interactions: Alteration in Dose or Regimen May Be Recommended Based on Drug Interaction Studies[a] or Predicted Interactions (Information in the table applies to REYATAZ with or without ritonavir, unless otherwise indicated)

Concomitant Drug Class: **Specific Drugs**	**Effect on Concentration of Atazanavir or Concomitant Drug**	**Clinical Comment**
PDE5 inhibitors sildenafil, tadalafil, vardenafil	↑ sildenafil ↑ tadalafil ↑ vardenafil	Coadministration with REYATAZ has not been studied but may result in an increase in PDE5 inhibitor-associated adverse events, including hypotension, syncope, visual disturbances, and priapism. ***Use of PDE5 inhibitors for pulmonary arterial hypertension (PAH):*** Use of REVATIO® (sildenafil) for the treatment of pulmonary hypertension (PAH) is contraindicated with REYATAZ [see *Contraindications (4)*]. The following dose adjustments are recommended for the use of ADCIRCA® (tadalafil) with REYATAZ: Coadministration of ADCIRCA® in patients on REYATAZ (with or without ritonavir): ▪ For patients receiving REYATAZ (with or without ritonavir) for at least one week, start ADCIRCA® at 20 mg once daily. Increase to 40 mg once daily based on individual tolerability. Coadministration of REYATAZ (with or without ritonavir) in patients on ADCIRCA®: ▪ Avoid the use of ADCIRCA® when starting REYATAZ (with or without ritonavir). Stop ADCIRCA® at least 24 hours before starting REYATAZ (with or without ritonavir). At least one week after starting REYATAZ (with or without ritonavir), resume ADCIRCA® at 20 mg once daily. Increase to 40 mg once daily based on individual tolerability. ***Use of PDE5 inhibitors for erectile dysfunction:*** Use VIAGRA® (sildenafil) with caution at reduced doses of 25 mg every 48 hours with increased monitoring for adverse events. Use CIALIS® (tadalafil) with caution at reduced doses of 10 mg every 72 hours with increased monitoring for adverse events. ***REYATAZ/ritonavir:*** Use LEVITRA® (vardenafil) with caution at reduced doses of no more than 2.5 mg every 72 hours with increased monitoring for adverse events. ***REYATAZ:*** Use LEVITRA® (vardenafil) with caution at reduced doses of no more than 2.5 mg every 24 hours with increased monitoring for adverse events.
Proton-pump inhibitors omeprazole	↓ atazanavir	Plasma concentrations of atazanavir were substantially decreased when REYATAZ 400 mg or REYATAZ 300 mg/ritonavir 100 mg once daily was administered with omeprazole 40 mg once daily, which may result in loss of therapeutic effect and development of resistance. ***In treatment-naive patients:*** The proton-pump inhibitor dose should not exceed a dose comparable to omeprazole 20 mg and must be taken approximately 12 hours prior to the REYATAZ 300 mg with ritonavir 100 mg dose. ***In treatment-experienced patients:*** Proton-pump inhibitors should not be used in treatment-experienced patients receiving REYATAZ.

Table 14: Established and Other Potentially Significant Drug Interactions: Alteration in Dose or Regimen May Be Recommended Based on Drug Interaction Studies[a] or Predicted Interactions (Information in the table applies to REYATAZ with or without ritonavir, unless otherwise indicated)

Concomitant Drug Class: Specific Drugs	Effect on Concentration of Atazanavir or Concomitant Drug	Clinical Comment

[a] For magnitude of interactions see *Clinical Pharmacology, Tables 18* and *19 (12.3).*

[b] See *Contraindications (4), Table 4* for orally administered midazolam.

[c] In combination with atazanavir 300 mg and ritonavir 100 mg once daily.

[d] In combination with atazanavir 400 mg once daily.

7.4 Drugs with No Observed or Predicted Interactions with REYATAZ

Clinically significant interactions are not expected between atazanavir and substrates of CYP2C19, CYP2C9, CYP2D6, CYP2B6, CYP2A6, CYP1A2, or CYP2E1. Clinically significant interactions are not expected between atazanavir when administered with ritonavir and substrates of CYP2C8. See the complete prescribing information for NORVIR® for information on other potential drug interactions with ritonavir.

Based on known metabolic profiles, clinically significant drug interactions are not expected between REYATAZ (atazanavir sulfate) and fluvastatin, pravastatin, dapsone, trimethoprim/sulfamethoxazole, azithromycin, or erythromycin. REYATAZ does not interact with substrates of CYP2D6 (eg, nortriptyline, desipramine, metoprolol). Additionally, no clinically significant drug interactions were observed when REYATAZ was coadministered with methadone, fluconazole, acetaminophen, or atenolol. [See *Clinical Pharmacology*, *Tables 18* and *19 (12.3).*]

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category B

Antiretroviral Pregnancy Registry: To monitor maternal-fetal outcomes of pregnant women exposed to REYATAZ, an Antiretroviral Pregnancy Registry has been established. Physicians are encouraged to register patients by calling 1-800-258-4263.

Risk Summary

Atazanavir has been evaluated in a limited number of women during pregnancy and postpartum. Available human and animal data suggest that atazanavir does not increase the risk of major birth defects overall compared to the background rate. However, because the studies in humans cannot rule out the possibility of harm, REYATAZ should be used during pregnancy only if clearly needed.

Cases of lactic acidosis syndrome, sometimes fatal, and symptomatic hyperlactatemia have occurred in pregnant women using REYATAZ in combination with nucleoside analogues. Nucleoside analogues are associated with an increased risk of lactic acidosis syndrome.

Hyperbilirubinemia occurs frequently in patients who take REYATAZ, including pregnant women. All infants, including neonates exposed to REYATAZ in-utero, should be monitored for the development of severe hyperbilirubinemia during the first few days of life.

Clinical Considerations

Dosing During Pregnancy and the Postpartum Period:

- REYATAZ should not be administered without ritonavir.
- REYATAZ should only be administered to pregnant women with HIV-1 strains susceptible to atazanavir.
- For pregnant patients, no dose adjustment is required for REYATAZ with the following exceptions:
    - For treatment-experienced pregnant women during the second or third trimester, when REYATAZ is coadministered with either an H_2-receptor antagonist **or** tenofovir, REYATAZ 400 mg with ritonavir 100 mg once daily is recommended. There are insufficient data to recommend a REYATAZ dose for use with both an H_2-receptor antagonist *and* tenofovir in treatment-experienced pregnant women.
- No dose adjustment is required for postpartum patients. However, patients should be closely monitored for adverse events because atazanavir exposures could be higher during the first 2 months after delivery. [See *Dosage and Administration (2, 2.3)* and *Clinical Pharmacology (12.3)*.]

Human Data

Clinical Trials: In clinical trial AI424-182, REYATAZ/ritonavir (300/100 mg or 400/100 mg) in combination with zidovudine/lamivudine was administered to 41 HIV-infected pregnant women during the second or third trimester. Among the 39 women who completed the study, 38 women achieved an HIV RNA <50 copies/mL at time of delivery. Six of 20 (30%) women on REYATAZ/ritonavir 300/100 mg and 13 of 21 (62%) women on REYATAZ/ritonavir 400/100 mg experienced hyperbilirubinemia (total bilirubin greater than or equal to 2.6 times the upper limit of normal). There were no cases of lactic acidosis observed in clinical trial AI424-182.

Atazanavir drug concentrations in fetal umbilical cord blood were approximately 12–19% of maternal concentrations. Among the 40 infants born to 40 HIV-infected pregnant women, all had test results that were negative for HIV-1 DNA at the time of delivery and/or during the first 6 months postpartum. All 40 infants received antiretroviral prophylactic treatment containing zidovudine. No evidence of severe hyperbilirubinemia (total bilirubin levels greater than 20 mg/dL) or acute or chronic bilirubin encephalopathy was observed among neonates in this study. However, 10/36 (28%) infants (6 greater than or equal to 38 weeks gestation and 4 less than 38 weeks gestation) had bilirubin levels of 4 mg/dL or greater within the first day of life.

Lack of ethnic diversity was a study limitation. In the study population, 33/40 (83%) infants were Black/African American, who have a lower incidence of neonatal hyperbilirubinemia than Caucasians and Asians. In addition, women with Rh incompatibility were excluded, as well as women who had a previous infant who developed hemolytic disease and/or had neonatal pathologic jaundice (requiring phototherapy).

Additionally, of the 38 infants who had glucose samples collected in the first day of life, 3 had adequately collected serum glucose samples with values of <40 mg/dL that could not be attributed to maternal glucose intolerance, difficult delivery, or sepsis.

Antiretroviral Pregnancy Registry Data: As of January 2010, the Antiretroviral Pregnancy Registry (APR) has received prospective reports of 635 exposures to atazanavir-containing regimens (425 exposed in the first trimester and 160 and 50 exposed in second and third trimester, respectively). Birth defects occurred in 9 of 393 (2.3%) live births (first trimester exposure) and 5 of 212 (2.4%) live births (second/third trimester exposure). Among pregnant women in the U.S. reference population, the background rate of birth defects is 2.7%. There was no association between atazanavir and overall birth defects observed in the APR.

Pharmacokinetics of Atazanavir in Pregnancy

[See *Clinical Pharmacology (12.3)*.]

Animal Data

In animal reproduction studies, there was no evidence of teratogenicity in offspring born to animals at systemic drug exposure levels (AUC) 0.7 (in rabbits) to 1.2 (in rats) times those observed at the human clinical dose (300 mg/day atazanavir boosted with 100 mg/day ritonavir). In pre- and post-natal development studies in the rat, atazanavir caused body weight loss or weight gain suppression in the animal offspring with maternal drug exposure (AUC) 1.3 times the human exposure at this clinical dose. However, maternal toxicity also occurred at this exposure level.

8.3 Nursing Mothers

The Centers for Disease Control and Prevention recommend that HIV-infected mothers not breast-feed their infants to avoid risking postnatal transmission of HIV. It is not known whether atazanavir is present in human milk. Because of both the potential for HIV transmission and the potential for serious adverse reactions in nursing infants, **mothers should be instructed not to breast-feed if they are taking REYATAZ**.

8.4 Pediatric Use

REYATAZ should not be administered to pediatric patients below the age of 3 months due to the risk of kernicterus.

The safety, activity, and pharmacokinetic profiles of REYATAZ in pediatric patients ages 3 months to less than 6 years have not been established.

The safety, pharmacokinetic profile, and virologic response of REYATAZ were evaluated in pediatric patients in an open-label, multicenter clinical trial PACTG 1020A [see *Clinical Pharmacology (12.3)* and *Clinical Studies (14.3)*]. The safety profile in pediatric patients was comparable to that observed in adults [see *Adverse Reactions (6.2)*]. Please see *Dosage and Administration (2.2)* for dosing recommendations for pediatric patients 6 years of age and older.

8.5 Geriatric Use

Clinical studies of REYATAZ did not include sufficient numbers of patients aged 65 and over to determine whether they respond differently from younger patients. Based on a comparison of

mean single-dose pharmacokinetic values for C_{max} and AUC, a dose adjustment based upon age is not recommended. In general, appropriate caution should be exercised in the administration and monitoring of REYATAZ in elderly patients reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

8.6 Age/Gender

A study of the pharmacokinetics of atazanavir was performed in young (n=29; 18–40 years) and elderly (n=30; ≥65 years) healthy subjects. There were no clinically important pharmacokinetic differences observed due to age or gender.

8.7 Impaired Renal Function

In healthy subjects, the renal elimination of unchanged atazanavir was approximately 7% of the administered dose. REYATAZ has been studied in adult subjects with severe renal impairment (n=20), including those on hemodialysis, at multiple doses of 400 mg once daily. The mean atazanavir C_{max} was 9% lower, AUC was 19% higher, and C_{min} was 96% higher in subjects with severe renal impairment not undergoing hemodialysis (n=10), than in age, weight, and gender matched subjects with normal renal function. Atazanavir was not appreciably cleared during hemodialysis. In a 4-hour dialysis session, 2.1% of the administered dose was removed. When atazanavir was administered either prior to, or following hemodialysis (n=10), the geometric means for C_{max}, AUC, and C_{min} were approximately 25 to 43% lower compared to subjects with normal renal function. The mechanism of this decrease is unknown. REYATAZ should not be administered to HIV-treatment-experienced patients with end stage renal disease managed with hemodialysis. [See *Dosage and Administration (2.4)*.]

8.8 Impaired Hepatic Function

Atazanavir is metabolized and eliminated primarily by the liver. REYATAZ (atazanavir sulfate) has been studied in adult subjects with moderate to severe hepatic impairment (14 Child-Pugh B and 2 Child-Pugh C subjects) after a single 400-mg dose. The mean $AUC_{(0-\infty)}$ was 42% greater in subjects with impaired hepatic function than in healthy volunteers. The mean half-life of atazanavir in hepatically impaired subjects was 12.1 hours compared to 6.4 hours in healthy volunteers. Increased concentrations of atazanavir are expected in patients with moderately or severely impaired hepatic function. The pharmacokinetics of REYATAZ in combination with ritonavir have not been studied in subjects with hepatic impairment. REYATAZ should not be administered to patients with severe hepatic impairment. REYATAZ/ritonavir is not

recommended for use in patients with hepatic impairment. [See *Dosage and Administration (2.5)* and *Warnings and Precautions (5.5)*.]

10 OVERDOSAGE

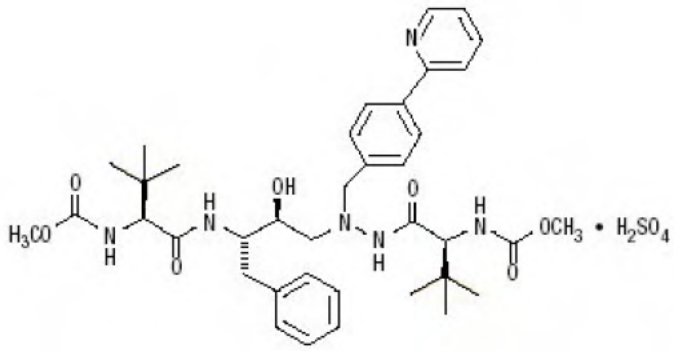
Human experience of acute overdose with REYATAZ is limited. Single doses up to 1200 mg have been taken by healthy volunteers without symptomatic untoward effects. A single self-administered overdose of 29.2 g of REYATAZ in an HIV-infected patient (73 times the 400-mg recommended dose) was associated with asymptomatic bifascicular block and PR interval prolongation. These events resolved spontaneously. At high doses that lead to high drug exposures, jaundice due to indirect (unconjugated) hyperbilirubinemia (without associated liver function test changes) or PR interval prolongation may be observed. [See *Warnings and Precautions (5.2, 5.4)* and *Clinical Pharmacology (12.2)*.]

Treatment of overdosage with REYATAZ should consist of general supportive measures, including monitoring of vital signs and ECG, and observations of the patient's clinical status. If indicated, elimination of unabsorbed atazanavir should be achieved by emesis or gastric lavage. Administration of activated charcoal may also be used to aid removal of unabsorbed drug. There is no specific antidote for overdose with REYATAZ. Since atazanavir is extensively metabolized by the liver and is highly protein bound, dialysis is unlikely to be beneficial in significant removal of this medicine.

11 DESCRIPTION

REYATAZ® (atazanavir sulfate) is an azapeptide inhibitor of HIV-1 protease.

The chemical name for atazanavir sulfate is (3*S*,8*S*,9*S*,12*S*)-3,12-Bis(1,1-dimethylethyl)-8-hydroxy-4,11-dioxo-9-(phenylmethyl)-6-[[4-(2-pyridinyl)phenyl]methyl]-2,5,6,10,13-pentaazatetradecanedioic acid dimethyl ester, sulfate (1:1). Its molecular formula is $C_{38}H_{52}N_6O_7 \bullet H_2SO_4$, which corresponds to a molecular weight of 802.9 (sulfuric acid salt). The free base molecular weight is 704.9. Atazanavir sulfate has the following structural formula:



Atazanavir sulfate is a white to pale yellow crystalline powder. It is slightly soluble in water (4–5 mg/mL, free base equivalent) with the pH of a saturated solution in water being about 1.9 at 24 ± 3° C.

REYATAZ Capsules are available for oral administration in strengths containing the equivalent of 100 mg, 150 mg, 200 mg, or 300 mg of atazanavir as atazanavir sulfate and the following inactive ingredients: crospovidone, lactose monohydrate, and magnesium stearate. The capsule shells contain the following inactive ingredients: gelatin, FD&C Blue #2, titanium dioxide, black iron oxide, red iron oxide, and yellow iron oxide. The capsules are printed with ink containing shellac, titanium dioxide, FD&C Blue #2, isopropyl alcohol, ammonium hydroxide, propylene glycol, n-butyl alcohol, simethicone, and dehydrated alcohol.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Atazanavir is an antiviral drug [see *Clinical Pharmacology (12.4)*].

12.2 Pharmacodynamics

Effects on Electrocardiogram

Concentration- and dose-dependent prolongation of the PR interval in the electrocardiogram has been observed in healthy volunteers receiving atazanavir. In a placebo-controlled study (AI424-076), the mean (±SD) maximum change in PR interval from the predose value was 24 (±15) msec following oral dosing with 400 mg of atazanavir (n=65) compared to 13 (±11) msec following dosing with placebo (n=67). The PR interval prolongations in this study were asymptomatic. There is limited information on the potential for a pharmacodynamic interaction in humans between atazanavir and other drugs that prolong the PR interval of the electrocardiogram. [See *Warnings and Precautions (5.2)*.]

Electrocardiographic effects of atazanavir were determined in a clinical pharmacology study of 72 healthy subjects. Oral doses of 400 mg and 800 mg were compared with placebo; there was no concentration-dependent effect of atazanavir on the QTc interval (using Fridericia's correction). In 1793 HIV-infected patients receiving antiretroviral regimens, QTc prolongation was comparable in the atazanavir and comparator regimens. No atazanavir-treated healthy subject or HIV-infected patient in clinical trials had a QTc interval >500 msec. [See *Warnings and Precautions (5.2).*]

In a pharmacokinetic study between atazanavir 400 mg once daily and diltiazem 180 mg once daily, a CYP3A substrate, there was a 2-fold increase in the diltiazem plasma concentration and an additive effect on the PR interval. In a pharmacokinetic study between atazanavir 400 mg once daily and atenolol 50 mg once daily, there was no substantial additive effect of atazanavir and atenolol on the PR interval. [See *Warnings and Precautions (5.2).*]

12.3 Pharmacokinetics

The pharmacokinetics of atazanavir were evaluated in healthy adult volunteers and in HIV-infected patients after administration of REYATAZ 400 mg once daily and after administration of REYATAZ 300 mg with ritonavir 100 mg once daily (see Table 15).

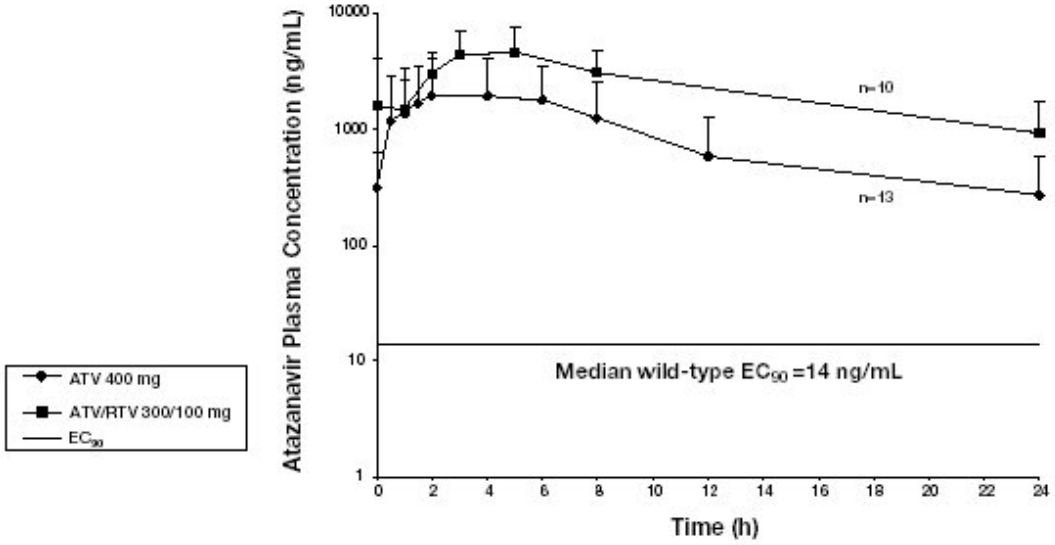
Table 15: Steady-State Pharmacokinetics of Atazanavir in Healthy Subjects or HIV-Infected Patients in the Fed State

	400 mg once daily		300 mg with ritonavir 100 mg once daily	
Parameter	**Healthy Subjects (n=14)**	**HIV-Infected Patients (n=13)**	**Healthy Subjects (n=28)**	**HIV-Infected Patients (n=10)**
C_{max} (ng/mL)				
Geometric mean (CV%)	5199 (26)	2298 (71)	6129 (31)	4422 (58)
Mean (SD)	5358 (1371)	3152 (2231)	6450 (2031)	5233 (3033)
T_{max} (h)				
Median	2.5	2.0	2.7	3.0
AUC (ng•h/mL)				
Geometric mean (CV%)	28132 (28)	14874 (91)	57039 (37)	46073 (66)
Mean (SD)	29303 (8263)	22262 (20159)	61435 (22911)	53761 (35294)
T-half (h)				
Mean (SD)	7.9 (2.9)	6.5 (2.6)	18.1 (6.2)[a]	8.6 (2.3)
C_{min} (ng/mL)				
Geometric mean (CV%)	159 (88)	120 (109)	1227 (53)	636 (97)
Mean (SD)	218 (191)	273 (298)[b]	1441 (757)	862 (838)

[a] n=26.
[b] n=12.

Figure 1 displays the mean plasma concentrations of atazanavir at steady state after REYATAZ 400 mg once daily (as two 200-mg capsules) with a light meal and after REYATAZ 300 mg (as two 150-mg capsules) with ritonavir 100 mg once daily with a light meal in HIV-infected adult patients.

Figure 1: Mean (SD) Steady-State Plasma Concentrations of Atazanavir 400 mg (n=13) and 300 mg with Ritonavir (n=10) for HIV-Infected Adult Patients



Absorption

Atazanavir is rapidly absorbed with a T_{max} of approximately 2.5 hours. Atazanavir demonstrates nonlinear pharmacokinetics with greater than dose-proportional increases in AUC and C_{max} values over the dose range of 200–800 mg once daily. Steady state is achieved between Days 4 and 8, with an accumulation of approximately 2.3-fold.

Food Effect

Administration of REYATAZ with food enhances bioavailability and reduces pharmacokinetic variability. Administration of a single 400-mg dose of REYATAZ with a light meal (357 kcal, 8.2 g fat, 10.6 g protein) resulted in a 70% increase in AUC and 57% increase in C_{max} relative to the fasting state. Administration of a single 400-mg dose of REYATAZ with a high-fat meal (721 kcal, 37.3 g fat, 29.4 g protein) resulted in a mean increase in AUC of 35% with no change in C_{max} relative to the fasting state. Administration of REYATAZ (atazanavir sulfate) with either a light meal or high-fat meal decreased the coefficient of variation of AUC and C_{max} by approximately one-half compared to the fasting state.

Coadministration of a single 300-mg dose of REYATAZ and a 100-mg dose of ritonavir with a light meal (336 kcal, 5.1 g fat, 9.3 g protein) resulted in a 33% increase in the AUC and a 40% increase in both the C_{max} and the 24-hour concentration of atazanavir relative to the fasting state. Coadministration with a high-fat meal (951 kcal, 54.7 g fat, 35.9 g protein) did not affect the

AUC of atazanavir relative to fasting conditions and the C_{max} was within 11% of fasting values. The 24-hour concentration following a high-fat meal was increased by approximately 33% due to delayed absorption; the median T_{max} increased from 2.0 to 5.0 hours. Coadministration of REYATAZ with ritonavir with either a light or a high-fat meal decreased the coefficient of variation of AUC and C_{max} by approximately 25% compared to the fasting state.

Distribution

Atazanavir is 86% bound to human serum proteins and protein binding is independent of concentration. Atazanavir binds to both alpha-1-acid glycoprotein (AAG) and albumin to a similar extent (89% and 86%, respectively). In a multiple-dose study in HIV-infected patients dosed with REYATAZ 400 mg once daily with a light meal for 12 weeks, atazanavir was detected in the cerebrospinal fluid and semen. The cerebrospinal fluid/plasma ratio for atazanavir (n=4) ranged between 0.0021 and 0.0226 and seminal fluid/plasma ratio (n=5) ranged between 0.11 and 4.42.

Metabolism

Atazanavir is extensively metabolized in humans. The major biotransformation pathways of atazanavir in humans consisted of monooxygenation and dioxygenation. Other minor biotransformation pathways for atazanavir or its metabolites consisted of glucuronidation, N-dealkylation, hydrolysis, and oxygenation with dehydrogenation. Two minor metabolites of atazanavir in plasma have been characterized. Neither metabolite demonstrated *in vitro* antiviral activity. *In vitro* studies using human liver microsomes suggested that atazanavir is metabolized by CYP3A.

Elimination

Following a single 400-mg dose of ^{14}C-atazanavir, 79% and 13% of the total radioactivity was recovered in the feces and urine, respectively. Unchanged drug accounted for approximately 20% and 7% of the administered dose in the feces and urine, respectively. The mean elimination half-life of atazanavir in healthy volunteers (n=214) and HIV-infected adult patients (n=13) was approximately 7 hours at steady state following a dose of 400 mg daily with a light meal.

Special Populations

Pediatrics

The pharmacokinetic data from pediatric patients receiving REYATAZ Capsules with ritonavir based on body surface area are presented in Table 16.

Table 16: Steady-State Pharmacokinetics of Atazanavir with ritonavir in HIV-Infected Pediatric Patients (6 to less than 18 years of age) in the Fed State

	205 mg/m^2 atazanavir with 100 mg/m^2 ritonavir once daily Age Range (years)	
	at least 6 to 13 (n=17)	**at least 13 to 18 (n=10)**
Dose mg		
Median	200	400
[min-max]	[150–400]	[250–500]
C_{max} ng/mL		
Geometric mean (CV%)	4451 (33)	3711 (46)
AUC ng•h/mL		
Geometric mean (CV%)	42503 (36)	44970 (34)
C_{min} ng/mL		
Geometric mean (CV%)	535 (62)	1090 (60)

Pregnancy

The pharmacokinetic data from HIV-infected pregnant women receiving REYATAZ Capsules with ritonavir are presented in Table 17.

Table 17: Steady-State Pharmacokinetics of Atazanavir with ritonavir in HIV-Infected Pregnant Women in the Fed State

Pharmacokinetic Parameter	**Atazanavir 300 mg with ritonavir 100 mg**		
	2nd Trimester (n=5[a])	**3rd Trimester (n=20)**	**Postpartum[b] (n=34)**
C_{max} ng/mL	3078.85	3291.46	5721.21
Geometric mean (CV%)	(50)	(48)	(31)
AUC ng•h/mL	27657.1	34251.5	61990.4
Geometric mean (CV%)	(43)	(43)	(32)
C_{min} ng/mL[c]	538.70	668.48	1462.59
Geometric mean (CV%)	(46)	(50)	(45)

[a] Available data during the 2nd trimester are limited.

Table 17: Steady-State Pharmacokinetics of Atazanavir with ritonavir in HIV-Infected Pregnant Women in the Fed State

	Atazanavir 300 mg with ritonavir 100 mg

[b] Atazanvir peak concentrations and AUCs were found to be approximately 28–43% higher during the postpartum period (4–12 weeks) than those observed historically in HIV-infected, non-pregnant patients. Atazanavir plasma trough concentrations were approximately 2.2-fold higher during the postpartum period when compared to those observed historically in HIV-infected, non-pregnant patients.

[c] C_{min} is concentration 24 hours post-dose.

Drug Interaction Data

Atazanavir is a metabolism-dependent CYP3A inhibitor, with a K_{inact} value of 0.05 to 0.06 min^{-1} and K_i value of 0.84 to 1.0 µM. Atazanavir is also a direct inhibitor for UGT1A1 (K_i=1.9 µM) and CYP2C8 (K_i=2.1 µM).

Atazanavir has been shown *in vivo* not to induce its own metabolism, nor to increase the biotransformation of some drugs metabolized by CYP3A. In a multiple-dose study, REYATAZ decreased the urinary ratio of endogenous 6β-OH cortisol to cortisol versus baseline, indicating that CYP3A production was not induced.

Drug interaction studies were performed with REYATAZ and other drugs likely to be coadministered and some drugs commonly used as probes for pharmacokinetic interactions. The effects of coadministration of REYATAZ on the AUC, C_{max}, and C_{min} are summarized in Tables 18 and 19. For information regarding clinical recommendations, see *Drug Interactions (7)*.

Table 18: Drug Interactions: Pharmacokinetic Parameters for Atazanavir in the Presence of Coadministered Drugs[a]

Coadministered Drug	Coadministered Drug Dose/Schedule	REYATAZ Dose/Schedule	Ratio (90% Confidence Interval) of Atazanavir Pharmacokinetic Parameters with/without Coadministered Drug; No Effect = 1.00		
			C_{max}	AUC	C_{min}
atenolol	50 mg QD, d 7–11 (n=19) and d 19–23	400 mg QD, d 1–11 (n=19)	1.00 (0.89, 1.12)	0.93 (0.85, 1.01)	0.74 (0.65, 0.86)
clarithromycin	500 mg BID, d 7–10 (n=29) and d 18–21	400 mg QD, d 1–10 (n=29)	1.06 (0.93, 1.20)	1.28 (1.16, 1.43)	1.91 (1.66, 2.21)
didanosine (ddI) (buffered tablets) plus stavudine (d4T)[b]	ddI: 200 mg x 1 dose, d4T: 40 mg x 1 dose (n=31)	400 mg x 1 dose simultaneously with ddI and d4T (n=31)	0.11 (0.06, 0.18)	0.13 (0.08, 0.21)	0.16 (0.10, 0.27)

Table 18: Drug Interactions: Pharmacokinetic Parameters for Atazanavir in the Presence of Coadministered Drugs[a]

Coadministered Drug	Coadministered Drug Dose/Schedule	REYATAZ Dose/Schedule	Ratio (90% Confidence Interval) of Atazanavir Pharmacokinetic Parameters with/without Coadministered Drug; No Effect = 1.00		
			C_{max}	AUC	C_{min}
	ddI: 200 mg x 1 dose, d4T: 40 mg x 1 dose (n=32)	400 mg x 1 dose 1 h after ddI + d4T (n=32)	1.12 (0.67, 1.18)	1.03 (0.64, 1.67)	1.03 (0.61, 1.73)
ddI (enteric-coated [EC] capsules)[c]	400 mg d 8 (fed) (n=34) 400 mg d 19 (fed) (n=31)	400 mg QD, d 2–8 (n=34) 300 mg/ritonavir 100 mg QD, d 9–19 (n=31)	1.03 (0.93, 1.14) 1.04 (1.01, 1.07)	0.99 (0.91, 1.08) 1.00 (0.96, 1.03)	0.98 (0.89, 1.08) 0.87 (0.82, 0.92)
diltiazem	180 mg QD, d 7–11 (n=30) and d 19–23	400 mg QD, d 1–11 (n=30)	1.04 (0.96, 1.11)	1.00 (0.95, 1.05)	0.98 (0.90, 1.07)
efavirenz	600 mg QD, d 7–20 (n=27)	400 mg QD, d 1–20 (n=27)	0.41 (0.33, 0.51)	0.26 (0.22, 0.32)	0.07 (0.05, 0.10)
	600 mg QD, d 7–20 (n=13)	400 mg QD, d 1–6 (n=23) then 300 mg/ritonavir 100 mg QD, 2 h before efavirenz, d 7–20 (n=13)	1.14 (0.83, 1.58)	1.39 (1.02, 1.88)	1.48 (1.24, 1.76)
	600 mg QD, d 11–24 (pm) (n=14)	300 mg QD/ritonavir 100 mg QD, d 1–10 (pm) (n=22), then 400 mg QD/ritonavir 100 mg QD, d 11–24 (pm), (simultaneous with efavirenz) (n=14)	1.17 (1.08, 1.27)	1.00 (0.91, 1.10)	0.58 (0.49, 0.69)
famotidine	40 mg BID, d 7–12 (n=15)	400 mg QD, d 1–6 (n=45), d 7–12 (simultaneous administration) (n=15)	0.53 (0.34, 0.82)	0.59 (0.40, 0.87)	0.58 (0.37, 0.89)
	40 mg BID, d 7–12 (n=14)	400 mg QD (pm), d 1–6 (n=14), d 7–12 (10 h after, 2 h before famotidine) (n=14)	1.08 (0.82, 1.41)	0.95 (0.74, 1.21)	0.79 (0.60, 1.04)
	40 mg BID, d 11–20 (n=14)[d]	300 mg QD/ritonavir 100 mg QD, d 1–10 (n=46), d 11–20[d] (simultaneous administration) (n=14)	0.86 (0.79, 0.94)	0.82 (0.75, 0.89)	0.72 (0.64, 0.81)
	20 mg BID, d 11–17 (n=18)	300 mg QD/ritonavir 100 mg QD/tenofovir 300 mg QD, d 1–10 (am) (n=39), d 11–17 (am) (simultaneous administration with am famotidine) (n=18)[e,f]	0.91 (0.84, 0.99)	0.90 (0.82, 0.98)	0.81 (0.69, 0.94)

Table 18: Drug Interactions: Pharmacokinetic Parameters for Atazanavir in the Presence of Coadministered Drugs[a]

Coadministered Drug	Coadministered Drug Dose/Schedule	REYATAZ Dose/Schedule	Ratio (90% Confidence Interval) of Atazanavir Pharmacokinetic Parameters with/without Coadministered Drug; No Effect = 1.00		
			C_{max}	AUC	C_{min}
	40 mg QD (pm), d 18–24 (n=20)	300 mg QD/ritonavir 100 mg QD/tenofovir 300 mg QD, d 1–10 (am) (n=39), d 18–24 (am) (12 h after pm famotidine) (n=20)[f]	0.89 (0.81, 0.97)	0.88 (0.80, 0.96)	0.77 (0.63, 0.93)
	40 mg BID, d 18–24 (n=18)	300 mg QD/ritonavir 100 mg QD/tenofovir 300 mg QD, d 1–10 (am) (n=39), d 18–24 (am) (10 h after pm famotidine and 2 h before am famotidine) (n=18)[f]	0.74 (0.66, 0.84)	0.79 (0.70, 0.88)	0.72 (0.63, 0.83)
	40 mg BID, d 11–20 (n=15)	300 mg QD/ritonavir 100 mg QD, d 1–10 (am) (n=46), then 400 mg QD/ritonavir 100 mg QD, d 11–20 (am) (n=15)	1.02 (0.87, 1.18)	1.03 (0.86, 1.22)	0.86 (0.68, 1.08)
fluconazole	200 mg QD, d 11–20 (n=29)	300 mg QD/ritonavir 100 mg QD, d 1–10 (n=19), d 11–20 (n=29)	1.03 (0.95, 1.11)	1.04 (0.95, 1.13)	0.98 (0.85, 1.13)
ketoconazole	200 mg QD, d 7–13 (n=14)	400 mg QD, d 1–13 (n=14)	0.99 (0.77, 1.28)	1.10 (0.89, 1.37)	1.03 (0.53, 2.01)
nevirapine[g,h]	200 mg BID, d 1–23 (n=23)	300 mg QD/ritonavir 100 mg QD, d 4–13, then 400 mg QD/ritonavir 100 mg QD, d 14–23 (n=23)[i]	0.72 (0.60, 0.86) 1.02 (0.85, 1.24)	0.58 (0.48, 0.71) 0.81 (0.65, 1.02)	0.28 (0.20, 0.40) 0.41 (0.27, 0.60)
omeprazole	40 mg QD, d 7–12 (n=16)[j]	400 mg QD, d 1–6 (n=48), d 7–12 (n=16)	0.04 (0.04, 0.05)	0.06 (0.05, 0.07)	0.05 (0.03, 0.07)
	40 mg QD, d 11–20 (n=15)[j]	300 mg QD/ritonavir 100 mg QD, d 1–20 (n=15)	0.28 (0.24, 0.32)	0.24 (0.21, 0.27)	0.22 (0.19, 0.26)
	20 mg QD, d 17–23 (am) (n=13)	300 mg QD/ritonavir 100 mg QD, d 7–16 (pm) (n=27), d 17–23 (pm) (n=13)[k,l]	0.61 (0.46, 0.81)	0.58 (0.44, 0.75)	0.54 (0.41, 0.71)
	20 mg QD, d 17–23 (am) (n=14)	300 mg QD/ritonavir 100 mg QD, d 7–16 (am) (n=27), then 400 mg QD/ritonavir 100 mg QD, d 17–23 (am) (n=14)[m,n]	0.69 (0.58, 0.83)	0.70 (0.57, 0.86)	0.69 (0.54, 0.88)
rifabutin	150 mg QD, d 15–28 (n=7)	400 mg QD, d 1–28 (n=7)	1.34 (1.14, 1.59)	1.15 (0.98, 1.34)	1.13 (0.68, 1.87)

Table 18: Drug Interactions: Pharmacokinetic Parameters for Atazanavir in the Presence of Coadministered Drugs[a]

Coadministered Drug	Coadministered Drug Dose/Schedule	REYATAZ Dose/Schedule	Ratio (90% Confidence Interval) of Atazanavir Pharmacokinetic Parameters with/without Coadministered Drug; No Effect = 1.00		
			C_{max}	AUC	C_{min}
rifampin	600 mg QD, d 17–26 (n=16)	300 mg QD/ritonavir 100 mg QD, d 7–16 (n=48), d 17–26 (n=16)	0.47 (0.41, 0.53)	0.28 (0.25, 0.32)	0.02 (0.02, 0.03)
ritonavir[o]	100 mg QD, d 11–20 (n=28)	300 mg QD, d 1–20 (n=28)	1.86 (1.69, 2.05)	3.38 (3.13, 3.63)	11.89 (10.23, 13.82)
tenofovir[p]	300 mg QD, d 9–16 (n=34)	400 mg QD, d 2–16 (n=34)	0.79 (0.73, 0.86)	0.75 (0.70, 0.81)	0.60 (0.52, 0.68)
	300 mg QD, d 15–42 (n=10)	300 mg/ritonavir 100 mg QD, d 1–42 (n=10)	0.72[q] (0.50, 1.05)	0.75[q] (0.58, 0.97)	0.77[q] (0.54, 1.10)

[a] Data provided are under fed conditions unless otherwise noted.

[b] All drugs were given under fasted conditions.

[c] 400 mg ddI EC and REYATAZ were administered together with food on Days 8 and 19.

[d] REYATAZ 300 mg plus ritonavir 100 mg once daily coadministered with famotidine 40 mg twice daily resulted in atazanavir geometric mean C_{max} that was similar and AUC and C_{min} values that were 1.79- and 4.46-fold higher relative to REYATAZ 400 mg once daily alone.

[e] Similar results were noted when famotidine 20 mg BID was administered 2 hours after and 10 hours before atazanavir 300 mg and ritonavir 100 mg plus tenofovir 300 mg.

[f] Atazanavir/ritonavir/tenofovir was administered after a light meal.

[g] Study was conducted in HIV-infected individuals.

[h] Compared with atazanavir 400 mg historical data without nevirapine (n=13), the ratio of geometric means (90% confidence intervals) for $C_{max,}$ AUC, and C_{min} were 1.42 (0.98, 2.05), 1.64 (1.11, 2.42), and 1.25 (0.66, 2.36), respectively, for atazanavir/ritonavir 300/100 mg; and 2.02 (1.42, 2.87), 2.28 (1.54, 3.38), and 1.80 (0.94, 3.45), respectively, for atazanavir/ritonavir 400/100 mg.

[i] Parallel group design; n=23 for atazanavir/ritonavir plus nevirapine, n=22 for atazanavir 300 mg/ritonavir 100 mg without nevirapine. Subjects were treated with nevirapine prior to study entry.

[j] Omeprazole 40 mg was administered on an empty stomach 2 hours before REYATAZ.

[k] Omeprazole 20 mg was administered 30 minutes prior to a light meal in the morning and REYATAZ 300 mg plus ritonavir 100 mg in the evening after a light meal, separated by 12 hours from omeprazole.

[l] REYATAZ 300 mg plus ritonavir 100 mg once daily separated by 12 hours from omeprazole 20 mg daily resulted in increases in atazanavir geometric mean AUC (10%) and C_{min} (2.4-fold), with a decrease in C_{max} (29%) relative to REYATAZ 400 mg once daily in the absence of omeprazole (study days 1–6).

[m] Omeprazole 20 mg was given 30 minutes prior to a light meal in the morning and REYATAZ 400 mg plus ritonavir 100 mg once daily after a light meal, 1 hour after omeprazole. Effects on atazanavir concentrations were similar when REYATAZ 400 mg plus ritonavir 100 mg was separated from omeprazole 20 mg by 12 hours.

[n] REYATAZ 400 mg plus ritonavir 100 mg once daily administered with omeprazole 20 mg once daily resulted in increases in

Table 18: Drug Interactions: Pharmacokinetic Parameters for Atazanavir in the Presence of Coadministered Drugs[a]

Coadministered Drug	Coadministered Drug Dose/Schedule	REYATAZ Dose/Schedule	Ratio (90% Confidence Interval) of Atazanavir Pharmacokinetic Parameters with/without Coadministered Drug; No Effect = 1.00		
			C_{max}	AUC	C_{min}

atazanavir geometric mean AUC (32%) and C_{min} (3.3-fold), with a decrease in C_{max} (26%) relative to REYATAZ 400 mg once daily in the absence of omeprazole (study days 1–6).

[o] Compared with atazanavir 400 mg QD historical data, administration of atazanavir/ritonavir 300/100 mg QD increased the atazanavir geometric mean values of C_{max}, AUC, and C_{min} by 18%, 103%, and 671%, respectively.

[p] Note that similar results were observed in studies where administration of tenofovir and REYATAZ was separated by 12 hours.

[q] Ratio of atazanavir plus ritonavir plus tenofovir to atazanavir plus ritonavir. Atazanavir 300 mg plus ritonavir 100 mg results in higher atazanavir exposure than atazanavir 400 mg (see footnote[o]). The geometric mean values of atazanavir pharmacokinetic parameters when coadministered with ritonavir and tenofovir were: C_{max} = 3190 ng/mL, AUC = 34459 ng•h/mL, and C_{min} = 491 ng/mL. Study was conducted in HIV-infected individuals.

Table 19: Drug Interactions: Pharmacokinetic Parameters for Coadministered Drugs in the Presence of REYATAZ[a]

Coadministered Drug	Coadministered Drug Dose/Schedule	REYATAZ Dose/Schedule	Ratio (90% Confidence Interval) of Coadministered Drug Pharmacokinetic Parameters with/without REYATAZ; No Effect = 1.00		
			C_{max}	AUC	C_{min}
acetaminophen	1 gm BID, d 1–20 (n=10)	300 mg QD/ritonavir 100 mg QD, d 11–20 (n=10)	0.87 (0.77, 0 99)	0 97 (0 91, 1.03)	1 26 (1.08, 1.46)
atenolol	50 mg QD, d 7–11 (n=19) and d 19–23	400 mg QD, d 1–11 (n=19)	1.34 (1.26, 1.42)	1.25 (1.16, 1.34)	1.02 (0.88, 1.19)
clarithromycin	500 mg BID, d 7–10 (n=21) and d 18–21	400 mg QD, d 1–10 (n=21)	1.50 (1.32, 1.71) OH-clarithromycin: 0.28 (0.24, 0.33)	1.94 (1.75, 2.16) OH-clarithromycin: 0.30 (0.26, 0.34)	2.60 (2.35, 2.88) OH-clarithromycin: 0.38 (0.34, 0.42)
didanosine (ddI) (buffered tablets) plus stavudine (d4T)[b]	ddI: 200 mg x 1 dose, d4T: 40 mg x 1 dose (n=31)	400 mg x 1 dose simultaneous with ddI and d4T (n=31)	ddI: 0.92 (0.84, 1.02) d4T: 1.08 (0 96, 1 22)	ddI: 0.98 (0 92, 1.05) d4T: 1.00 (0 97, 1.03)	NA d4T: 1.04 (0.94, 1 16)
ddI (enteric-coated [EC] capsules)[c]	400 mg d 1 (fasted), d 8 (fed) (n=34)	400 mg QD, d 2–8 (n=34)	0.64 (0 55, 0.74)	0.66 (0.60, 0.74)	1 13 (0 91, 1.41)
	400 mg d 1 (fasted), d 19 (fed) (n=31)	300 mg QD/ritonavir 100 mg QD, d 9–19 (n=31)	0.62 (0 52, 0.74)	0.66 (0 59, 0.73)	1 25 (0 92, 1.69)
diltiazem	180 mg QD, d 7–11 (n=28) and d 19–23	400 mg QD, d 1–11 (n=28)	1 98 (1.78, 2 19) desacetyl-diltiazem: 2.72 (2.44, 3.03)	2 25 (2.09, 2.16) desacetyl-diltiazem: 2.65 (2.45, 2.87)	2.42 (2 14, 2.73) desacetyl-diltiazem: 2 21 (2.02, 2.42)
ethinyl estradiol & norethindrone[d]	Ortho-Novum® 7/7/7 QD, d 1–29 (n=19)	400 mg QD, d 16–29 (n=19)	ethinyl estradiol: 1.15 (0.99, 1.32) norethindrone: 1.67 (1.42, 1.96)	ethinyl estradiol: 1.48 (1 31, 1.68) norethindrone: 2.10 (1.68, 2.62)	ethinyl estradiol: 1.91 (1.57, 2.33) norethindrone: 3.62 (2 57, 5.09)
ethinyl estradiol & norgestimate[e]	Ortho Tri-Cyclen® QD, d 1–28 (n=18), then Ortho Tri-Cyclen® LO QD, d 29–42[f] (n=14)	300 mg QD/ritonavir 100 mg QD, d 29–42 (n=14)	ethinyl estradiol: 0.84 (0.74, 0.95) 17-deacetyl norgestimate:[g] 1.68 (1.51, 1.88)	ethinyl estradiol: 0.81 (0.75, 0.87) 17-deacetyl norgestimate:[g] 1.85 (1.67, 2.05)	ethinyl estradiol: 0.63 (0.55, 0.71) 17-deacetyl norgestimate:[g] 2.02 (1.77, 2.31)
fluconazole	200 mg QD, d 1–10 (n=11) and 200 mg QD, d 11–20 (n=29)	300 mg QD/ritonavir 100 mg QD, d 11–20 (n=29)	1.05 (0 99, 1 10)	1.08 (1.02, 1.15)	1.07 (1.00, 1.15)

Table 19: Drug Interactions: Pharmacokinetic Parameters for Coadministered Drugs in the Presence of REYATAZ[a]

Coadministered Drug	Coadministered Drug Dose/Schedule	REYATAZ Dose/Schedule	Ratio (90% Confidence Interval) of Coadministered Drug Pharmacokinetic Parameters with/without REYATAZ; No Effect = 1.00		
			C_{max}	AUC	C_{min}
methadone	Stable maintenance dose, d 1–15 (n=16)	400 mg QD, d 2–15 (n=16)	(R)-methadone[h] 0 91 (0.84, 1.0) total: 0.85 (0.78, 0 93)	(R)-methadone[h] 1.03 (0 95, 1 10) total: 0.94 (0.87, 1.02)	(R)-methadone[h] 1 11 (1.02, 1 20) total: 1.02 (0 93, 1 12)
nevirapine[i,j]	200 mg BID, d 1–23 (n=23)	300 mg QD/ ritonavir 100 mg QD, d 4–13, then	1.17 (1.09, 1.25)	1.25 (1.17, 1.34)	1.32 (1.22, 1.43)
		400 mg QD/ ritonavir 100 mg QD, d 14–23 (n=23)	1.21 (1.11, 1.32)	1.26 (1.17, 1.36)	1.35 (1.25, 1.47)
omeprazole[k]	40 mg single dose, d 7 and d 20 (n=16)	400 mg QD, d 1–12 (n=16)	1.24 (1.04, 1.47)	1.45 (1.20, 1.76)	NA
rifabutin	300 mg QD, d 1–10 then 150 mg QD, d 11–20 (n=3)	600 mg QD,[l] d 11–20 (n=3)	1 18 (0.94, 1.48) 25-O-desacetyl-rifabutin: 8.20 (5.90, 11.40)	2.10 (1.57, 2.79) 25-O-desacetyl-rifabutin: 22.01 (15.97, 30 34)	3.43 (1.98, 5.96) 25-O-desacetyl-rifabutin: 75.6 (30.1, 190.0)
	150 mg twice weekly, d 1–15 (n=7)	300 mg QD/ ritonavir 100 mg QD, d 1–17 (n=7)	2.49[m] (2.03, 3.06) 25-O-desacetyl-rifabutin: 7.77 (6.13, 9.83)	1.48[m] (1.19, 1.84) 25-O-desacetyl-rifabutin: 10.90 (8.14, 14.61)	1.40[m] (1.05, 1.87) 25-O-desacetyl-rifabutin: 11.45 (8.15, 16.10)
rosiglitazone[n]	4 mg single dose, d 1, 7, 17 (n=14)	400 mg QD, d 2–7, then	1.08 (1.03, 1.13)	1.35 (1.26, 1.44)	NA
		300 mg QD/ ritonavir 100 mg QD, d 8–17 (n=14)	0.97 (0.91, 1.04)	0.83 (0.77, 0.89)	NA
saquinavir[o] (soft gelatin capsules)	1200 mg QD, d 1–13 (n=7)	400 mg QD, d 7–13 (n=7)	4.39 (3.24, 5.95)	5.49 (4.04, 7.47)	6.86 (5.29, 8.91)
tenofovir[p]	300 mg QD, d 9–16 (n=33) and d 24–30 (n=33)	400 mg QD, d 2–16 (n=33)	1.14 (1.08, 1.20)	1.24 (1.21, 1.28)	1.22 (1.15, 1.30)
	300 mg QD, d 1–7 (pm) (n=14) d 25–34 (pm) (n=12)	300 mg QD/ritonavir 100 mg QD, d 25–34 (am) (n=12)[q]	1 34 (1 20, 1 51)	1 37 (1 30, 1.45)	1 29 (1 21, 1.36)

Table 19: Drug Interactions: Pharmacokinetic Parameters for Coadministered Drugs in the Presence of REYATAZ[a]

Coadministered Drug	Coadministered Drug Dose/Schedule	REYATAZ Dose/Schedule	Ratio (90% Confidence Interval) of Coadministered Drug Pharmacokinetic Parameters with/without REYATAZ; No Effect = 1.00		
			C_{max}	AUC	C_{min}
lamivudine + zidovudine	150 mg lamivudine + 300 mg zidovudine BID, d 1–12 (n=19)	400 mg QD, d 7–12 (n=19)	lamivudine: 1.04 (0 92, 1 16) zidovudine: 1.05 (0.88, 1 24) zidovudine glucuronide: 0.95 (0.88, 1.02)	lamivudine: 1.03 (0 98, 1.08) zidovudine: 1.05 (0 96, 1 14) zidovudine glucuronide: 1.00 (0 97, 1.03)	lamivudine: 1.12 (1.04, 1.21) zidovudine: 0.69 (0 57, 0.84) zidovudine glucuronide: 0.82 (0.62, 1.08)

[a] Data provided are under fed conditions unless otherwise noted.

[b] All drugs were given under fasted conditions.

[c] 400 mg ddI EC and REYATAZ were administered together with food on Days 8 and 19.

[d] Upon further dose normalization of ethinyl estradiol 25 mcg with atazanavir relative to ethinyl estradiol 35 mcg without atazanavir, the ratio of geometric means (90% confidence intervals) for C_{max}, AUC, and C_{min} were 0.82 (0.73, 0.92), 1.06 (0.95, 1.17), and 1.35 (1.11, 1.63), respectively.

[e] Upon further dose normalization of ethinyl estradiol 35 mcg with atazanavir/ritonavir relative to ethinyl estradiol 25 mcg without atazanavir/ritonavir, the ratio of geometric means (90% confidence intervals) for C_{max}, AUC, and C_{min} were 1.17 (1.03, 1.34), 1.13 (1.05, 1.22), and 0.88 (0.77, 1.00), respectively.

[f] All subjects were on a 28 day lead-in period; one full cycle of Ortho Tri-Cyclen®. Ortho Tri-Cyclen® contains 35 mcg of ethinyl estradiol. Ortho Tri-Cyclen® LO contains 25 mcg of ethinyl estradiol. Results were dose normalized to an ethinyl estradiol dose of 35 mcg.

[g] 17-deacetyl norgestimate is the active component of norgestimate.

[h] (R)-methadone is the active isomer of methadone.

[i] Study was conducted in HIV-infected individuals.

[j] Subjects were treated with nevirapine prior to study entry.

[k] Omeprazole was used as a metabolic probe for CYP2C19. Omeprazole was given 2 hours after REYATAZ on Day 7; and was given alone 2 hours after a light meal on Day 20.

[l] Not the recommended therapeutic dose of atazanavir.

[m] When compared to rifabutin 150 mg QD alone d1–10 (n=14). Total of Rifabutin + 25-O-desacetyl-rifabutin: AUC 2.19 (1.78, 2.69).

[n] Rosiglitazone used as a probe substrate for CYP2C8.

[o] The combination of atazanavir and saquinavir 1200 mg QD produced daily saquinavir exposures similar to the values produced by the standard therapeutic dosing of saquinavir at 1200 mg TID. However, the C_{max} is about 79% higher than that for the standard dosing of saquinavir (soft gelatin capsules) alone at 1200 mg TID.

[p] Note that similar results were observed in a study where administration of tenofovir and REYATAZ was separated by 12 hours.

[q] Administration of tenofovir and REYATAZ was temporally separated by 12 hours.

NA = not available.

12.4 Microbiology

Mechanism of Action

Atazanavir (ATV) is an azapeptide HIV-1 protease inhibitor (PI). The compound selectively inhibits the virus-specific processing of viral Gag and Gag-Pol polyproteins in HIV-1 infected cells, thus preventing formation of mature virions.

Antiviral Activity in Cell Culture

Atazanavir exhibits anti-HIV-1 activity with a mean 50% effective concentration (EC_{50}) in the absence of human serum of 2 to 5 nM against a variety of laboratory and clinical HIV-1 isolates grown in peripheral blood mononuclear cells, macrophages, CEM-SS cells, and MT-2 cells. ATV has activity against HIV-1 Group M subtype viruses A, B, C, D, AE, AG, F, G, and J isolates in cell culture. ATV has variable activity against HIV-2 isolates (1.9 to 32 nM), with EC_{50} values above the EC_{50} values of failure isolates. Two-drug combination antiviral activity studies with ATV showed no antagonism in cell culture with NNRTIs (delavirdine, efavirenz, and nevirapine), PIs (amprenavir, indinavir, lopinavir, nelfinavir, ritonavir, and saquinavir), NRTIs (abacavir, didanosine, emtricitabine, lamivudine, stavudine, tenofovir, zalcitabine, and zidovudine), the HIV-1 fusion inhibitor enfuvirtide, and two compounds used in the treatment of viral hepatitis, adefovir and ribavirin, without enhanced cytotoxicity.

Resistance

In Cell Culture: HIV-1 isolates with a decreased susceptibility to ATV have been selected in cell culture and obtained from patients treated with ATV or atazanavir/ritonavir (ATV/RTV). HIV-1 isolates with 93- to 183-fold reduced susceptibility to ATV from three different viral strains were selected in cell culture by 5 months. The substitutions in these HIV-1 viruses that contributed to ATV resistance include I50L, N88S, I84V, A71V, and M46I. Changes were also observed at the protease cleavage sites following drug selection. Recombinant viruses containing the I50L substitution without other major PI substitutions were growth impaired and displayed increased susceptibility in cell culture to other PIs (amprenavir, indinavir, lopinavir, nelfinavir, ritonavir, and saquinavir). The I50L and I50V substitutions yielded selective resistance to ATV and amprenavir, respectively, and did not appear to be cross-resistant.

Clinical Studies of Treatment-Naive Patients: Comparison of Ritonavir-Boosted REYATAZ vs. Unboosted REYATAZ: Study AI424-089 compared REYATAZ 300 mg once daily with ritonavir 100 mg vs. REYATAZ 400 mg once daily when administered with lamivudine and extended-release stavudine in HIV-infected treatment-naive patients. A summary of the number of

virologic failures and virologic failure isolates with ATV resistance in each arm is shown in Table 20.

Table 20: Summary of Virologic Failures[a] at Week 96 in Study AI424-089: Comparison of Ritonavir Boosted REYATAZ vs. Unboosted REYATAZ: Randomized Patients

	REYATAZ 300 mg + ritonavir 100 mg (n=95)	REYATAZ 400 mg (n=105)
Virologic Failure (≥50 copies/mL) at Week 96	15 (16%)	34 (32%)
Virologic Failure with Genotypes and Phenotypes Data	5	17
Virologic Failure Isolates with ATV-resistance at Week 96	0/5 (0%)[b]	4/17 (24%)[b]
Virologic Failure Isolates with I50L Emergence at Week 96[c]	0/5 (0%)[b]	2/17 (12%)[b]
Virologic Failure Isolates with Lamivudine Resistance at Week 96	2/5 (40%)[b]	11/17 (65%)[b]

[a] Virologic failure includes patients who were never suppressed through Week 96 and on study at Week 96, had virologic rebound or discontinued due to insufficient viral load response.

[b] Percentage of Virologic Failure Isolates with genotypic and phenotypic data.

[c] Mixture of I50I/L emerged in 2 other ATV 400 mg-treated patients. Neither isolate was phenotypically resistant to ATV.

Clinical Studies of Treatment-Naive Patients Receiving REYATAZ 300 mg With Ritonavir 100 mg: In Phase III study AI424-138, an as-treated genotypic and phenotypic analysis was conducted on samples from patients who experienced virologic failure (HIV-1 RNA ≥400 copies/mL) or discontinued before achieving suppression on ATV/RTV (n=39; 9%) and LPV/RTV (n=39; 9%) through 96 weeks of treatment. In the ATV/RTV arm, one of the virologic failure isolates had a 56-fold decrease in ATV susceptibility emerge on therapy with the development of PI resistance-associated substitutions L10F, V32I, K43T, M46I, A71I, G73S, I85I/V, and L90M. The NRTI resistance-associated substitution M184V also emerged on treatment in this isolate conferring emtricitabine resistance. Two ATV/RTV-virologic failure isolates had baseline phenotypic ATV resistance and IAS-defined major PI resistance-associated substitutions at baseline. The I50L substitution emerged on study in one of these failure isolates and was associated with a 17-fold decrease in ATV susceptibility from baseline and the other failure isolate with baseline ATV resistance and PI substitutions (M46M/I and I84I/V) had additional IAS-defined major PI substitutions (V32I, M46I, and I84V) emerge on ATV treatment associated with a 3-fold decrease in ATV susceptibility from baseline. Five of the treatment failure isolates in the ATV/RTV arm developed phenotypic emtricitabine resistance with the

emergence of either the M184I (n=1) or the M184V (n=4) substitution on therapy and none developed phenotypic tenofovir disoproxil resistance. In the LPV/RTV arm, one of the virologic failure patient isolates had a 69-fold decrease in LPV susceptibility emerge on therapy with the development of PI substitutions L10V, V11I, I54V, G73S, and V82A in addition to baseline PI substitutions L10L/I, V32I, I54I/V, A71I, G73G/S, V82V/A, L89V, and L90M. Six LPV/RTV virologic failure isolates developed the M184V substitution and phenotypic emtricitabine resistance and two developed phenotypic tenofovir disoproxil resistance.

Clinical Studies of Treatment-Naive Patients Receiving REYATAZ 400 mg Without Ritonavir: ATV-resistant clinical isolates from treatment-naive patients who experienced virologic failure on REYATAZ 400 mg treatment without ritonavir often developed an I50L substitution (after an average of 50 weeks of ATV therapy), often in combination with an A71V substitution, but also developed one or more other PI substitutions (eg, V32I, L33F, G73S, V82A, I85V, or N88S) with or without the I50L substitution. In treatment-naive patients, viral isolates that developed the I50L substitution, without other major PI substitutions, showed phenotypic resistance to ATV but retained in cell culture susceptibility to other PIs (amprenavir, indinavir, lopinavir, nelfinavir, ritonavir, and saquinavir); however, there are no clinical data available to demonstrate the effect of the I50L substitution on the efficacy of subsequently administered PIs.

Clinical Studies of Treatment-Experienced Patients: In studies of treatment-experienced patients treated with ATV or ATV/RTV, most ATV-resistant isolates from patients who experienced virologic failure developed substitutions that were associated with resistance to multiple PIs and displayed decreased susceptibility to multiple PIs. The most common protease substitutions to develop in the viral isolates of patients who failed treatment with ATV 300 mg once daily and RTV 100 mg once daily (together with tenofovir and an NRTI) included V32I, L33F/V/I, E35D/G, M46I/L, I50L, F53L/V, I54V, A71V/T/I, G73S/T/C, V82A/T/L, I85V, and L89V/Q/M/T. Other substitutions that developed on ATV/RTV treatment including E34K/A/Q, G48V, I84V, N88S/D/T, and L90M occurred in less than 10% of patient isolates. Generally, if multiple PI resistance substitutions were present in the HIV-1 virus of the patient at baseline, ATV resistance developed through substitutions associated with resistance to other PIs and could include the development of the I50L substitution. The I50L substitution has been detected in treatment-experienced patients experiencing virologic failure after long-term treatment. Protease cleavage site changes also emerged on ATV treatment but their presence did not correlate with the level of ATV resistance.

Cross-Resistance

Cross-resistance among PIs has been observed. Baseline phenotypic and genotypic analyses of clinical isolates from ATV clinical trials of PI-experienced patients showed that isolates cross-resistant to multiple PIs were cross-resistant to ATV. Greater than 90% of the isolates with substitutions that included I84V or G48V were resistant to ATV. Greater than 60% of isolates containing L90M, G73S/T/C, A71V/T, I54V, M46I/L, or a change at V82 were resistant to ATV, and 38% of isolates containing a D30N substitution in addition to other changes were resistant to ATV. Isolates resistant to ATV were also cross-resistant to other PIs with >90% of the isolates resistant to indinavir, lopinavir, nelfinavir, ritonavir, and saquinavir, and 80% resistant to amprenavir. In treatment-experienced patients, PI-resistant viral isolates that developed the I50L substitution in addition to other PI resistance-associated substitution were also cross-resistant to other PIs.

Baseline Genotype/Phenotype and Virologic Outcome Analyses

Genotypic and/or phenotypic analysis of baseline virus may aid in determining ATV susceptibility before initiation of ATV/RTV therapy. An association between virologic response at 48 weeks and the number and type of primary PI resistance-associated substitutions detected in baseline HIV-1 isolates from antiretroviral-experienced patients receiving ATV/RTV once daily or lopinavir (LPV)/RTV twice daily in Study AI424-045 is shown in Table 21.

Overall, both the number and type of baseline PI substitutions affected response rates in treatment-experienced patients. In the ATV/RTV group, patients had lower response rates when 3 or more baseline PI substitutions, including a substitution at position 36, 71, 77, 82, or 90, were present compared to patients with 1–2 PI substitutions, including one of these substitutions.

Table 21: HIV RNA Response by Number and Type of Baseline PI Substitution, Antiretroviral-Experienced Patients in Study AI424-045, As-Treated Analysis

	Virologic Response = HIV RNA <400 copies/mL[b]	
Number and Type of Baseline PI Substitutions[a]	**ATV/RTV (n=110)**	**LPV/RTV (n=113)**
3 or more primary PI substitutions including:[c]		
D30N	75% (6/8)	50% (3/6)
M36I/V	19% (3/16)	33% (6/18)
M46I/L/T	24% (4/17)	23% (5/22)

Table 21: HIV RNA Response by Number and Type of Baseline PI Substitution, Antiretroviral-Experienced Patients in Study AI424-045, As-Treated Analysis

I54V/L/T/M/A	31% (5/16)	31% (5/16)
A71V/T/I/G	34% (10/29)	39% (12/31)
G73S/A/C/T	14% (1/7)	38% (3/8)
V77I	47% (7/15)	44% (7/16)
V82A/F/T/S/I	29% (6/21)	27% (7/26)
I84V/A	11% (1/9)	33% (2/6)
N88D	63% (5/8)	67% (4/6)
L90M	10% (2/21)	44% (11/25)
Number of baseline primary PI substitutions[a]		
All patients, as-treated	58% (64/110)	59% (67/113)
0–2 PI substitutions	75% (50/67)	75% (50/67)
3–4 PI substitutions	41% (14/34)	43% (12/28)
5 or more PI substitutions	0% (0/9)	28% (5/18)

[a] Primary substitutions include any change at D30, V32, M36, M46, I47, G48, I50, I54, A71, G73, V77, V82, I84, N88, and L90.
[b] Results should be interpreted with caution because the subgroups were small.
[c] There were insufficient data (n<3) for PI substitutions V32I, I47V, G48V, I50V, and F53L.

The response rates of antiretroviral-experienced patients in Study AI424-045 were analyzed by baseline phenotype (shift in susceptibility in cell culture relative to reference, Table 22). The analyses are based on a select patient population with 62% of patients receiving an NNRTI-based regimen before study entry compared to 35% receiving a PI-based regimen. Additional data are needed to determine clinically relevant break points for REYATAZ.

Table 22: Baseline Phenotype by Outcome, Antiretroviral-Experienced Patients in Study AI424-045, As-Treated Analysis

Baseline Phenotype[a]	**Virologic Response = HIV RNA <400 copies/mL[b]**	
	ATV/RTV (n=111)	**LPV/RTV (n=111)**
0–2	71% (55/78)	70% (56/80)
>2–5	53% (8/15)	44% (4/9)
>5–10	13% (1/8)	33% (3/9)
>10	10% (1/10)	23% (3/13)

[a] Fold change susceptibility in cell culture relative to the wild-type reference.
[b] Results should be interpreted with caution because the subgroups were small.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

Long-term carcinogenicity studies in mice and rats were carried out with atazanavir for two years. In the mouse study, drug-related increases in hepatocellular adenomas were found in females at 360 mg/kg/day. The systemic drug exposure (AUC) at the NOAEL (no observable adverse effect level) in females, (120 mg/kg/day) was 2.8 times and in males (80 mg/kg/day) was 2.9 times higher than those in humans at the clinical dose (300 mg/day atazanavir boosted with 100 mg/day ritonavir, non-pregnant patients). In the rat study, no drug-related increases in tumor incidence were observed at doses up to 1200 mg/kg/day, for which AUCs were 1.1 (males) or 3.9 (females) times those measured in humans at the clinical dose.

Mutagenesis

Atazanavir tested positive in an *in vitro* clastogenicity test using primary human lymphocytes, in the absence and presence of metabolic activation. Atazanavir tested negative in the *in vitro* Ames reverse-mutation assay, *in vivo* micronucleus and DNA repair tests in rats, and *in vivo* DNA damage test in rat duodenum (comet assay).

Impairment of Fertility

At the systemic drug exposure levels (AUC) 0.9 (in male rats) or 2.3 (in female rats) times that of the human clinical dose, (300 mg/day atazanavir boosted with 100 mg/day ritonavir) significant effects on mating, fertility, or early embryonic development were not observed.

14 CLINICAL STUDIES

14.1 Adult Patients Without Prior Antiretroviral Therapy

Study AI424-138: a 96-week study comparing the antiviral efficacy and safety of atazanavir/ritonavir with lopinavir/ritonavir, each in combination with fixed-dose tenofovir-emtricitabine in HIV-1 infected treatment naive subjects. Study AI424-138 is a 96-week open-label, randomized, multicenter study, comparing REYATAZ (300 mg once daily) with ritonavir (100 mg once daily) to lopinavir with ritonavir (400/100 mg twice daily), each in combination with fixed-dose tenofovir with emtricitabine (300/200 mg once daily), in 878 antiretroviral treatment-naive treated patients. Patients had a mean age of 36 years (range: 19–72), 49% were

Caucasian, 18% Black, 9% Asian, 23% Hispanic/Mestizo/mixed race, and 68% were male. The median baseline plasma CD4+ cell count was 204 cells/mm^3 (range: 2 to 810 cells/mm^3) and the mean baseline plasma HIV-1 RNA level was 4.94 log_{10} copies/mL (range: 2.60 to 5.88 log_{10} copies/mL). Treatment response and outcomes through Week 96 are presented in Table 23.

Table 23: Outcomes of Treatment Through Week 96 (Study AI424-138)

Outcome	REYATAZ 300 mg + ritonavir 100 mg (once daily) with tenofovir/emtricitabine (once daily)[a] (n=441) 96 Weeks	lopinavir 400 mg + ritonavir 100 mg (twice daily) with tenofovir/emtricitabine (once daily)[a] (n=437) 96 Weeks
Responder[b,c,d]	75%	68%
Virologic failure[e]	17%	19%
Rebound	8%	10%
Never suppressed through Week 96	9%	9%
Death	1%	1%
Discontinued due to adverse event	3%	5%
Discontinued for other reasons[f]	4%	7%

[a] As a fixed-dose combination: 300 mg tenofovir, 200 mg emtricitabine once daily.

[b] Patients achieved HIV RNA <50 copies/mL at Week 96. Roche Amplicor®, v1.5 ultra-sensitive assay.

[c] Pre-specified ITT analysis at Week 48 using as-randomized cohort: ATV/RTV 78% and LPV/RTV 76% [difference estimate: 1.7% (95% confidence interval: −3.8%, 7.1%)].

[d] Pre-specified ITT analysis at Week 96 using as-randomized cohort: ATV/RTV 74% and LPV/RTV 68% [difference estimate: 6.1% (95% confidence interval: 0.3%, 12.0%)].

[e] Includes viral rebound and failure to achieve confirmed HIV RNA <50 copies/mL through Week 96.

[f] Includes lost to follow-up, patient's withdrawal, noncompliance, protocol violation, and other reasons.

Through 96 weeks of therapy, the proportion of responders among patients with high viral loads (ie, baseline HIV RNA ≥100,000 copies/mL) was comparable for the REYATAZ/ritonavir (165 of 223 patients, 74%) and lopinavir/ritonavir (148 of 222 patients, 67%) arms. At 96 weeks, the median increase from baseline in CD4+ cell count was 261 cells/mm^3 for the REYATAZ/ritonavir arm and 273 cells/mm^3 for the lopinavir/ritonavir arm.

Study AI424-034: REYATAZ once daily compared to efavirenz once daily, each in combination with fixed-dose lamivudine + zidovudine twice daily. Study AI424-034 was a randomized, double-blind, multicenter trial comparing REYATAZ (400 mg once daily) to efavirenz (600 mg once daily), each in combination with a fixed-dose combination of lamivudine (3TC) (150 mg)

and zidovudine (ZDV) (300 mg) given twice daily, in 810 antiretroviral treatment-naive patients. Patients had a mean age of 34 years (range: 18 to 73), 36% were Hispanic, 33% were Caucasian, and 65% were male. The mean baseline CD4+ cell count was 321 cells/mm^3 (range: 64 to 1424 cells/mm^3) and the mean baseline plasma HIV-1 RNA level was 4.8 log_{10} copies/mL (range: 2.2 to 5.9 log_{10} copies/mL). Treatment response and outcomes through Week 48 are presented in Table 24.

Table 24: Outcomes of Randomized Treatment Through Week 48 (Study AI424-034)

Outcome	REYATAZ 400 mg once daily + lamivudine + zidovudine[d] (n=405)	efavirenz 600 mg once daily + lamivudine + zidovudine[d] (n=405)
Responder[a]	67% (32%)	62% (37%)
Virologic failure[b]	20%	21%
Rebound	17%	16%
Never suppressed through Week 48	3%	5%
Death	–	<1%
Discontinued due to adverse event	5%	7%
Discontinued for other reasons[c]	8%	10%

[a] Patients achieved and maintained confirmed HIV RNA <400 copies/mL (<50 copies/mL) through Week 48. Roche Amplicor® HIV-1 Monitor™ Assay, test version 1.0 or 1.5 as geographically appropriate.
[b] Includes viral rebound and failure to achieve confirmed HIV RNA <400 copies/mL through Week 48.
[c] Includes lost to follow-up, patient's withdrawal, noncompliance, protocol violation, and other reasons.
[d] As a fixed-dose combination: 150 mg lamivudine, 300 mg zidovudine twice daily.

Through 48 weeks of therapy, the proportion of responders among patients with high viral loads (ie, baseline HIV RNA ≥100,000 copies/mL) was comparable for the REYATAZ and efavirenz arms. The mean increase from baseline in CD4+ cell count was 176 cells/mm^3 for the REYATAZ arm and 160 cells/mm^3 for the efavirenz arm.

Study AI424-008: REYATAZ 400 mg once daily compared to REYATAZ 600 mg once daily, and compared to nelfinavir 1250 mg twice daily, each in combination with stavudine and lamivudine twice daily. Study AI424-008 was a 48-week, randomized, multicenter trial, blinded to dose of REYATAZ, comparing REYATAZ at two dose levels (400 mg and 600 mg once daily) to nelfinavir (1250 mg twice daily), each in combination with stavudine (40 mg) and lamivudine (150 mg) given twice daily, in 467 antiretroviral treatment-naive patients. Patients had a mean

age of 35 years (range: 18 to 69), 55% were Caucasian, and 63% were male. The mean baseline CD4+ cell count was 295 cells/mm^3 (range: 4 to 1003 cells/mm^3) and the mean baseline plasma HIV-1 RNA level was 4.7 log_{10} copies/mL (range: 1.8 to 5.9 log_{10} copies/mL). Treatment response and outcomes through Week 48 are presented in Table 25.

Table 25: Outcomes of Randomized Treatment Through Week 48 (Study AI424-008)

Outcome	REYATAZ 400 mg once daily + lamivudine + stavudine (n=181)	nelfinavir 1250 mg twice daily + lamivudine + stavudine (n=91)
Responder[a]	67% (33%)	59% (38%)
Virologic failure[b]	24%	27%
Rebound	14%	14%
Never suppressed through Week 48	10%	13%
Death	<1%	–
Discontinued due to adverse event	1%	3%
Discontinued for other reasons[c]	7%	10%

[a] Patients achieved and maintained confirmed HIV RNA <400 copies/mL (<50 copies/mL) through Week 48. Roche Amplicor® HIV-1 Monitor™ Assay, test version 1.0 or 1.5 as geographically appropriate.
[b] Includes viral rebound and failure to achieve confirmed HIV RNA <400 copies/mL through Week 48.
[c] Includes lost to follow-up, patient's withdrawal, noncompliance, protocol violation, and other reasons.

Through 48 weeks of therapy, the mean increase from baseline in CD4+ cell count was 234 cells/mm^3 for the REYATAZ 400-mg arm and 211 cells/mm^3 for the nelfinavir arm.

14.2 Adult Patients With Prior Antiretroviral Therapy

Study AI424-045: REYATAZ once daily + ritonavir once daily compared to REYATAZ once daily + saquinavir (soft gelatin capsules) once daily, and compared to lopinavir + ritonavir twice daily, each in combination with tenofovir + one NRTI. Study AI424-045 is an ongoing, randomized, multicenter trial comparing REYATAZ (300 mg once daily) with ritonavir (100 mg once daily) to REYATAZ (400 mg once daily) with saquinavir soft gelatin capsules (1200 mg once daily), and to lopinavir + ritonavir (400/100 mg twice daily), each in combination with tenofovir and one NRTI, in 347 (of 358 randomized) patients who experienced virologic failure on HAART regimens containing PIs, NRTIs, and NNRTIs. The mean time of prior exposure to antiretrovirals was 139 weeks for PIs, 283 weeks for NRTIs, and 85 weeks for NNRTIs. The mean age was 41 years (range: 24 to 74); 60% were Caucasian, and 78% were male. The mean

baseline CD4+ cell count was 338 cells/mm^3 (range: 14 to 1543 cells/mm^3) and the mean baseline plasma HIV-1 RNA level was 4.4 $\log_{10}$ copies/mL (range: 2.6 to 5.88 $\log_{10}$ copies/mL).

Treatment outcomes through Week 48 for the REYATAZ/ritonavir and lopinavir/ritonavir treatment arms are presented in Table 26. REYATAZ/ritonavir and lopinavir/ritonavir were similar for the primary efficacy outcome measure of time-averaged difference in change from baseline in HIV RNA level. Study AI424-045 was not large enough to reach a definitive conclusion that REYATAZ/ritonavir and lopinavir/ritonavir are equivalent on the secondary efficacy outcome measure of proportions below the HIV RNA lower limit of detection. [See *Clinical Pharmacology, Tables 21* and *22 (12.4).*]

Table 26: Outcomes of Treatment Through Week 48 in Study AI424-045 (Patients with Prior Antiretroviral Experience)

Outcome	REYATAZ 300 mg + ritonavir 100 mg once daily + tenofovir + 1 NRTI (n=119)	lopinavir/ritonavir (400/100 mg) twice daily + tenofovir + 1 NRTI (n=118)	Difference[a] (REYATAZ-lopinavir/ritonavir) (CI)
HIV RNA Change from Baseline ($\log_{10}$ copies/mL)[b]	−1.58	−1.70	+0.12[c] (−0.17, 0.41)
CD4+ Change from Baseline (cells/mm^3)[d]	116	123	−7 (−67, 52)
Percent of Patients Responding[e]			
HIV RNA <400 copies/mL[b]	55%	57%	−2.2% (−14.8%, 10.5%)
HIV RNA <50 copies/mL[b]	38%	45%	−7.1% (−19.6%, 5.4%)

[a] Time-averaged difference through Week 48 for HIV RNA; Week 48 difference in HIV RNA percentages and CD4+ mean changes, REYATAZ/ritonavir vs lopinavir/ritonavir; CI = 97.5% confidence interval for change in HIV RNA; 95% confidence interval otherwise.

[b] Roche Amplicor® HIV-1 Monitor™ Assay, test version 1.5.

[c] Protocol-defined primary efficacy outcome measure.

[d] Based on patients with baseline and Week 48 CD4+ cell count measurements (REYATAZ/ritonavir, n=85; lopinavir/ritonavir, n=93).

[e] Patients achieved and maintained confirmed HIV-1 RNA <400 copies/mL (<50 copies/mL) through Week 48.

No patients in the REYATAZ/ritonavir treatment arm and three patients in the lopinavir/ritonavir treatment arm experienced a new-onset CDC Category C event during the study.

In Study AI424-045, the mean change from baseline in plasma HIV-1 RNA for REYATAZ 400 mg with saquinavir (n=115) was –1.55 $\log_{10}$ copies/mL, and the time-averaged difference in

change in HIV-1 RNA levels versus lopinavir/ritonavir was 0.33. The corresponding mean increase in CD4+ cell count was 72 cells/mm^3. Through 48 weeks of treatment, the proportion of patients in this treatment arm with plasma HIV-1 RNA <400 (<50) copies/mL was 38% (26%). In this study, coadministration of REYATAZ and saquinavir did not provide adequate efficacy [see *Drug Interactions (7)*].

Study AI424-045 also compared changes from baseline in lipid values. [See *Adverse Reactions (6.1).*]

Study AI424-043: Study AI424-043 was a randomized, open-label, multicenter trial comparing REYATAZ (400 mg once daily) to lopinavir/ritonavir (400/100 mg twice daily), each in combination with two NRTIs, in 300 patients who experienced virologic failure to only one prior PI-containing regimen. Through 48 weeks, the proportion of patients with plasma HIV-1 RNA <400 (<50) copies/mL was 49% (35%) for patients randomized to REYATAZ (n=144) and 69% (53%) for patients randomized to lopinavir/ritonavir (n=146). The mean change from baseline was –1.59 $\log_{10}$ copies/mL in the REYATAZ treatment arm and –2.02 $\log_{10}$ copies/mL in the lopinavir/ritonavir arm. Based on the results of this study, REYATAZ without ritonavir is inferior to lopinavir/ritonavir in PI-experienced patients with prior virologic failure and is not recommended for such patients.

14.3 Pediatric Patients

Assessment of the pharmacokinetics, safety, tolerability, and efficacy of REYATAZ is based on data from the open-label, multicenter clinical trial PACTG 1020A conducted in patients from 3 months to 21 years of age. In this study, 182 patients (83 antiretroviral-naive and 99 antiretroviral-experienced) received once daily REYATAZ, with or without ritonavir, in combination with two NRTIs.

Ninety-nine patients (6 to less than 18 years of age) treated with the REYATAZ capsule formulation, with or without ritonavir, were evaluated. In this cohort, the overall proportions of antiretroviral-naive and -experienced patients with HIV RNA <400 copies/mL at week 24 were 68% (28/41) and 33% (19/58), respectively. The overall proportions of antiretroviral-naive and -experienced patients with HIV RNA <50 copies/mL at week 24 were 59% (24/41) and 24% (14/58), respectively. The median increase from baseline in absolute CD4 count at 20 weeks of therapy was 171 cells/mm^3 in antiretroviral-naive patients and 116 cells/mm^3 in antiretroviral-experienced patients.

16 HOW SUPPLIED/STORAGE AND HANDLING

REYATAZ® (atazanavir sulfate) Capsules are available in the following strengths and configurations of plastic bottles with child-resistant closures.

Product Strength*	Capsule Shell Color (cap/body)	Markings on Capsule (ink color)		Capsules per Bottle	NDC Number
		cap	body		
100 mg	blue/white	BMS 100 mg (white)	3623 (blue)	60	0003-3623-12
150 mg	blue/powder blue	BMS 150 mg (white)	3624 (blue)	60	0003-3624-12
200 mg	blue/blue	BMS 200 mg (white)	3631 (white)	60	0003-3631-12
300 mg	red/blue	BMS 300 mg (white)	3622 (white)	30	0003-3622-12
* atazanavir equivalent as atazanavir sulfate.					

REYATAZ (atazanavir sulfate) Capsules should be stored at 25° C (77° F); excursions permitted to 15–30° C (59–86° F) [see USP Controlled Room Temperature].

17 PATIENT COUNSELING INFORMATION

See *FDA-Approved Patient Labeling.*

A statement to patients and healthcare providers is included on the product's bottle label: **ALERT: Find out about medicines that should NOT be taken with REYATAZ**.

Patients should be informed that REYATAZ is not a cure for HIV infection and that they may continue to develop opportunistic infections and other complications associated with HIV disease. Patients should be told that there are currently no data demonstrating that therapy with REYATAZ can reduce the risk of transmitting HIV to others through sexual contact.

17.1 Dosing Instructions

Patients should be told that sustained decreases in plasma HIV RNA have been associated with a reduced risk of progression to AIDS and death. Patients should remain under the care of a physician while using REYATAZ. Patients should be advised to take REYATAZ with food every day and take other concomitant antiretroviral therapy as prescribed. REYATAZ must always be used in combination with other antiretroviral drugs. Patients should not alter the dose or discontinue therapy without consulting with their doctor. If a dose of REYATAZ is missed,

patients should take the dose as soon as possible and then return to their normal schedule. However, if a dose is skipped the patient should not double the next dose.

17.2 Drug Interactions

REYATAZ may interact with some drugs; therefore, patients should be advised to report to their doctor the use of any other prescription, nonprescription medication, or herbal products, particularly St. John's wort.

Patients receiving a PDE5 inhibitor and atazanavir should be advised that they may be at an increased risk of PDE5 inhibitor-associated adverse events including hypotension, syncope, visual disturbances, and priapism, and should promptly report any symptoms to their doctor.

Patients should be informed that REVATIO® (used to treat pulmonary arterial hypertension) is contraindicated with REYATAZ and that dose adjustments are necessary when REYATAZ is used with CIALIS®, LEVITRA®, or VIAGRA® (used to treat erectile dysfunction), or ADCIRCA® (used to treat pulmonary arterial hypertension).

17.3 Cardiac Conduction Abnormalities

Patients should be informed that atazanavir may produce changes in the electrocardiogram (eg, PR prolongation). Patients should consult their physician if they are experiencing symptoms such as dizziness or lightheadedness.

17.4 Rash

Patients should be informed that mild rashes without other symptoms have been reported with REYATAZ use. These rashes go away within two weeks with no change in treatment. However, there have been a few reports of severe skin reactions (eg, Stevens-Johnson syndrome, erythema multiforme, and toxic skin eruptions) with REYATAZ use. Patients developing signs or symptoms of severe skin reactions or hypersensitivity reactions (including, but not limited to, severe rash or rash accompanied by one or more of the following: fever, general malaise, muscle or joint aches, blisters, oral lesions, conjunctivitis, facial edema, hepatitis, eosinophilia, granulocytopenia, lymphadenopathy, and renal dysfunction) must discontinue REYATAZ and seek medical evaluation immediately.

17.5 Hyperbilirubinemia

Patients should be informed that asymptomatic elevations in indirect bilirubin have occurred in patients receiving REYATAZ. This may be accompanied by yellowing of the skin or whites of the eyes and alternative antiretroviral therapy may be considered if the patient has cosmetic concerns.

17.6 Fat Redistribution

Patients should be informed that redistribution or accumulation of body fat may occur in patients receiving antiretroviral therapy including protease inhibitors and that the cause and long-term health effects of these conditions are not known at this time. It is unknown whether long-term use of REYATAZ will result in a lower incidence of lipodystrophy than with other protease inhibitors.

FDA-Approved Patient Labeling

Patient Information

REYATAZ® (RAY-ah-taz)

(generic name = **atazanavir sulfate**)

Capsules

ALERT: Find out about medicines that should NOT be taken with REYATAZ. Read the section "What important information should I know about taking REYATAZ with other medicines?"

Read the Patient Information that comes with REYATAZ before you start using it and each time you get a refill. There may be new information. This leaflet provides a summary about REYATAZ and does not include everything there is to know about your medicine. This information does not take the place of talking with your healthcare provider about your medical condition or treatment.

What is REYATAZ?

REYATAZ is a prescription medicine used with other anti-HIV medicines to treat people 6 years of age and older who are infected with the human immunodeficiency virus (HIV). HIV is the virus that causes acquired immune deficiency syndrome (AIDS). REYATAZ is a type of anti-

HIV medicine called a protease inhibitor. HIV infection destroys CD4+ (T) cells, which are important to the immune system. The immune system helps fight infection. After a large number of (T) cells are destroyed, AIDS develops. REYATAZ helps to block HIV protease, an enzyme that is needed for the HIV virus to multiply. REYATAZ may lower the amount of HIV in your blood, help your body keep its supply of CD4+ (T) cells, and reduce the risk of death and illness associated with HIV.

Does REYATAZ cure HIV or AIDS?

REYATAZ does not cure HIV infection or AIDS. At present there is no cure for HIV infection. People taking REYATAZ may still get opportunistic infections or other conditions that happen with HIV infection. Opportunistic infections are infections that develop because the immune system is weak. Some of these conditions are pneumonia, herpes virus infections, and *Mycobacterium avium* complex (MAC) infections. **It is very important that you see your healthcare provider regularly while taking REYATAZ.**

REYATAZ does not lower your chance of passing HIV to other people through sexual contact, sharing needles, or being exposed to your blood. For your health and the health of others, it is important to always practice safer sex by using a latex or polyurethane condom or other barrier to lower the chance of sexual contact with semen, vaginal secretions, or blood. Never use or share dirty needles.

Who should not take REYATAZ?

Do not take REYATAZ if you:

- **are taking certain medicines.** (See "What important information should I know about taking REYATAZ with other medicines?") Serious life-threatening side effects or death may happen. Before you take REYATAZ, tell your healthcare provider about all medicines you are taking or planning to take. These include other prescription and nonprescription medicines, vitamins, and herbal supplements.
- **are allergic to REYATAZ or to any of its ingredients.** The active ingredient is atazanavir sulfate. See the end of this leaflet for a complete list of ingredients in REYATAZ. Tell your healthcare provider if you think you have had an allergic reaction to any of these ingredients.

What should I tell my healthcare provider before I take REYATAZ?

Tell your healthcare provider:

- **If you are pregnant or plan to become pregnant.** REYATAZ use during pregnancy has not been associated with an increase in birth defects. Pregnant women have experienced serious side effects when taking REYATAZ with other HIV medicines called nucleoside analogues. You and your healthcare provider will need to decide if REYATAZ is right for you. If you use REYATAZ while you are pregnant, talk to your healthcare provider about the Antiretroviral Pregnancy Registry.
    - **After your baby is born,** tell your healthcare provider if your baby's skin or the white part of his/her eyes turns yellow.
- **If you are breast-feeding.** You should not breast-feed if you are HIV-positive because of the chance of passing HIV to your baby. Also, it is not known if REYATAZ can pass into your breast milk and if it can harm your baby. If you are a woman who has or will have a baby, talk with your healthcare provider about the best way to feed your baby.
- **If you have liver problems or are infected with the hepatitis B or C virus.** See "What are the possible side effects of REYATAZ?"
- **If you have end stage kidney disease** managed with hemodialysis.
- **If you have diabetes.** See "What are the possible side effects of REYATAZ?"
- **If you have hemophilia.** See "What are the possible side effects of REYATAZ?"
- **About all the medicines you take** including prescription and nonprescription medicines, vitamins, and herbal supplements. Keep a list of your medicines with you to show your healthcare provider. For more information, see "What important information should I know about taking REYATAZ with other medicines?" and "Who should not take REYATAZ?" Some medicines can cause serious side effects if taken with REYATAZ.

How should I take REYATAZ?

- **Take REYATAZ once every day exactly as instructed by your healthcare provider.** Your healthcare provider will prescribe the amount of REYATAZ that is right for you.
- **Always take REYATAZ with food** (a meal or snack) to help it work better. Swallow the capsules whole. **Do not open the capsules.** Take REYATAZ at the same time each day.
- **If you are taking antacids or didanosine (VIDEX® or VIDEX® EC)**, take REYATAZ 2 hours before or 1 hour after these medicines.

- **If you are taking medicines for indigestion, heartburn, or ulcers such as AXID® (nizatidine), PEPCID AC® (famotidine), TAGAMET® (cimetidine), ZANTAC® (ranitidine), AcipHex® (rabeprazole), NEXIUM® (esomeprazole), PREVACID® (lansoprazole), PRILOSEC® (omeprazole), or PROTONIX® (pantoprazole)**, talk to your healthcare provider.
- **Do not change your dose or stop taking REYATAZ without first talking with your healthcare provider.** It is important to stay under a healthcare provider's care while taking REYATAZ.
- **When your supply of REYATAZ starts to run low**, get more from your healthcare provider or pharmacy. It is important not to run out of REYATAZ. The amount of HIV in your blood may increase if the medicine is stopped for even a short time.
- **If you miss a dose of REYATAZ**, take it as soon as possible and then take your next scheduled dose at its regular time. If, however, it is within 6 hours of your next dose, do not take the missed dose. Wait and take the next dose at the regular time. Do not double the next dose. **It is important that you do not miss any doses of REYATAZ or your other anti-HIV medicines.**
- **If you take more than the prescribed dose of REYATAZ**, call your healthcare provider or poison control center right away.

What are the possible side effects of REYATAZ?

The following list of side effects is **not** complete. Report any new or continuing symptoms to your healthcare provider. If you have questions about side effects, ask your healthcare provider. Your healthcare provider may be able to help you manage these side effects.

The following side effects have been reported with REYATAZ:

- **mild rash** (redness and itching) without other symptoms sometimes occurs in patients taking REYATAZ, most often in the first few weeks after the medicine is started. Rashes usually go away within 2 weeks with no change in treatment. Tell your healthcare provider if rash occurs.
- **severe rash:** Rash may develop in association with other symptoms which could be serious and potentially cause death.

  If you develop a rash with any of the following symptoms stop using REYATAZ and call your healthcare provider right away:

- shortness of breath
- general ill feeling or “flu-like” symptoms
- fever
- muscle or joint aches
- conjunctivitis (red or inflamed eyes, like “pink eye”)
- blisters
- mouth sores
- swelling of your face

- **yellowing of the skin or eyes.** These effects may be due to increases in bilirubin levels in the blood (bilirubin is made by the liver). Although these effects may not be damaging to your liver, skin, or eyes, call your healthcare provider promptly if your skin or the white part of your eyes turn yellow.

- **a change in the way your heart beats (heart rhythm change).** Call your healthcare provider right away if you get dizzy or lightheaded. These could be symptoms of a heart problem.

- **diabetes and high blood sugar (hyperglycemia)** sometimes happen in patients taking protease inhibitor medicines like REYATAZ. Some patients had diabetes before taking protease inhibitors while others did not. Some patients may need changes in their diabetes medicine.

- **if you have liver disease** including hepatitis B or C, your liver disease may get worse when you take anti-HIV medicines like REYATAZ.
- **kidney stones** have been reported in patients taking REYATAZ. If you develop signs or symptoms of kidney stones (pain in your side, blood in your urine, pain when you urinate) tell your healthcare provider promptly.
- **some patients with hemophilia** have increased bleeding problems with protease inhibitors like REYATAZ.
- **changes in body fat.** These changes may include an increased amount of fat in the upper back and neck (“buffalo hump”), breast, and around the trunk. Loss of fat from the legs, arms, and face may also happen. The cause and long-term health effects of these conditions are not known at this time.
- **immune reconstitution syndrome.** In some patients with advanced HIV infection (AIDS) and a history of opportunistic infection, signs and symptoms of inflammation from previous infections may occur soon after anti-HIV treatment, including REYATAZ, is started.

Other common side effects of REYATAZ taken with other anti-HIV medicines include nausea; headache; stomach pain; vomiting; diarrhea; depression; fever; dizziness; trouble sleeping; numbness, tingling, or burning of hands or feet; and muscle pain.

Gallbladder disorders (which may include gallstones and gallbladder inflammation) have been reported in patients taking REYATAZ.

What important information should I know about taking REYATAZ with other medicines?

Do not take REYATAZ if you take the following medicines (not all brands may be listed; tell your healthcare provider about all the medicines you take). REYATAZ may cause serious, life-threatening side effects or death when used with these medicines.

- Ergot medicines: dihydroergotamine, ergonovine, ergotamine, and methylergonovine such as CAFERGOT®, MIGRANAL®, D.H.E. 45®, ergotrate maleate, METHERGINE®, and others (used for migraine headaches).
- ORAP® (pimozide, used for Tourette's disorder).
- PROPULSID® (cisapride, used for certain stomach problems).
- Triazolam, also known as HALCION® (used for insomnia).
- Midazolam, also known as VERSED® (used for sedation), when taken by mouth.

Do not take the following medicines with REYATAZ because of possible serious side effects:

- CAMPTOSAR® (irinotecan, used for cancer).
- CRIXIVAN® (indinavir, used for HIV infection). Both REYATAZ and CRIXIVAN sometimes cause increased levels of bilirubin in the blood.
- Cholesterol-lowering medicines MEVACOR® (lovastatin) or ZOCOR® (simvastatin).
- UROXATRAL® (alfuzosin, used to treat benign enlargement of the prostate).
- REVATIO® (sildenafil, used to treat pulmonary arterial hypertension).

Do not take the following medicines with REYATAZ because they may lower the amount of REYATAZ in your blood. This may lead to an increased HIV viral load. Resistance to REYATAZ or cross-resistance to other HIV medicines may develop:

- Rifampin (also known as RIMACTANE®, RIFADIN®, RIFATER®, or RIFAMATE®, used for tuberculosis).
- St. John's wort (*Hypericum perforatum*), an herbal product sold as a dietary supplement, or products containing St. John's wort.
- VIRAMUNE® (nevirapine, used for HIV infection).

The following medicines are not recommended with REYATAZ:

- SEREVENT DISKUS® (salmeterol) and ADVAIR® (salmeterol with fluticasone), used to treat asthma, emphysema/chronic obstructive pulmonary disease also known as COPD.

Do not take the following medicine if you are taking REYATAZ and NORVIR® together:

- VFEND® (voriconazole).

The following medicines may require your healthcare provider to monitor your therapy more closely (for some medicines a change in the dose or dose schedule may be needed):

- CIALIS® (tadalafil), LEVITRA® (vardenafil), or VIAGRA® (sildenafil), used to treat erectile dysfunction. REYATAZ may increase the chances of serious side effects that can happen with CIALIS, LEVITRA, or VIAGRA. Do not use CIALIS, LEVITRA, or VIAGRA while you are taking REYATAZ unless your healthcare provider tells you it is okay.
- ADCIRCA® (tadalafil) or TRACLEER® (bosentan), used to treat pulmonary arterial hypertension.
- LIPITOR® (atorvastatin) or CRESTOR® (rosuvastatin). There is an increased chance of serious side effects if you take REYATAZ with this cholesterol-lowering medicine.
- Medicines for abnormal heart rhythm: CORDARONE® (amiodarone), lidocaine, quinidine (also known as CARDIOQUIN®, QUINIDEX®, and others).
- MYCOBUTIN® (rifabutin, an antibiotic used to treat tuberculosis).
- BUPRENEX®, SUBUTEX®, SUBOXONE®, (buprenorphine or buprenorphine/naloxone, used to treat pain and addiction to narcotic painkillers).
- VASCOR® (bepridil, used for chest pain).
- COUMADIN® (warfarin).

- Tricyclic antidepressants such as ELAVIL® (amitriptyline), NORPRAMIN® (desipramine), SINEQUAN® (doxepin), SURMONTIL® (trimipramine), TOFRANIL®(imipramine), or VIVACTIL® (protriptyline).
- Medicines to prevent organ transplant rejection: SANDIMMUNE® or NEORAL® (cyclosporin), RAPAMUNE® (sirolimus), or PROGRAF® (tacrolimus).
- The antidepressant trazodone (DESYREL® and others).
- Fluticasone propionate (FLONASE®, FLOVENT®), given by nose or inhaled to treat allergic symptoms or asthma. Your doctor may choose not to keep you on fluticasone, especially if you are also taking NORVIR®.
- Colchicine (COLCRYS®), used to prevent or treat gout or treat familial Mediterranean fever.

The following medicines may require a change in the dose or dose schedule of either REYATAZ or the other medicine:

- INVIRASE® (saquinavir).
- NORVIR® (ritonavir).
- SUSTIVA® (efavirenz).
- Antacids or buffered medicines.
- VIDEX® (didanosine).
- VIREAD® (tenofovir disoproxil fumarate).
- MYCOBUTIN® (rifabutin).
- Calcium channel blockers such as CARDIZEM® or TIAZAC® (diltiazem), COVERA-HS® or ISOPTIN SR® (verapamil) and others.
- BIAXIN® (clarithromycin).
- Medicines for indigestion, heartburn, or ulcers such as AXID® (nizatidine), PEPCID AC® (famotidine), TAGAMET® (cimetidine), or ZANTAC® (ranitidine).

Talk to your healthcare provider about choosing an effective method of contraception.
REYATAZ may affect the safety and effectiveness of hormonal contraceptives such as birth

control pills or the contraceptive patch. Hormonal contraceptives do not prevent the spread of HIV to others.

Remember:

1. **Know all the medicines you take.**
2. **Tell your healthcare provider about all the medicines you take.**
3. **Do not start a new medicine without talking to your healthcare provider.**

How should I store REYATAZ?

- Store REYATAZ Capsules at room temperature, 59° to 86° F (15° to 30° C). Do **not** store this medicine in a damp place such as a bathroom medicine cabinet or near the kitchen sink.
- Keep your medicine in a tightly closed container.
- Keep all medicines out of the reach of children and pets at all times. Do not keep medicine that is out of date or that you no longer need. Dispose of unused medicines through community take-back disposal programs when available or place REYATAZ in an unrecognizable, closed container in the household trash.

General information about REYATAZ

This medicine was prescribed for your particular condition. Do not use REYATAZ for another condition. Do not give REYATAZ to other people, even if they have the same symptoms you have. It may harm them. **Keep REYATAZ and all medicines out of the reach of children and pets.**

This summary does not include everything there is to know about REYATAZ. Medicines are sometimes prescribed for conditions that are not mentioned in patient information leaflets. Remember no written summary can replace careful discussion with your healthcare provider. If you would like more information, talk with your healthcare provider or you can call 1-800-321-1335.

What are the ingredients in REYATAZ?

Active Ingredient: atazanavir sulfate

Inactive Ingredients: Crospovidone, lactose monohydrate (milk sugar), magnesium stearate, gelatin, FD&C Blue #2, and titanium dioxide.

Bristol-Myers Squibb Company

Princeton, NJ 08543 USA

XXXXXXXXX Rev XXXX XXXX

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-567/S025

OFFICER/EMPLOYEE LIST

Officer/Employee List
NDA 21-567/S-025

The following officers or employees of FDA participated in the decision to approve this application and consented to be identified:

1. Birnkrant, Debra
2. Cao, Kelly Yoojung
3. Durmowicz, Elizabeth
4. El Hage, Antoine N.
5. Feibus, Karen
6. Ghantous, Hanan
7. Hammerstrom, Thomas S.
8. Holquist, Carol
9. Mada, Sripal
10. Marcus, Kendall
11. Mathis, Lisa
12. Murray, Jeffrey S.
13. Naeger, Lisa
14. O'Rear, Julian
15. Patel, Hasmukh B.
16. Robertson, Sarah
17. Rogers, Brian D.
18. Sachs, Hari
19. Safarik, Michelle
20. Sahin, Leyla
21. Shapiro, Alan
22. Singer, Mary
23. Taylor, Kellie
24. Toliver, Kristina
25. Tyson, Victoria
26. Yau, Martin
27. Zheng, Jenny H.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-567/S025

CROSS DISCIPLINE TEAM LEADER REVIEW

CROSS DISCIPLINE TEAM LEADER REVIEW

Date	January 23, 2010
From	Sarah Robertson, Pharm.D.
Subject	Cross Discipline Team Leader Review
NDA #	21-567 (S-025)
Applicant	Bristol-Myers Squibb
Date of Submission	August 6, 2010
PDUFA Goal Date	February 6, 2011
Proprietary Name / Established (USAN) names	REYATAZ (atazanavir sulfate)
Dosage forms / Strength	100 mg, 150 mg, 200 mg and 300 mg capsules
Approved Indication(s)	Treatment of HIV-1 infection in combination with other antiretroviral agents
Recommended:	Approval, with revisions to the label

1. Introduction

This review summarizes the multi-disciplinary evaluation of the information submitted by Bristol-Myers Squibb to update the atazanavir label with the results of trial AI424182, which evaluated the safety, efficacy and PK of atazanavir/ritonavir (ATV/r) in HIV-infected pregnant women. The applicant has proposed the following labeling revisions: (b) (4)

To obtain regulatory approval, the data submitted must provide evidence that approved doses of atazanavir will result in similar exposure in pregnant women compared to non-pregnant HIV-infected adults and will not result in unacceptable maternal or fetal toxicity.

2. Background

Atazanavir is a protease inhibitor (PI) approved for the treatment of HIV-1 in adults and children ≥ 6 years of age. It was originally approved for adults in June 2003. Studies evaluating atazanavir (+/- ritonavir) in children < 6 years of age are currently ongoing. As outlined below, the approved adult dose of atazanavir differs based on concomitant medications and previous treatment experience.

Table 1 Approved Atazanavir Dosing Regimens†

Treatment-Naïve Patients	Atazanavir 300 mg + ritonavir 100 mg once daily
If unable to tolerate ritonavir	Atazanavir 400 mg once daily
When combined with any of the following: • Tenofovir • H_2-receptor antagonists • Proton-pump inhibitors	Atazanavir 300 mg + ritonavir 100 mg once daily • The H_2-receptor antagonist dose should not exceed a dose comparable to famotidine 40 mg twice daily. Administer REYATAZ and ritonavir simultaneously with, and/or at least 10 hours after the H_2-receptor antagonist. • If unable to tolerate ritonavir, administer REYATAZ 400 mg once daily at least 2 hours before and at least 10 hours after the H_2-receptor antagonist. No single dose of the H_2-receptor antagonist should exceed a dose comparable to famotidine 20 mg and the total daily dose should not exceed a dose comparable to Famotidine 40 mg. • The proton-pump inhibitor dose should not exceed a dose comparable to omeprazole 20 mg daily and must be taken approximately 12 hours prior to REYATAZ and ritonavir.

When combined with efavirenz	Atazanavir 400 mg + ritonavir 100 mg once daily • Efavirenz should be administered on an empty stomach, preferably at bedtime.
Treatment-Experienced Patients*	Atazanavir 300 mg + ritonavir 100 mg once daily
When given with H_2-receptor antagonists	Atazanavir 300 mg + ritonavir 100 mg once daily • The H_2-receptor antagonist dose should not exceed a dose comparable to famotidine 20 mg twice daily. Administer REYATAZ and ritonavir simultaneously with, and/or at least 10 hours after the H_2-receptor antagonist.
When given with both tenofovir *and* an H_2-receptor antagonist	Atazanavir 400 mg + ritonavir 100 mg once daily • The H_2-receptor antagonist dose should not exceed a dose comparable to famotidine 20 mg twice daily. Administer REYATAZ and ritonavir simultaneously with, and/or at least 10 hours after the H_2-receptor antagonist.
*Do not co-administer with proton-pump inhibitors or efavirenz	

† All REYATAZ dosing regimens are to be administered with food

AI424182 was a multi-center, open-label, prospective, single-arm trial conducted to determine an appropriate ATV/r dose for use in pregnant women and to evaluate the efficacy and safety of ATV/r in pregnant women and their neonates. HIV-1 infected pregnant women with a CD_4 cell count ≥ 200 cells/mm^3 and between gestational weeks 12-32 were eligible for enrollment. Subjects were to be either antiretroviral (ARV) naïve or stable on an ARV regimen with an HIV-1 RNA < 50 copies/mL. Subjects with a history of exposure to a PI other than ATV were eligible if there was no virologic failure while on the PI. Subjects with a history of > 3 weeks of ATV were ineligible. A total of 69 women were enrolled at 6 clinical sites, including 1 site in Puerto Rico (N=14), 2 sites in the Unites States (N=8) and 3 sites in South Africa (N=47).

The first 12 subjects to meet inclusion/exclusion criteria received ATV/r 300/100 mg QD with food + zidovudine/lamivudine (ZDV/3TC) BID. A planned interim PK analysis was conducted when the first 12 subjects reached steady-state (2 weeks on drug) while in the 3rd trimester (Weeks 28-36 gestation). The ATV AUC value at the interim analysis did not meet the pre-defined criterion (≥ 30,000 ng·h/mL); thus, the protocol was amended to evaluate an increased dose of 400/100 mg QD in the 3rd trimester in a new set of subjects. The protocol amendment specifying a dose increase in the 3rd trimester also allowed for the collection of PK data in the 2nd trimester at a dose of 300/100 mg. The protocol was also amended to change the reference group for PK comparisons from the within-study postpartum cohort to historical data in HIV patients, due to unexpectedly high postpartum ATV exposures in the current study. While the interim analysis was being performed, an additional 8 mothers entered the study and were dosed with ATV/r 300/100 mg QD in the 3rd trimester. After the protocol amendment, 20 additional mothers were enrolled and dosed with 400/100 mg in their 3rd trimester and dosed with 300/100 mg during their 2nd trimester if enrolled early enough. In total, 41 women received ATV/r in their 3rd trimester, including 20 subjects dosed with 300/100 mg and 21 subjects dosed with 400/100 mg, and 9 women received ATV/r in their 2nd trimester at a dose of 300/100 mg.

3. CMC/Device

Not applicable. No new information submitted.

4. Nonclinical Pharmacology/Toxicology

No new nonclinical data were submitted with this supplement. However, changes to the Pharmacology/Toxicology sections of the label were proposed by Dr. Kuei-Meng Wu. I agree with Dr. Wu's recommendations for the label.

5. Clinical Pharmacology

The applicant has proposed that [redacted] (b) (4) Thus, revisions to the applicant's proposal have been recommended by the clinical pharmacology reviewer to address dosing in these specific situations, as follows:

Dosing During Pregnancy and the Postpartum Period:

- REYATAZ should not be administered without ritonavir.
- REYATAZ should only be administered to pregnant women with HIV-1 strains susceptible to atazanavir.
- For pregnant patients, no dose adjustment is required for REYATAZ with the following exceptions:
  - For treatment-experienced pregnant women during the second or third trimester, when REYATAZ is coadministered with either an H_2-receptor antagonist *or* tenofovir, REYATAZ 400 mg with ritonavir 100 mg once daily is recommended. There are insufficient data to recommend a REYATAZ dose for use with both an H_2-receptor antagonist *and* tenofovir in treatment-experienced pregnant women.
- No dose adjustment is required for postpartum patients. However, patients should be closely monitored for adverse events because atazanavir exposures could be higher during the first 2 months after delivery. [See *Use in Specific Populations (8.1) and Clinical Pharmacology (12.3)*.]

The design of trial AI424182 and results of the PK assessment are described in full detail in Dr. Jenny Zheng's review. I concur with Dr. Zheng's interpretation of the findings and conclusions. The following is a summary of pertinent findings which support the review team's recommendation for dosage and administration in pregnancy.

Intensive PK sampling was performed in pregnant women between 30-36 weeks gestation and at Weeks 4-8 postpartum. An additional intensive PK assessment was later added at 18-24 weeks gestation to obtain data in the 2nd trimester. The final PK analysis included data for 9 women treated with ATV/r 300/100 mg in the 2nd trimester, 20 women treated with 300/100 mg in the 3rd trimester, 20 women treated with 400/100 mg in the 3rd trimester, and 36 women treated with 300/100 mg in the postpartum period. Due to the unexpected high exposure in the postpartum period relative to historical control data, the protocol was amended such that historical data were used as the control. I agree with Dr. Zheng's assessment that ATV exposures are likely higher for women immediately after delivery, with levels returning slowly to pre-pregnancy levels over time. This observation of higher exposure in the postpartum period has been reported for other protease inhibitors, including ATV, in previous investigations, as described in Dr. Zheng's review. The postpartum evaluation was conducted at a mean of 5.8 ± 2.1 weeks (range 3-10 weeks) following delivery. We agree with use of historical data obtained from HIV-infected patients as the control for PK comparisons.

The Division of Scientific Investigation (DSI) performed inspections of the clinical and analytical portions of AI424182, including 4 clinical sites (1 in Puerto Rico and 3 in South Africa) and the single analytical laboratory [redacted] (b) (4). As a result of the inspections, Form FDA-483 was issued to [redacted] (b) (4) outlining several errors with the analytical assay. Most notably, [redacted] (b) (4) did not adequately resolve carry-over effects in several analytical runs. These include 3 runs of the protein binding assay and one of the analytical runs for assessment of atazanavir concentrations (Run #20). DSI recommended that subject samples from these runs not be used in the analysis of data, due to questionable validity of results. The Applicant was subsequently requested to reanalyze the PK data for atazanavir with the samples from Run #20 excluded. Exclusion of samples from Run #20 resulted in the exclusion of PK results for 4 subjects from the 2nd trimester cohort, 2 subjects from the postpartum cohort, and 3 subjects in the 400/100 mg 3rd trimester cohort. The following is a summary of the PK results with and without Run #20:

Steady-State Pharmacokinetics of ATV in HIV-Infected Pregnant Women and Non-Pregnant Historical Controls

Geo.Mean (%CV)	ATV/RTV 300/100 mg QD					ATV/RTV 400/100 mg QD		Reference (label)		
	2nd Trimester		3rd Trimester	Postpartum		3rd Trimester		Non-Pregnant HIV Patients		
	Original (N=9)	Excluding Run 20 (N=5)	N=20 (no samples excluded)	Original (N=36)	Excluding Run 20 (N=34)	Original (N=20)	Excluding Run 20 (N=17)	ATV/RTV 300/100 mg (N=10)	ATV 400 mg (N=13)	ATV 300/100 mg + TDF (N=10)
Cmax (ng/mL)	3729.09 (39)	3078.85 (50)	3291.46 (48)	5649.10 (31)	5721.21 (31)	4210.8 (38)	4098.6 (42)	4422 (58)	2298 (71)	3190 (NR)
AUC_T (ng.h/mL)	34399.1 (37)	27657.1 (43)	34251.5 (43)	60532.7 (33)	61990.4 (32)	46602.4 (43)	44780.1 (47)	46073 (66)	14874 (91)	34459 (NR)
Cmin (ng/mL)	663.78 (36)	538.70 (46)	668.48 (50)	1420.64 (47)	1462.59 (45)	916.63 (60)	890.3 (65)	636 (97)	120 (109)	491 (NR)

NR = Not Reported

Exclusion of data from Run #20 resulted in only 5 subjects with useable 2nd trimester data. Mean ATV exposure in these 5 subjects was lower than that of subjects receiving the same dose in the 3rd trimester. One would have expected similar or higher exposure in the 2nd trimester relative to the 3rd trimester. Before exclusion of the data from Run #20, ATV exposure was similar between the 2nd and 3rd trimesters. Given the low subject number with interpretable data for this cohort (n=5), we cannot conclude with certainty the observation of lower exposure in the 2nd trimester. However, the data for this cohort were considered along with that of the 3rd trimester data when considering dosing recommendations.

As shown in the table above, ATV AUC and Cmin in the 2nd and 3rd trimesters in women receiving 300/100 mg QD were lower than that of historical data for the same dose. However, AUC and Cmin were comparable to exposure associated with concomitant tenofovir use and well in excess of exposure associated with a 400 mg QD regimen (historical data). Thus, a dose of 300/100 mg QD is considered sufficient for treatment-naïve pregnant women in all trimesters. In addition, concomitant tenofovir, H_2-receptor antagonist (H2RA) or proton-pump inhibitor (PPI) use in treatment-naïve pregnant women would be acceptable, as the additional 25-42% decrease in AUC and 25-46% decrease in Cmin associated with these concomitant medications would still maintain exposure above that of a 400 mg QD regimen.

The magnitude of difference in ATV exposure observed in the 3rd trimester 300/100 mg QD cohort (relative to historical control data) is similar to the magnitude of effect from tenofovir coadministration (~25% lower AUC). Tenofovir coadministration with ATV/r 300/100 mg QD does not result in reduced rates of efficacy in the general HIV population, including treatment-experienced patients. Further, mean Cmin values in the 2nd and 3rd trimesters were similar to that of historical control data. Thus, a dose of 300/100 mg is likely to result in similar efficacy rates during the 3rd trimester of pregnancy, including in women with previous treatment experience. A higher dose of 400/100 mg is not considered to be necessary from an efficacy perspective, while causing slightly higher rates of hyperbilirubinemia in the mother. However, exposure at the 300/100 mg dose could be too low for pregnant women with more extensive PI experience or resistance, particularly when the lower mean values in the 2nd trimester cohort are considered. Therefore, the recommended regimen should only be administered to pregnant women with HIV-1 strains susceptible to atazanavir.

In the event ATV/r is combined with tenofovir or an H2RA, which reduces ATV exposure to a similar magnitude as tenofovir, a dose of 300/100 mg QD may not be sufficient for a treatment-experienced pregnant woman. As described in Dr. Zheng's review, results of study PACTG 1026s indicate the effect of tenofovir coadministration on ATV exposure during pregnancy is similar in magnitude to that observed in non-pregnant patients. Thus, the additive effect of pregnancy plus tenofovir or H2RA therapy would be expected to result in approximately 18-37% lower ATV Cmin than that of non-pregnant patients receiving 300/100 mg QD. In order to match the exposure of 300/100 mg QD, an ATV/RTV dose increase to 400/100 mg QD is recommended during the 2nd and 3rd trimesters in treatment-experienced pregnant women on concomitant tenofovir or an H2RA. There are

insufficient data to recommend a dose for treatment-experienced pregnant women on tenofovir *and* an H2RA. PPIs are currently not recommended for co-administration with ATV/r for any treatment-experienced patients.

Maternal plasma protein binding (87-91%) was similar regardless of gestation time, dosing regimen, or time post-dose, and was similar to that reported for non-pregnant adults (86%). Postpartum maternal plasma protein binding was similar to that observed during pregnancy. Plasma protein binding in cord blood was lower than in maternal blood, with unbound fraction (23%) approximately twice that of maternal blood. The ratio of cord blood to maternal peripartum ATV concentration was approximately 19% and 12% for the 300/100 mg and ATV/RTV 400/100 mg dose cohorts, respectively, similar to rates reported previously for ATV in pregnancy.

6. Clinical Microbiology

I concur with the summary of results and conclusions as outlined in the microbiology review of Dr. Lisa Naeger. Dr. Naeger has concluded the virology data submitted with this supplement support the approved dose of atazanavir for use in pregnant women.

Genotypic and phenotypic resistance testing was conducted in all mothers with an HIV-1 RNA > 400 copies/mL at baseline or at the time of virologic rebound while on treatment, as well as in all mothers discontinuing ARVs postpartum. Baseline genotype and phenotype results were available for 37 of 41 mothers at baseline. None of the subjects had any major International AIDS Society (IAS) PI substitutions at baseline. One subject had a 2.34-fold decrease in susceptibility to ATV at baseline. Two subjects had resistance testing performed while on treatment, including one subject who had a genotype sent on Day 15 when her HIV-1 RNA was declining but not yet undetectable and another subject with resistance testing performed on Day 19. Four subjects had virologic blips to > 400 copies/mL while on ARVs, but resistance testing was not performed in any of these cases. Sixteen (16) mothers had resistance testing performed following discontinuation of ARVs postpartum. No major IAS PI mutations emerged on or off therapy in any subject. One subject had a minor PI substitution (T74/T/S) emerge when tested off treatment (postpartum).

Phenotypic resistance emerged in an isolate from the subject with 2.34-fold reduced susceptibility at baseline. This subject received the ATV/r 400/100 mg regimen. She achieved < 50 copies/mL by Day 29 and remained undetectable through Day 140, at which time she was discontinued form ARVs post-partum; she had one blip (81 copies/mL) on Day 57. Postpartum resistance testing of this subject showed reduced susceptibility (fold-change 7.19); though no new PI mutations were observed.

7. Clinical/Statistical- Efficacy

The primary efficacy endpoints evaluated in AI424182 included the proportion of pregnant women with HIV RNA <400 copies/mL and <50 copies/mL at the time of delivery, the magnitude of HIV RNA reduction from baseline, and the proportion of neonates with HIV-1 infection at birth through Week 16. The efficacy results are described in full detail in Dr. Alan Shapiro's review. I agree with Dr. Shapiro's assessment of the efficacy results.

The clinical efficacy analysis includes data from 41 atazanavir-treated mothers and 40 infants enrolled in the study. One mother in the 300/100 mg cohort and 2 mothers in the 400/100 mg cohort discontinued ATV/r prior to delivery due to AEs. Nineteen mothers completed the study in each of the two dosing cohorts. All 41 enrolled mothers achieved HIV-1 RNA <50 copies/mL at or before delivery. Of the 39 mothers with an HIV RNA test at delivery, all had HIV RNA <400 copies/mL and 38 of 39 mothers had <50 copies/mL. The one mother not suppressed to <50 copies/mL at delivery was undetectable at <50 copies/mL at the 3 visits prior to delivery and was again suppressed to <50 copies/mL post-delivery. The median CD4 cell count change from baseline was +89 and +174 cells for mothers on ATV/r 300/100 mg and 400/100 mg regimens, respectively.

All ATV exposed infants received post-natal prophylaxis that included zidovudine up to six weeks of age. One infant from each ATV/r dose cohorts discontinued post-natal prophylaxis early due to an AE. All infants were HIV-negative through 6 months of life. From an efficacy perspective, there was no difference between ATV/r 300/100 mg and 400/100 dose cohorts in this population of pregnant women with limited prior PI experience.

8. Safety

The safety of ATV/r in pregnant women and their infants was assessed by the medical officer, Dr. Shapiro, as well as by the Pediatric and Maternal Health Staff (Drs. Elizabeth Durmowicz and Leyla Sahin). Please see Dr. Shapiro's and the PMHS reviews for full details. I agree with the assessments made by Dr. Shapiro, Dr. Durmowicz and Dr. Sahin regarding the risks of atazanavir in pregnancy. As summarized by Dr. Shapiro, the primary safety concerns associated with ATV exposure include hyperbilirubinemia, P-R interval prolongation and glucose intolerance, all of which were assessed in AI424182, along with standard laboratory and vital sign assessments. In addition, developmental effects were assessed in infants at 4 and 6 months of age using the Denver II Developmental Screening Test. Overall, there were no concerning safety signals observed for either pregnant women or their infants in AI424182. Furthermore, ATV exposed infants did not appear to have markedly increased incidence or severity of hyperbilirubinemia in the first 12-96 hours of life as compared to otherwise healthy infants. Further details regarding the occurrence of hyperbilirubinemia in AI424182 are described below.

Eight of 40 mothers (20%) had a total serum bilirubin (TSB) elevation of 3 mg/dL or higher at some point during pregnancy. Three (7.5%) had a bilirubin level ≥5 mg/dL at some point during pregnancy and 2 mothers (5%) had a level ≥5 mg/dL at birth. Both infants born to the 2 mothers with a level ≥5 mg/dL at birth (1 from each dose cohort) had bilirubin levels greater than 95% for age in hours within the first 24 hours of life (based on normative data from term infants). Neither infant received phototherapy and both resolved their hyperbilirubinemia without complication. Bilirubin data in the first 24 hours of life are available for 6 of the 8 infants born to mothers with a TSB ≥3 mg/dL at some point in pregnancy. Of these 6 infants, 5 had a bilirubin greater than 95% for age in hours within the first 24 hours of life. Four of the 5 were in the 400/100 mg cohort and 3 of the 5 were premature (<37 weeks gestation at birth). The available data are inadequate to establish a correlation between maternal and infant serum bilirubin levels at birth.

The safety of the two dosing regimens, 300/100 mg and 400/100 mg, were comparable, with the exception of increased rates of total bilirubin (> 3 mg/dL) and a higher incidence of Grade 3-4 unconjugated hyperbilirubinemia in mothers treated with 400/100 mg. Grade 3-4 increases in total bilirubin were observed in 7 of 40 infants, including 3 infants from the 300/100 mg cohort and 4 infants from the 400/100 mg cohort. More infants in the 400/100 mg cohort approached the threshold identified for initiation of phototherapy, as outlined below (Table 4, from the PMHS review). The cumulative data indicate infants exposed to the higher ATV/r dose of 400/100 mg may have increased incidence and severity of hyperbilirubinemia as compared to the 300/100 mg dose, though the data cannot be considered conclusive.

Location of the Infants on the Nomogram for the Guideline for the Initiation of Phototherapy (PT)				
Dosing Exposure Cohort	Number of patients that surpassed the PT threshold	Number of patients that were within 1 mg/dL of the PT threshold	Number of patients within 1-2 mg/dL of the PT threshold	Number of patients 2 mg/dL or more below the PT threshold.
300 mg ATV	2	0	1	17
400 mg ATV	0	4	7	9

Source: Table 4 of the PMHS review (1-12-2011)

Prolonged jaundice (up to 15-18 days of life) was observed in 3 of 20 infants (15%) from the 300/100 mg cohort and 4 of 20 (20%) from the 400/100 mg cohort. Four infants had a TSB ≥1.5x ULN at a timepoint after 42 days of life. Hyperbilirubinemia typically resolves within the first 2-3 weeks of life, although premature infants are more likely to have protracted courses of hyperbilirubinemia.

Women with risk factors known to increase the risk of "pathologic jaundice" in neonates were excluded from participation in the study, including patients positive for Rhesus antibody, previous birth of an infant who developed hemolytic disease as a newborn or had neonatal pathologic jaundice requiring phototherapy, and a history of glucose-6-phosphate dehydrogenase (G6PD) deficiency. According to the PMHS reviewers, these exclusion criteria limit the ability to adequately assess the potential risk of hyperbilirubinemia following ATV exposure in a general mother/infant population. In addition, the small sample size, incomplete data collection, incomplete information on potential confounding factors, such as ABO blood incompatibility and lack of Coombs testing, and the paucity of normative data on bilirubin levels in the first 24 hours of life in normal term and

preterm infants, makes a determination of the correlation between maternal and infant serum bilirubin levels at birth difficult. Further, the majority of subjects (>80%) were Black/African American, a race with a lower incidence of neonatal hyperbilirubinemia relative to Caucasians and Asians. However, as summarized by the PMHS reviewers, given the rare occurrence of acute or chronic bilirubin encephalopathy in infants overall, if ATV exposed infants are carefully monitored, the risk of developing bilirubin encephalopathy is low, even if ATV increases the risk of hyperbilirubinemia. Additional clinical studies or nonclinical studies are unlikely to provide additional informative data regarding the risk to infants.

SAEs were reported for 14 enrolled infants (35%), including 10 from the 300/100 mg cohort and 4 from the 400/100 mg cohort. The most commonly reported SAEs (reported for more than 1 subject) were anemia and bronchiolitis, each reported in 2 subjects. There was one infant from the 300/100 mg cohort who had a cardiorespiratory arrest at three days of life believed to be due to a restrictive cardiomyopathy. As a result of this event, the subject had a seizure with cerebral ischemia and had subsequent developmental abnormalities on Denver II screening.

SAEs were reported for 15 of 41 (36%) treated mothers overall; SAE rates were comparable for both ATV dosing regimens. The majority of maternal SAEs were pregnancy related events, including pre-eclampsia, pregnancy induced hypertension, premature rupture of membranes, amniotic fluid leak, postpartum bleeding, postpartum endometritis, and postpartum abdominal hernia. There were no cases of lactic acidosis. There were 4 out of 41 mothers (3 treated with 300/100 mg and 1 treated with 400/100 mg) who had SAEs that may have been therapy-related, including anemia (zidovudine), sinus node dysfunction (atazanavir) and hyperbilirubinemia (atazanavir). The most commonly reported SAEs (reported in more than 1 subject) were anemia (3/41, 7.3%), endometritis decidual (2/41, 4.8%), and pre-eclampsia (2/41, 4.8%). One SAE in a subject receiving 400/100 mg (ALT of 564 and AST of 340) led to study drug discontinuation 4 days prior to delivery. The subject subsequently developed increased blood pressure, proteinuria, and pedal edema. This subject was diagnosed with pre-eclampsia 3 days prior to delivery and was hospitalized. The subject had two eclamptic seizures. The subject had an emergency C-section and the newborn had mild respiratory distress at birth and required brief ventilation as part of the newborn resuscitation.

The results of the Denver II Developmental Test showed suspect evaluations at Month 4 in 4 of 40 infants, while 7 infants showed suspect evaluations at Month 6. A “suspect evaluation” includes any noted evidence of developmental delay requiring follow-up. The findings of these evaluations are described in further detail in Dr. Shapiro’s review. In general, none of the developmental delays were directly attributed to ATV exposure in utero.

The Office of Surveillance and Epidemiology, Division of Pharmacovigilance was consulted to evaluate postmarketing cases of infant hyperbilirubinemia, kernicterus and hypoglycemia in neonates exposed to atazanavir in utero. Please see the review by Dr. Kelly Cao for full details of their findings. The review by Dr. Cao describes 6 unique cases identified in the AERS database, which included the following events: hyperbilirubinemia (n=6), jaundice (n=1) and hypoglycemia (n=3). There were no reports of kernicterus. Most of the 6 cases were significantly confounded by underlying conditions and risk factors. In addition, the cases included only limited information by which to evaluate an association with ATV exposure. Thus, no conclusions can be made regarding the association between in utero exposure to ATV and any of the events.

9. Advisory Committee Meeting

Not applicable.

10. Pediatrics

Please refer to the description of Safety and Efficacy from AI424182 for the impact of in utero exposure to ATV/r on infant HIV status and potential toxicity concerns.

11. Other Relevant Regulatory Issues

The following Phase 4 commitment is outstanding:

A pediatric study or studies under PREA for the treatment of HIV infection in pediatric patients ages greater than or equal to 3 months to 18 years to determine safe and appropriate dosing.

12. Labeling

The applicant has proposed the following changes to the product label:

2 DOSAGE AND ADMINISTRATION

(b) (4)

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

(b) (4)

1 Page(s) have been Withheld in Full as b4 (CCI/TS) immediately following this page

12.3 Pharmacokinetics

Special Populations

(b) (4)

The applicant's proposed changes to the package insert (label) and medication guide have been reviewed by the clinical, clinical pharmacology, virology and pharmacology/toxicology reviewers, as well as by the Pediatric and Maternal Health Staff (PMHS), Division of Drug Marketing, Advertising and Communications (DDMAC) and Division of Medication Error Prevention and Analysis (DMEPA). The review team has recommended substantive changes to Sections 2 (Dosage and Administration), 8.1 (Use in Specific Populations, Pregnancy) and 12.3 (Pharmacokinetics). The review team's revisions should be incorporated into the final label. The following dosing recommendations for pregnant women have been agreed upon with the applicant:

Dosing During Pregnancy and the Postpartum Period:

- REYATAZ should not be administered without ritonavir.
- REYATAZ should only be administered to pregnant women with HIV-1 strains susceptible to atazanavir.
- For pregnant patients, no dose adjustment is required for REYATAZ with the following exceptions:
- For treatment-experienced pregnant women during the second or third trimester, when REYATAZ is coadministered with either an H_2-receptor antagonist *or* tenofovir, REYATAZ 400 mg with ritonavir 100 mg once daily is recommended. There are insufficient data to recommend a REYATAZ dose for use with both an H_2-receptor antagonist *and* tenofovir in treatment-experienced pregnant women.
- No dose adjustment is required for postpartum patients. However, patients should be closely monitored for adverse events because atazanavir exposures could be higher during the first 2 months after delivery. [See *Use in Specific Populations (8.1) and Clinical Pharmacology (12.3)*.]

13 Recommendations/Risk Benefit Assessment

- Recommended Regulatory Action

I concur with the assessments made by the review team and recommend that the final doses agreed upon with the applicant be approved for use in pregnant women. The labeling revisions recommended by the review team should be incorporated into the final label.

- Risk Benefit Assessment

The risk-benefit assessment considered several factors:

- Estimates of ATV exposure, most notably AUC and Cmin, during pregnancy should match that of historical control data for non-pregnant adults to ensure adequate efficacy during pregnancy.
- Doses were identified for pregnant women based on PK results obtained in the 2nd and 3rd trimester of pregnancy, and include consideration for previous treatment experience and concomitant therapy with tenofovir, H_2-receptor antagonists and proton-pump inhibitors.
- The potential risks associated with atazanavir use in pregnancy include risks to the mother as well as her infant. Important toxicities that were evaluated more closely include hyperbilirubinemia, jaundice, and hypoglycemia in the infant. Overall, there were no concerning safety signals observed for either pregnant women or their infants in AI424182. Further, ATV exposed infants did not appear to have markedly increased incidence or severity of hyperbilirubinemia in the first week of life as compared to otherwise healthy infants. Recommended doses for pregnant women should not result in ATV exposure in excess of that observed in either trimester of pregnancy in trial AI424182.

- Recommendation for Postmarketing Risk Management Activities

  No postmarketing risk management activities are required for this application.

- Recommendation for other Postmarketing Study Commitments

  No postmarketing study commitments are required for this application

- Recommended Comments to Applicant

  No additional comments to convey to the applicant.

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/s/

SARAH M ROBERTSON
02/03/2011

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-567/S025

MEDICAL REVIEW(S)

CLINICAL REVIEW

Application Type	NDA 21-567
Application Number(s)	SE5
Priority or Standard	P
Submit Date(s)	August 6, 2010
Received Date(s)	August 6, 2010
PDUFA Goal Date	February 6, 2010
Division / Office	DAVP/ OAP
Reviewer Name(s)	Alan M. Shapiro, MD, Ph.D.
Review Completion Date	February 1, 2011
Established Name	Atazanavir (ATV)
(Proposed) Trade Name	Reyataz
Therapeutic Class	HIV Protease Inhibitor
Applicant	Bristol Myers Squibb
Formulation(s)	Capsule
Dosing Regimen	300mg or 400mg orally daily plus ritonavir (RTV) 100mg daily
Indication(s)	Treatment of HIV-1 infection
Intended Population(s)	Pregnant Women

Template Version: March 6, 2009

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

FDA review of study AI424182 of 41 ATV/RTV treated mothers and 40 ATV/RTV exposed infants supports the approval of the Applicant's proposed (b) (4) [redacted] The pharmacokinetics and the safety of both ATV/RTV 300/100 mg and 400/100mg regimens in pregnancy and effects on the exposed infants were evaluated. (b) (4) [redacted] There were no significant safety findings among pregnant women or their infants exposed to ATV/RTV *in utero* in Study AI424182; however the study's small size and design flaws do not completely rule-out subtle effects of atazanavir on the exposed fetuses.

In study AI424182, 38 out of 39 women receiving either ATV/RTV 300/100mg and 400/100mg had HIV viral loads <50 copies per mL at delivery. One women had a HIV viral load of 59 copies/mL at delivery but <50 copies/mL prior to delivery. None of the 40 infants born to HIV positive mothers exposed to ATV/RTV in utero became HIV infected.

With regards to safety, there were no deaths observed in this study, but there were two serious adverse events (SAEs), one in a mother and another in infant. These SAEs did not appear to be study drug related. The primary safety concern for this study was unconjugated hypebilirubinemia, an adverse event commonly associated with atazanavir use. Grade 3-4 total bilirubinemia was reported in 19/41 (46%) mothers. The frequency of hyperbilirubinemia reported in this study was similar to the frequency reported in boosted (co-administered with ritonavir) atazanavir's Phase 3 clinical trials in adults (44-49%). Infants in study AI424182 exposed to atazanavir *in utero* appear to have a small increase in hyperbilirubinemia as compared to normal (HIV-negative) infants, but none of the infants had total bilirubin levels that exceeded 20mg/dL. Above 20mg/dL, clinicians become concerned about the possibility of bilirubin neurotoxicity. Of note, the majority of enrolled mothers in this study were at lower risk for having an infant with hyperbilirubinemia. Therefore, it is important in labeling to convey

both reassurance that none of the exposed infants experienced any serious toxicity due to hyperbilirubinemia and a caution that these results may not be applicable to infants with an increased risk of severe hyperbilirubinemia (e.g. non-black race, ABO or Rh incompatibility).

Hypoglycemia in the first day of life was noted in three infants in this study (two born to mothers treated with ATV/RTV 300/100mg, and one born to mother treated with ATV/RTV 400/100mg). The hypoglycemia in these infants could not be explained by maternal glucose intolerance, difficult delivery or sepsis. It is not clear whether the observed hypoglycemia was due to atazanavir exposure *in utero.* Protease inhibitors have been associated with glucose intolerance in adult patients; however this association did not appear to be an issue in pregnant women who were studied with other protease inhibitors, namely nelfinavir and/or lopinavir-ritonavir (Hitti et al. 2007, Tang et al. 2006, Dinsmoor and Forrest 2002). However, one published study of HIV positive mothers treated with the protease inhibitor, nelfinavir, suggested that HIV protease inhibitors could cause hypoglycemia in exposed neonates even when in the absence of clinically apparent maternal glucose intolerance (Dinsmoor and Forrest 2002). Based on this concern and the lack of feasibility of doing another study of infants born to pregnant mothers treated with atazanavir, the review team believes that the observation of hypoglycemia should be described in labeling.

1.2 Risk Benefit Assessment

While the study was not designed to compare efficacy between the ATV/RTV 300/100-mg and 400/100-mg dosing regimens, the Applicant was able to demonstrate full suppression of HIV viral load (< 50 copies/mL) at delivery in 38 out of the 39 pregnant mothers in the study and none of the infants demonstrated any evidence of HIV transmission at six months of age. Overall there was no difference in efficacy as defined by proportion of pregnant women that achieved HIV viral load < 50 copies/mL between the ATV 300/100mg and 400/100mg regimens. However, there was a difference in safety profiles for the two regimens. In general, mothers on the ATV/RTV 400/100mg regimen had a higher frequency of Grade 3-4 hyperbilirubinemia than mothers on ATV 300/100mg. The difference between the severity of post-natal hyperbilirubinemia in neonates exposed to ATV/RTV 300/100mg versus 400/100mg was small and not statistically significant.

Even though none of the ATV-exposed infants had evidence of neurotoxicity related to *in utero* ATV exposure, it is theoretically possible that ATV-exposed infants could have developed subtle neurotoxicity (e.g. sensineural hearing loss or intellectual handicaps) that were not detected in this study. Therefore, it is prudent to recommend the lower ATV/RTV 300/100mg dose in mothers not receiving any interacting concomitant medications since there was no difference

in efficacy between the two ATV/RTV doses and mothers treated with the lower dose had acceptable pharmacokinetics.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies (REMS)

No REMS is recommended for this supplement.

1.4 Recommendations for Postmarket Requirements and Commitments (PMC)

No PMR is recommended for this supplemental application. The following Phase 4 commitment is outstanding:

> A pediatric study or studies under PREA for the treatment of HIV infection in pediatric patients ages greater than or equal to 3 months to 18 years to determine safe and appropriate dosing.

In NDA 21-567 SE5-015 (letter date: September 27, 2007), the Applicant submitted data for the ATV capsule formulation in patients six years to 18 years of age. In that submission, the Applicant requested a partial pediatric deferral of this requirement specific to pediatric patients who are three months or older to less than six years of age. A partial waiver of PREA requirements for pediatric patients younger than three months was previously granted due to the potential issue of neonatal and/or infant hyperbilirubinemia. The clinical review team recommended granting the partial deferral pending the submission of the pediatric supplement for the powder formulation. From a preliminary review of the data from pediatric patients who received the powder formulation (to be formally submitted in the future), the review team was concerned that the Applicant will not have the safety data for a minimum of 100 patients treated at or above the recommended ATV dose for 24 weeks. On March 25, 2008, the review team recommended the following PREA requirement that was accepted by the Applicant:

> Deferred pediatric study or studies under PREA for the treatment of HIV-1 infection in pediatric patients ages $\geq$ 3 months to 18 years to obtain a minimum of 100 patients followed for safety for a minimum of 24 weeks at the recommended dose or any higher doses studied during pediatric development.

2 Introduction and Regulatory Background

2.1 Product Information

Established Name: Atazanavir
Trade Name: Reyataz
Chemical: $C_{38}H_{52}N_6O_7 \cdot H_2SO_4$
Class: Protease Inhibitor
Formulation: Capsules (100 mg, 200 mg, 300 mg, 400 mg)
Dosage: 1) 300 mg daily and RTV 100 mg daily for treatment-naïve and treatment-experienced adults
2) 400 mg daily for treatment-naïve adults who are intolerant to ritonavir
3) 400 ATV and 100mg RTV for treatment experienced patients who are receiving concomitant tenofovir and an H_2-receptor antagonist
4) ATV-boosted RTV should not be co-administered with proton-pump inhibitors or efavirenz in treatment-experienced patients

2.2 Tables of Currently Available Treatments for Proposed Indications

The use of combination antiretroviral therapy is recommended for all pregnant, HIV-infected women, regardless of plasma HIV RNA copy number or CD4+ cell count. Such therapy is recommended both in women who require therapy for their own health and in women not requiring therapy (Panel on Treatment of HIV-Infected Pregnant Women and Prevention of Perinatal Transmission 2010). Zidovudine is the only antiretroviral that is approved for the prevention of maternal-fetal transmission.

Table 1: Approved Antiretrovirals

Drug Class	Generic Name	Trade Name
NRTI*	Zidovudine	Retrovir®
	Didanosine	Videx®
	Stavudine	Zerit®
	Lamivudine	Epivir®
	Abacavir	Ziagen®

	Tenofovir	Viread®
	Emtricitabine	Emtriva®
	Zalcitabine*	Hivid®
NNRTI	Delavridine	Rescriptor®
	Nevirapine	Viramune®
	Efavirenz	Sustiva®
	Etravirine	Intelence®
PI	Indinavir	Crixivan®
	Ritonavir	Norvir®
	Saquinavir, hard gel	Invirase®
	Saquinavir, soft gel*	Fortovase®
	Nelfinavir	Viracept®
	Amprenavir*	Agenerase®
	Fosamprenavir	Lexiva®
	Atazanavir	Reyataz®
	Lopinavir/ritonavir fixed dose combination	Kaletra®
	Tipranavir	Aptivus®
	Darunavir	Prezista®
Fusion Inhibitor	Enfuvirtide	Fuzeon®
CCR5 Inhibitor	Maraviroc	Selzentry®
Integrase Inhibitor	Raltegravir	Isentress®

*Sale and distribution of zalcitabine (ddC, Hivid®) was discontinued on December 31, 2006. Sale and distribution of saquinavir soft gelatin capsules (SQV, Fortovase) was discontinued on February 15, 2006. Sale and distribution of amprenavir (AMP, Agenerase®) was discontinued on October 31, 2007 (Reference: Drug Discontinuation. Available at: http://www.fda.gov/CDER/Drug/shortages/default.htm#disc

2.3 Availability of Proposed Active Ingredient in the United States

The active moiety is currently approved and available for use in the US.

2.4 Important Safety Issues with Consideration to Related Drugs

Class-related adverse events/laboratory abnormalities and potential for significant drug-drug interaction potential are common for the approved protease inhibitors (PIs). Ritonavir (RTV) has significant drug-drug interactions due to its potent inhibition of CYP3A4 metabolism. As with other PIs, the ATV label includes warnings and precautions for new onset diabetes, hyperglycemia, hepatotoxicity, rash, lipodystrophy, (b) (4) increased bleeding episodes in patients with hemophilia, and fat redistribution.

With regards to glucose intolerance associated with protease inhibitors, the study under review examined the frequency of glucose abnormalities during pregnancy for women receiving atazanavir therapy since glucose intolerance manifesting during pregnancy is a common occurrence. A single literature report noted that hypoglycemia appeared to be more common in infants exposed to protease inhibitor nelfinavir *in utero* compared to other infants who were not exposed to a protease inhibitor as part of their perinatal HIV prophylaxis (Dinsmoor and Forrest Infect Dis Obstet Gynecol 2002; 10:187-191). However, more recently, investigators have not found an association between protease inhibitors and increased glucose intolerance in pregnancy.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

- The original protocol for AI424182 was submitted by the Applicant on September 30, 2005 as IND 56,897 serial number 688 and was received by DAVP on October 14, 2005 and was deemed safe to proceed with comments provided. See Dr. Struble's review of November 2, 2005 for additional details.

- A third amendment to change the inclusion and exclusion criteria enrollment IND 56,897 serial 729 was submitted on October 30, 2006 and accepted without comment. See Dr. Struble's review of November 24, 2006 for additional details.

- An interim report of study data IND 56,897 serial 770 was submitted on March 18, 2008 and reviewed. See Dr. Chan-Tack's review of March 25, 2008 for additional details.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

Since this submission involved sites not recently visited by DSI, a request for Biopharmaceutical Inspections was made to have DSI inspect Site 4, University of Puerto Rico, Rio Piedras, Puerto Rico and Site 5 in South Africa, which included Helen Joseph Hospital, Johannesburg Hospital, and Coronation Hospital.

DSI report:
Site 4 in Puerto Rico was inspected and no 483 was issued.
Site 5 was issued a 483 and the clinical Establishment Inspection Report (EIR) is pending.

Clinical Inspection:
The 483 items are listed below:

1) Failure to prepare or maintain accurate case histories with respect to observations and data pertaining to the clinical investigation. (For the study conducted at Helen Joseph Hospital). Two subjects (initials (b) (6) and (b) (6)) were consented, did not meet all inclusion criteria. These two subjects were not identified as screening failures. This resulted in inaccuracies of the total number of subjects screened and screening failures as reported to the Ethics Committee and appearing in Final Reports. Total of 33 screened vs. 31 reported. DSI recommends that this observation has no significant impact on data integrity or subject safety.

Reviewer Comment: The two unreported screening failures will not affect the safety conclusions made from this application.

2. Investigation was not conducted in accordance with the investigational plan. (for the study conducted at Helen Joseph Hospital). Specifically, there were no records of PK blood processing to document that the samples were handled and processed according to protocol section 7.3.11.1: There were no records of the times between collection and centrifugation; times and temperatures of centrifugation; times between centrifugation and storage; and storage temperatures until shipment to the laboratory.

The analytic site, (b) (4), provided stability data that minimized the impact of the lack of records.

ANALYTICAL INSPECTION:

The inspection of the analytical portion was conducted at (b) (4) (b) (4) (b) (4)

[redacted]

Reviewer Comments: Based on further communications, (b) (4) [redacted]

See Section 4,4 Clinical Pharmacology for additional details.

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3.2 Compliance with Good Clinical Practices

(see Section 3.1 above)

3.3 Financial Disclosures

Form FDA 3454 and list of investigators with financial disclosure information was reviewed and found to be acceptable.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

This sNDA contained no new chemistry, manufacturing and controls (CMC) data. Please refer to the original NDA review for CMC information.

4.2 Clinical Virology

At or before delivery, all 41 mothers achieved HIV-1 RNA < 50 copies/mL. On the actual day of delivery, all mothers had HIV-1 RNA < 400 copies/mL (virologic response-observed cases [VR-OC]) and 38 of 39 mothers who completed the study had HIV-1 RNA < 50 copies/mL at delivery. One mother achieved an undetectable HIV-1 RNA of < 50 copies/mL for the 3 visits prior to delivery, and again suppressed to < 50 copies/mL post delivery. Through 6 months of life, all infants were HIV-1 negative.

The virology team concluded that no major differences in genotypic and phenotypic changes to ATV were observed between the two doses and no ATV resistance development on treatment was associated with failure to fully suppress viral load.

See Dr. Lisa Naeger's review for additional details.

4.3 Preclinical Pharmacology/Toxicology

This sNDA contained no new preclinical pharmacology/toxicology data. Please refer to the original FDA review of the NDA for additional information. However, there was a reorganization of labeling of the Pharmacology-Toxicology related sections and the Pharmacology-Toxicology team edited the proposed labeling to maintain accuracy and relevance to dosing in pregnancy.

See Dr. Kuei-Meng Wu's review for additional details.

4.4 Clinical Pharmacology

Clinical Pharmacology's interpretation of the PK results from the Sponsor was affected by the results from the DSI inspection (see Section 3.1 Submission Quality and Integrity) which recommended the exclusion of data from questionable sample runs. Excluding these PK data mainly affected the PK results from the 2nd trimester mothers resulting in lower AUC and Cmax values than expected. Nevertheless, the following recommendations from Clinical Pharmacology were made and considered acceptable by DAVP:

- The clinical study submitted by the Applicant supports the approval of atazanavir (ATV)/ritonavir (RTV) use in pregnant women. The data indicated that for pregnant patients no dose adjustment is required for atazanavir (REYATAZ) with the following exceptions:
    - REYATAZ without ritonavir is not recommended.
    - REYATAZ should only be administered to pregnant women with HIV-1 strains susceptible to atazanavir.
    - For treatment-experienced pregnant women during the second or third trimester, when REYATAZ is co-administered with either tenofovir or an H2-receptor antagonist, atazanavir 400 mg with ritonavir 100 mg once daily is recommended. There is insufficient data to recommend a REYATAZ dose for use with tenofovir *and* H_2-receptor antagonists in treatment-experienced pregnant women.

- No dose adjustment is required for postpartum patients. However, adverse events should be closely monitored because atazanavir exposures could be higher during the first 2 months after delivery.

See Dr. Jenny H. Zheng's review for additional details of the Clinical Pharmacology results.

4.4.1 Mechanism of Action

ATV is an azapeptide HIV-1 protease inhibitor (PI). The compound selectively inhibits the virus-specific processing of viral Gag and Gag-Pol polyproteins in HIV-1 infected cells, thus preventing formation of mature virions.

4.4.2 Pharmacodynamics

See Dr. Jenny H. Zheng's review for details of the Clinical Pharmacology results

4.4.3 Pharmacokinetics

Atazanavir Levels in Maternal vs. Cord Blood**:**
The Applicant states that relative to the corresponding maternal ATV concentrations at the time of delivery, the ATV concentrations in cord blood were approximately 12% and 19% at ATV/RTV 300/100 mg and ATV/RTV 400/100 mg, respectively. The Applicant concluded that the ratio of ATV concentrations in maternal and umbilical cord blood indicates that ATV does not freely cross the placenta; however, it is not clear whether this small amount of ATV transferred to the fetus could inhibit the infant's UGT1A1 enzyme until the drug is cleared by the infant.

Comparison of Maternal and Infant Bilirubin Levels:
The Applicant concluded that the correlation between maternal bilirubin, both on the date of delivery and the mean level in the 4 weeks prior to delivery, with that of the infant on the day of delivery was low based on the r^2 in the provided scatterplots of the data:

Figure 1: Scatterplot of Infant vs. Mother's Total Bilirubin at Delivery Day:

5 Sources of Clinical Data

This review is primarily based on data from one Phase 4 study AI424138 conducted by the Applicant.

5.1 Tables of Studies/Clinical Trials

Only one clinical study, A1424182, was included with this sNDA application, as summarized in the following table.

Table 2:Clinical Study AI424138

Study	Study Type	Country or Continent	Design	Dose and Duration	Total No. of Subjects/ARV experience	Status
Phase 4 Study –HIV+ Pregnant Women						
AI424182	pharmacokinetics, safety and efficacy	North America including Puerto Rico and , South Africa	Multicenter, open-label, prospective, single-arm, efficacy, safety, & PK study	During Pregnancy; Median time on study therapy was 18.8 weeks for mothers on ATV/RTV 300/100 mg, 13.5 weeks on ATV/RTV	Mothers (41 total) ATV 300 mg/RTV: 20 subjects ATV 400 mg/RTV: 21 subjects Infants (40 total)	Completed

Study	Study Type	Country or Continent	Design	Dose and Duration	Total No. of Subjects/ARV experience	Status
				300/100 mg for mothers who switched to ATV/RTV 400/100 mg, and 10 weeks for mothers on ATV/RTV 400/100 mg after the switch	20 each whose mothers had been treated with ATV 300 mg/RTV or ATV 400 mg/RTV	

ATV/RTV, atazanavir/ritonavir

5.2 Review Strategy

Safety data review included case report tabulations and case report forms when applicable. FDA clinical, clinical pharmacology, and Pediatric and Maternal Health Staff reviewers collaborated extensively throughout the review process, particularly with pediatric bilirubin assessments, and with the reviewer's concerns about *in utero* bilirubin exposure and pregnancy labeling.

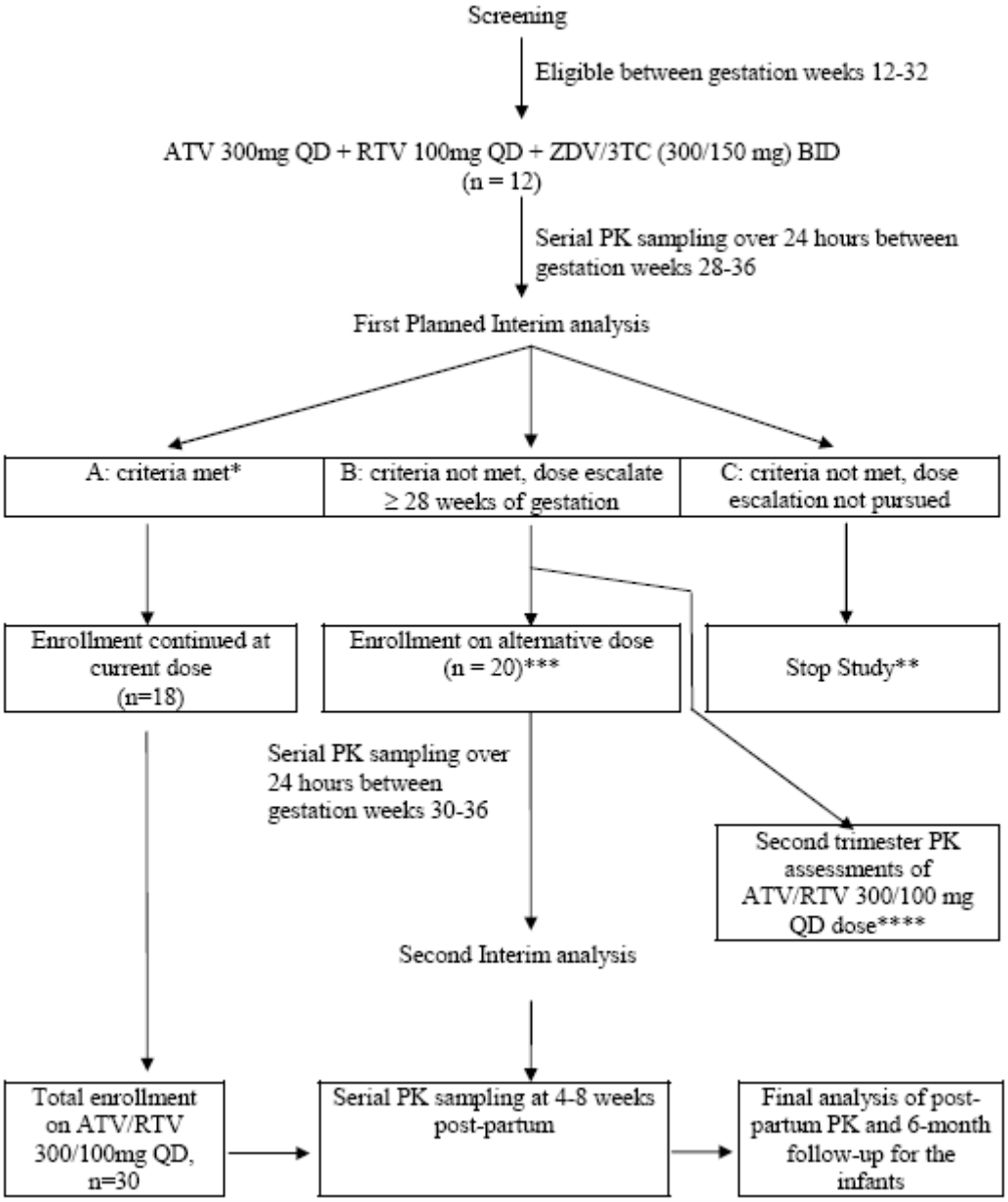
5.3 Discussion of Individual Studies/Clinical Trials

Discussion of Individual Studies

Study AI424182 was a multi-center, open-label, prospective, single-arm study designed to determine which dosing regimen of ATV/RTV produces adequate drug exposure during pregnancy compared to drug exposure of HIV-infected subjects from historical data. The first 12 subjects who met inclusion/eligibility criteria received the following dose: ATV/RTV 300/100 mg once daily (QD) with food + ZDV/3TC (Combivir) 300/150 mg fixed dose combination (FDC) twice daily (BID). A planned PK interim analysis was performed after 12 subjects reached steady state (2 weeks on drug) during the 3rd trimester of pregnancy to determine whether a dose adjustment would be warranted. The intensive PK sampling was conducted over a single 24-hour period during Week 28 to Week 36 of gestation. A planned PK interim analysis was performed after 12 subjects reached steady state (2 weeks on drug) during the 3rd trimester of pregnancy to determine whether a dose adjustment would be warranted. The intensive PK sampling was conducted over a single 24-hour period during Week 28 to Week 36 of gestation. Based on the interim analysis, dose adjustment to ATV/RTV 400/100 mg QD in the 3rd trimester was indicated. Because it was determined that dose escalation to ATV/RTV 400/100 mg was indicated, the following changes to the study execution were made: 1) subjects on study who were ≥ Week 14 and < Week 28 of gestation

continued to receive ATV/RTV 300/100 mg until Week 28 when they switched to ATV/RTV 400/100 mg; 2) subjects newly enrolled in the study whose baseline visit was ≥ Week 14 and < Week 28 of gestation received ATV/RTV 300/100 mg until they reached Week 28 of gestation at which time they switched to the ATV/RTV 400/100-mg dose; 3) newly enrolled subjects whose baseline visit was ≥ Week 28 of gestation immediately started on the ATV/RTV 400/100-mg dose; 4) subjects who were ≥ Week 28 of gestation immediately switched to the ATV/RTV 400/100-mg dose; 5) 2nd trimester intensive PK assessments were scheduled for all eligible subjects who reached steady state on ATV/RTV 300/100 mg and the 2nd trimester intensive PK assessment was completed between Week 18 and Week 24 of gestation; and 6) 3rd trimester PK for all subjects on the ATV/RTV 400/100-mg dose was performed at steady state between Weeks 30 to 36 of gestation. Figure 2 shows the study schematic. The study actually followed pathway B and a total of 20 subjects were treated with ATV/RTV 300/100mg and 21 subjects were treated with ATV/RTV 400/100mg.

Figure 2: Study Schematic



* Criteria for A were not met (see Section 5.3 Discussion of Individual Studies first paragraph for additional details).
**If subjects were enrolled on a suboptimal dose (whether ATV/RTV 300/100 mg QD or ATV/RTV 400/100 mg QD), they would have been offered alternative antiretroviral therapy determined by local investigators.
***A total of 41 subjects were enrolled since a dose escalation to ATV 400 mg QD/RTV 100 mg QD was mandated by the protocol (n = 12 on initial ATV/RTV 300/100 mg QD dose, then 21 on increased dose of ATV/RTV 400/100mg and an additional eight subjects on the original ATV/RTV 300/100mg QD).
****Second trimester intensive PK assessments were scheduled for all eligible subjects who have reached steady state on ATV 300 mg QD/RTV 100 mg QD. The 2nd trimester intensive PK assessment was completed between Week 18 and Week 24 of gestation.

TITLE OF STUDY

A Study of the Pharmacokinetics of Atazanavir (ATV)/Ritonavir (RTV) Administered as Part of HAART Therapy in HIV-1 Infected Pregnant Women

STUDY PERIOD:
Study Initiation Date: 12-Jun-2006
Study Completion Date: 10-Aug-2009

Key inclusion criteria:

- HIV Positive pregnant women age 18 years of age or older
- CD4 count >200 cells/mm^3
- Treatment-naive subjects with an HIV RNA > 400 copies/mL;
- Women currently on a highly-active antiretroviral regimen (HAART) (minimum of 3 drugs drawn from at least 2 classes) with an HIV RNA level< 50 copies/mL at Screening. In these subjects the investigator must document a medically compelling reason for switching to the study regimen (e.g. intolerance or laboratory abnormalities associated with current regimen).
- Not currently on ARVs but previously treated with ARVs and RNA > 400 copies/mL
    - Women with a history of exposure to a protease inhibitor (PI) other than atazanavir as a component of a HAART regimen(s) are eligible if it can be documented that the regimen(s) was (were) changed or discontinued for a reason other than virologic failure. Subjects who took an ATV-based HAART regimen for more than 3 weeks are ineligible, except in the case of exposure during a previous pregnancy.
    - Women who have received prior treatment with ddI, ddC, d4T, ZDV, tenofovir, and abacavir or any non-nucleoside reverse transcriptase inhibitor are eligible.
- Pregnancy with an estimated gestational age between Week 12 and Week 32; subjects whose screening ultrasound indicates a gestational age < 12 weeks will be allowed to undergo a second ultrasound without full re-screening if the repeat ultrasound is done within two weeks.
- Singleton pregnancy;
- Subjects must commit to exclusively feeding infants with formula for the duration of the study;
- Available for treatment through labor, delivery and to 8 weeks post-partum and for 6 months of follow-up for the infant.

Key exclusion criteria:

- Presence of a newly diagnosed HIV-related opportunistic infection or any medical or obstetric condition requiring acute therapy at the time of enrollment, including tuberculosis;
- Suspected primary (acute) HIV infection.
- Women who have been exposed to efavirenz or delavirdine during the current pregnancy;
- Screening Child-Pugh Score > 6 (Class B or C); Hepatitis B surface antigen positive or hepatitis C antibody positive;
- Rhesus antibody positive;
- Diabetes mellitus, current gestational diabetes mellitus, or a history of gestational diabetes;
    - i) Subjects whose 1-hour glucose tolerance test (GTT) glucose result is > 140 mg/dL (7.8 mmol/L) are ineligible for the study.
    - ii) Subjects whose 1-hour GTT result is > 130 mg/dL (7.2 mmol/L) and ≤ 140mg/dL (7.8 mmol/L) may undergo the 3-hour GTT at the discretion of the investigator to determine if they have gestational diabetes (GDM) (Per the American Diabetes Association definition for GDM, . If the 3-hour GTT is negative for GDM, the subject is eligible.
    - iii) Fasting glucose ≥ 126 mg/dL (7 mmol/L). Subjects with a screening level ≥ 100mg/dL (5.6 mmol/L) and < 126 mg/dL (7.0 mmol/L) have to undergo a 1-hour GTT.
- A previous infant who developed hemolytic disease of the newborn and/or had neonatal pathologic jaundice, that required phototherapy;
- A known history of Gilberts or Criggler-Najar Type I or II syndromes;
- A known history of glucose-6-phosphate dehydrogenase deficiency, sickle cell disease, hemophilia, or family history of galactosemia;
- Obstetrical complications in past pregnancies: poor obstetrical history including spontaneous abortions (3 or more), previous preterm (< 37 weeks) or low birth weight infant (< 2,500 g), major congenital anomalies, unexplained stillbirth, or unexplained neonatal loss;
- Obstetrical complications in this pregnancy including: presence of major congenital anomalies, multiple gestation, placenta previa or abruption, pre-eclampsia, eclampsia, or preterm premature rupture of membrane resulting in tocolysis;
- Evidence of any fetal anomalies; or placental, uterine, or amniotic fluid abnormalities, including abnormal amniotic fluid volume on entry, e.g., polyhydramnios (amniotic fluid index > 20.0 cm), or oligohydramnios (amniotic fluid index < 8.0 cm or subjectively decreased); or intrauterine growth restriction < 10th percentile for gestational age, or other abnormal condition (either maternal or fetal) seen on screening ultrasound
- Subjects with an adjusted maternal serum alpha fetoprotein (MSAFP) multiples of the median (MoM) ≥ 2.5 are excluded. Subjects who screen

between weeks 12 to 14 of gestation whose MSAFP is ≥ 2.5 MoM or for whom the results are inconclusive will need another MSAFP checked between weeks 15 to 19 of gestation, prior to treatment allocation. They will not have to undergo a full re-screening. For women > 20 weeks of gestation at Screening who did not have MSAFP test done as part of prenatal care, a normal level II ultrasound that documents the absence gross of neural tube defects (NTD) will be sufficient;

- Neurological conditions which may lead to pregnancy complications, including seizure disorders;
- Pulmonary conditions including moderate to severe asthma (chronic systemic and inhaled steroids are prohibited) and cystic fibrosis;
- Subjects with Cushing's syndrome;
- Subjects with a history of hypothyroidism or hyperthyroidism;
- Recent therapy with agents with significant systemic myelosuppressive, neurotoxic, pancreatotoxic, hepatotoxic or cytotoxic potential within 3 months of study start or the expected need for such therapy at the time of enrollment; or therapy with methadone or ribavirin/interferons; or treatment with neurotoxic drugs or drugs that affect CYP3A4
- Subjects with obstructive liver disease, proven or suspected acute hepatitis in the 30 days prior to study entry;
- Intractable diarrhea (≥ 6 loose stools/day for at least 7 consecutive days) within 30 days prior to study entry;
- Active peripheral neuropathy;
- Presence of cardiomyopathy (due to any cause) or any significant cardiovascular disease, such as unstable ischemic heart disease;
- Known, clinically significant cardiac conduction system disease. This includes severe first degree atrioventricular block (PR interval > 0.26 seconds) as well as second and third-degree atrioventricular block.
- Screening laboratory values measured as follows:
    - ALT/AST ≥ Grade 2, Amylase > 1.5 times upper limit of normal and/or abnormal lipase, Bicarbonate ≥ Grade 2, Serum creatinine > 1.5 mg/dL
    - Bilirubin ≥ Grade 1; a direct or total bilirubin levels ≥ Grade 1 will exclude subjects. For those on ATV at the time of screening, total bilirubin must be ≤ 7.5 mg/dL, and the direct bilirubin level must be ≤ 1 mg/dL.
    - Hematology ≥ Grade 2, except for anemia: exclude only women with hemoglobin < 9.0 g/dL and/or hematocrit < 27.3% (< 8.5 g/dL and/or hematocrit < 25.6% if currently on ZDV) at Screening; all subjects with anemia who enroll in the study must be receiving or start hematinics, including iron and folate supplements, immediately upon enrollment and continue until anemia resolves or end of pregnancy

OBJECTIVES:
Primary Objectives:

- To determine which dosing regimen of ATV/RTV produces adequate drug exposure during pregnancy compared to drug exposure in historical data in HIV-infected subjects

Secondary Objectives:

- To compare ATV/RTV drug exposure during the 3rd trimester of pregnancy to drug exposure in the same women in the study cohort during the postpartum period
- To explore ATV/RTV drug exposure during the 2nd trimester of pregnancy (if available)
- To compare ATV drug concentrations in plasma from cord blood with those in maternal plasma at the time of delivery
- To determine the plasma protein binding of ATV during pregnancy and postpartum
- To assess the safety and tolerability of an ATV/RTV-based HAART regimen during pregnancy
- To assess the virologic efficacy of an ATV/RTV-based HAART regimen during pregnancy
- To assess the efficacy of an ATV/RTV-based HAART regimen in preventing the mother-to-child-transmission (MTCT) of HIV-1 in formula fed infants
- To explore the relationship between UDP Glucuronosyltransferase 1A1 (UGT1A1) genotypes and bilirubin levels in pregnant women receiving ATV/RTV and in infants exposed to ATV/RTV in utero and at birth

Study Population:
HIV-1 infected, pregnant women with a CD4 count of ≥ 200 cells/mm3. Subjects were eligible for study enrollment between Week 12 and Week 32 of gestation. Subjects with a current or past medical history of conditions known to increase the risk of pathologic neonatal jaundice were not be eligible for the study.

Study Duration:
Subjects will become eligible between Week 12 and Week 32 of gestation. Subjects will receive orally administered study medication during the remainder of the pregnancy and intravenous zidovudine throughout labor and delivery. Subjects will continue to receive study medication until 4-8 weeks postpartum when the final PK analysis is performed.

Study Design:
Study AI424182 is a multi-center, open-label, prospective, single-arm study in HIV+ pregnant women to determine dosing of ATV/ritonavir (r) that achieves predefined AUC and Cmin targets in the third trimester. (see Section 5.3 Discussion of Individual Studies first paragraph for additional details) Safety

assessments on mothers and infants included clinical examination and laboratory testing at each study visit. ATV and RTV were analyzed by liquid chromatography (LC)/mass spectrometry (MS)/MS. Descriptive statistics for third trimester and post-partum pharmacokinetic parameters were calculated and compared with historical data in HIV+ subjects as a reference; all available safety data were reported

Criteria for Evaluation:

Primary PK Endpoints:
· AUC, Cmin, Cmax, T1/2, Tmax.
Secondary PK Endpoints:
· The ratio of cord blood ATV and RTV concentration to maternal blood concentration at the time of delivery;
· The percentage of ATV bound to plasma proteins during the third trimester and post-partum.

Safety Endpoints:
· The frequency and duration of hyperbilirubinemia in neonates at Days 1, 3, 5 and 7 postpartum;
· The frequency and severity of adverse events in neonates;
· The frequency and severity of adverse events in pregnant women.
· The frequency and occurrence of adverse pregnancy outcomes or adverse neonatal outcomes.

Efficacy Endpoints:
· The proportion of pregnant women with HIV RNA < 400 c/mL and < 50 c/mL at the time of delivery;
· The magnitude of HIV RNA reduction from baseline in pregnant women over time;
· The magnitude of CD4 cell count change from baseline in pregnant women over time;
· The proportion of neonates with HIV-1 infection at birth through Week 16, as determined by HIV-1 DNA PCR;
· The proportion of subjects who are adherent to each drug (ATV/RTV, ZDV/3TC) and adherent to the regimen over time as measured by the MACS Adherence Questionnaire.

Safety Issues:

Hyperbilirubinemia:

Unconjugated hyperbilirubinemia is a concern for the atazanavir-exposed unborn fetus and for neonates which could potentially exacerbate physiological jaundice.

Physiological jaundice is the increased unconjugated bilirubin concentration developed in the first week of life in many infants that is due to the imbalance of the production of bilirubin and its uptake/elimination. Markedly elevated unconjugated bilirubin > 20mg/dL has been associated with bilirubin neurotoxicity and more severe cases kernicterus. In atazanavir treated adults and pediatric patients, the incidence and severity of hyperbilirubinemia has been shown to be dose dependent,

P-R interval Prolongation:

Atazanavir has been associated with Type 1 AV block in a dose-dependent fashion in both adult and pediatric patients.

Glucose Abnormalities:

Glucose intolerance has been reported in adults treated with atazanavir and with other HIV protease inhibitors.

6 Review of Efficacy

Efficacy Summary

Study AI424182 was designed primarily as a pharmacokinetic and safety study and efficacy information was collected. Thirty eight out of 39 (97%) pregnant subjects treated with atazanavir achieved the virological endpoint of HIV-RNA <50 copies/mL at the time of delivery. None of the 40 infants born to the mothers treated with atazanavir became HIV positive during the six months of follow-up. Since the goal of antepartum HIV prophylaxis is to control HIV replication in the pregnant mother with a non-detectable HIV viral load at the time of delivery, the Applicant achieved this goal in their small study. In addition, none of the HIV exposed infants showed evidence of HIV transmission at six months of life.

Currently with successful maternal combination antiretroviral therapy (HIV viral load <400), intrapartum and infant postpartum zidovudine, maternal-fetal HIV transmission has been reduced to less than 1%. Given the small size and non-comparative design of Study AI424182, it is not possible to compare the ATV-ZDV-LMV regimen to the most commonly used regimen of lopinavir/ritonavir (LPV/RTV)-ZDV-LMV.

6.1 Indication

Reyataz (atazanavir sulfate) is indicated in combination with other antiretroviral agents for the treatment of HIV-1 infection in patients six years and older The

Applicant did not seek an indication for HIV perinatal prophylaxis. The purpose of the application under review is to add pharmacokinetic and safety information for atazanavir when used to treat pregnant women for the antepartum therapy component of HIV perinatal prophylaxis.

6.1.1 Methods

This review focuses primarily on the safety and efficacy data submitted for Study AI424182. The pharmocokinetics was reviewed by Dr. Jenny H. Zheng. Given the concerns about bilirubin toxicity to fetus and newborn infants, a consult was placed to Pediatric and Maternal Health Staff to address this issue. There were gaps in the information provided in the Applicant submission and a number of requests were made to the Applicant to fill in these gaps, including total bilirubin results in infants relative to the time of delivery in hours, glucose monitoring in the newborn infants, and others.

Demographics

Mothers
There were 20 pregnant women enrolled into the ATV/RTV 300/100mg cohort and 21 mothers into the ATV/RTV 400/100mg cohort (see Table 3). The majority of the enrolled mothers were Black/African (88%) whose infants are at lower risk for physiological jaundice. All of the mothers were less than 40 years of age. The median HIV viral load and CD4 count for mothers treated with ATV/RTV 300/100mg was approximately 3,200 copies/mL and 387 cells/mm^3, respectively, and for mothers treated with ATV/RTV 400/100mg was approximately 11,481 copies/mL and 355 cells/mm^3, respectively. All mothers treated in this study tested negative for hepatitis B virus and hepatitis C virus at baseline. The majority of mothers (> 71%) had infectious disease screening for syphilis, but not gonorrhea, chlamydia, or bacterial vaginosis. One mother tested positive for syphilis at screening.

Table 3: Demographics and Disease Characteristics - Treated Mothers

	NUMBER OF SUBJECTS (%)	
	3rd Trimester Treatment	
	ATV300/RTV N = 20	ATV400/RTV N = 21
Age (Years)		
MEAN (SE)	29 (1.1)	28 (1.0)
MEDIAN	29	28
MIN, MAX	21, 38	19, 37
MISSING	0	0
Gest. Age @ Baseline (Weeks)		
MEAN (SE)	23 (1.2)	23 (1.2)
MEDIAN	24	23
MIN, MAX	15, 31	15, 32
MISSING	0	0
Race: N (%)		
BLACK/AFRICAN AMERICAN	17 (85)	19 (90)
WHITE	3 (15)	1 (5)
OTHER: MIXED RACE	0	1 (5)
Region: N (%)		
AFRICA	14 (70)	15 (71)
NORTH AMERICA	6 (30)	6 (29)
HIV RNA Level (log10 c/mL)		
MEAN (SE)	3.52 (0.232)	4.02 (0.171)
MEDIAN	3.51	4.06
MIN, MAX	1.69, 5.11	1.69, 5.29
MISSING	0	0
HIV RNA Distribution (c/mL): N (%)		
< 50	3 (15)	1 (5)
50 - < 30000	13 (65)	13 (62)
30000 - < 100000	3 (15)	6 (29)
>= 100000	1 (5)	1 (5)
CD4 Cell Count (cells/mm3)		
MEAN (SE)	435 (39.2)	390 (25.0)
MEDIAN	387	355
MIN, MAX	236, 1028	220, 657
MISSING	0	0

Percentages are based on subjects with measurements.

Infants

There were 20 infants each born to the maternal cohorts of ATV/RTV 300/100mg and 400/100mg. Approximately n/N (83%) of infants followed in the study were Black/African American (see Table 4).

Table 4: Demographics and Disease Characteristics - Enrolled Infants

	NUMBER OF SUBJECTS (%)	
	Mothers 3rd Trimester Treatment	
	ATV300/RTV N = 20	ATV400/RTV N = 20
Gest. Age @ Delivery (Weeks)		
MEAN (SE)	38 (0.3)	38 (0.3)
MEDIAN	38	38
MIN, MAX	35, 40	35, 41
MISSING	0	0
Gender: N (%)		
MALE	12 (60)	9 (45)
FEMALE	8 (40)	11 (55)
Race: N (%)		
BLACK/AFRICAN AMERICAN	15 (75)	18 (90)
WHITE	5 (25)	1 (5)
OTHER: MIXED RACE	0	1 (5)
Region: N (%)		
AFRICA	14 (70)	14 (70)
NORTH AMERICA	6 (30)	6 (30)

Percentages are based on subjects with measurements.

Subject Disposition

Treated Mothers:

There was one mother in the ATV/RTV 300/100mg cohort and two mothers from the ATV/RTV 400/100mg cohort who discontinued ATV prior to delivery (see Table 5). Each of these subjects discontinued ATV/RTV due to an adverse event (see Section 7.3.3 below).

Table 5: Subject Disposition - Treated Mothers

	Number of Subjects 3rd Trimester Treatment	
	ATV300/RTV N = 20	ATV400/RTV N = 21
TREATED	20 (100)	21 (100)
DISCONTINUED FROM ATV TREATMENT	3 (15)	2 (10)
ADVERSE EVENT	1 (5)	1 (5)
OTHER	1 (5)	0
SUBJECT REQUEST	1 (5)	1 (5)
DISCONTINUED FROM ATV TREATMENT BEFORE DELIVERY	1 (5)	2 (10)
COMPLETED ATV TREATMENT	17 (85)	19 (90)
COMPLETED STUDY	19 (95)	19 (90)

Infants:

All ATV exposed infants received post-natal prophylaxis that included zidovudine from birth to six weeks of age. One infant from the ATV/RTV 300/100mg cohort and one infant from the ATV/RTV 400/100mg cohort were discontinued from post-natal prophylaxis due to an adverse event (see Table 6). Per protocol, only eight infants from the ATV/RTV 300/100mg cohort and nine infants from the ATV/RTV 400/100mg cohort received pneumocytis pneumonia (PCP) prophylaxis starting at six weeks of age. Infants with two negative HIV-1 DNA results prior to six weeks of age were not started on PCP prophylaxis. All 40 infants, 20 from each cohort completed study follow-up that included monitoring for possible HIV transmission.

Table 6: Subject Disposition - Enrolled Infants

	NUMBER OF SUBJECTS (%)	
	Mothers 3rd Trimester Treatment	
	ATV300/RTV N = 20	ATV400/RTV N = 20
ENROLLED	20	20
ALIVE	20 (100)	20 (100)
TREATED WITH ARV	20 (100)	20 (100)
DISCONTINUED FROM ARV TREATMENT	1 (5)	1 (5)
ADVERSE EVENT	1 (5)	1 (5)
COMPLETED ARV TREATMENT	19 (95)	19 (95)
RECEIVED PCP PROPHYLAXIS	8 (40)	9 (45)
DISCONTINUED PCP PROPHYLAXIS	2 (10)	2 (10)
OTHER	0	1 (5)
POOR/NON-COMPLIANCE	2 (10)	1 (5)
COMPLETED PCP PROPHYLAXIS	6 (30)	7 (35)
COMPLETED FOLLOW-UP	20 (100)	20 (100)

6.1.4 Analysis of Efficacy Endpoint(s)

HIV RNA Level -Treated Mothers

Of the 41 treated mothers, 2 mothers (5-0023 and 5-0045) discontinued study drug before delivery and did not have HIV RNA measurements at delivery (see Table 7). Of the 39 mothers with a HIV RNA test at delivery, all had a serum HIV RNA < 400 c/mL virologic response-observed cases (VR-OC) and 38 had HIV RNA < 50 c/mL (VR-OC). The one mother (14-0049) with HIV RNA > 50 c/mL at delivery had a viral load of 59 c/mL, had achieved an undetectable HIV RNA of < 50 c/mL for the 3 visits prior to delivery, and again suppressed to < 50 c/mL post-delivery.

CD4 Cell counts -Treated Mothers

At delivery, the median change from baseline in CD4 cell count (cells/mm3) was +89 and +174 for subjects on ATV/RTV 300/100 mg and ATV/RTV 400/100 mg, respectively (see Table 8).

Table 7: Efficacy Summary- Treated Mothers and Infants

	Responder/Evaluable (%)	
	Treatment Regimen in 3rd Trimester	
Endpoint	**ATV/RTV 300/100 mg**	**ATV/RTV 400/100 mg**
	Mothers at Delivery[a]	
HIV RNA < 400 c/mL		
VR-OC	19/19 (100)	20/20 (100)
HIV RNA < 50 c/mL		
VR-OC	19/19 (100)	19/20 (95)
HIV RNA, median reduction from baseline, log_{10} c/mL	-1.8	-2.37
CD4[b]**, median change from baseline, cells/mm^3**	89	174

Table 8: CD4 Cell Count and Change from Baseline at Delivery -Treated Mothers

		CD4 Cell Count (cells/mm^3)			
		Treatment Regimen			
		ATV300/RTV N = 20		ATV400/RTV N = 21	
Visit	Summary Statistics	Value	Change from B/L	Value	Change from B/L
Baseline	N #	20		21	
	MEAN (SE)	435 (39.2)		390 (25.0)	
	MEDIAN	387		355	
	Q1, Q3	339, 535		318, 481	
Delivery	N #	17	17	20	20
	MEAN (SE)	515 (48.7)	63 (52.5)	519 (47.6)	132 (42.8)
	MEDIAN	530	89	471	174
	Q1, Q3	370, 642	-75, 213	351, 713	-39, 257

Analysis of Clinical Information Relevant to Dosing Recommendations

Almost all enrolled mothers reached their efficacy endpoint of HIV RNA <50 copies/mL in both dosing cohorts. From an efficacy standpoint, although the cohorts were small, they were no differences observed between the ATV 300/100mg and 400/100mg cohorts.

7 Review of Safety

Safety Summary

Study AI424182 was a small study in pregnant women that examined the safety and general activity of combination antiretroviral therapy that included ATV/RTV. The Applicant compared two different regimens of RTV-boosted ATV (ATV/RTV 300/100mg versus 400/100mg) administered one daily with the backbone of zidovudine and lamivudine administered as Combivir administered twice daily. Given the concern about increased metabolism of protease inhibitors during the third trimester during pregnancy, the Applicant compared the standard adult regimen of ATV/RTV 300/100mg with 400/100mg. The two regimens were compared in the third trimester of pregnancy to compare their pharmacokinetics and safety. Safety issues associated with atazanavir exposure include hyperbilirubinemia, P-R interval prolongation, and glucose intolerance; and these were evaluated in this study. In addition, there was some developmental follow-up at four and six months of age using the Denver developmental screening tool.

Overall, there were no concerning safety signals from this study of atazanavir for use in the antenatal component of HIV perinatal prophylaxis. The safety of the two regimens of ATV/RTV 300/100mg and 400/100mg were comparable except for an increased frequency of Grade 3-4 unconjugated hyperbilirubinemia in mothers treated with ATV/RTV 400/100mg. The increased degree of hyperbilirubinemia did not appear to result in any significant clinical sequele.

7.1 Methods

Study AI424182 was reviewed with the help of the Pediatric and Maternal Health Team and the Office of Safety and Epidemiology with a focus on hyperbilirubinemia and hypoglycemia.

7.1.2 Categorization of Adverse Events

Adverse events were graded using the World Health Organization toxicity grading table (WHO Handbook for Reporting Results of Cancer Treatment).

7.2 Adequacy of Safety Assessments

Study AI424182 was a small study of 41 pregnant women and their infants that took approximately four years to enroll. The applicant did present standards of infant management in the protocol including U.S. based guidelines for management of hyperbilirubinemia and hypoglycemia however the physicians in South Africa were given some flexibility in their practice since the standard of care may differ there. There were some subjects both maternal and infant who had late or missing values but on the whole the Applicant provided a reasonable sampling of subject safety data. In regard to the glucose values, many infants did not have their samples handled appropriately to assure reliable results. In addition, some of the glucose samples obtained did not have collection times listed, which made it difficult to evaluate the accuracy of obtained laboratory values.

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

Forty one mothers were treated and 40 in utero exposed infants were followed. Twenty infants were exposed to each dosing cohort, i.e. ATV/RTV 300/100 mg n=20 infants, ATV/RTV 400/100 mg n=20 infants. One mother withdrew consent and her infant was not followed. Race was identified as “Black/African American” in 33 subjects, “White” in 6 subjects and as “Other: Mixed Race” in 1 subject. Twenty eight subjects were treated in several sites in South Africa, 10 subjects in Puerto Rico and 2 subjects in the US.

7.2.2 Explorations for Dose Response

With the exception of increased hyperbilirubinemia in treated mothers, there was no consistent safety signal in the ATV/RTV cohorts in which the higher dose ATV/RTV 400/100mg cohort had increased AEs as compared to the ATV/RTV 300/100mg.

7.2.4 Routine Clinical Testing

Mothers
During the study, maternal subjects had:

- regular physical exams with vital signs
- at least one ultrasound exam and maternal serum alpha fetoprotein to evaluate the fetus
- baseline, mid-third trimester and post-partum ECG

- evaluation for glucose intolerance
- monitoring response to antiretroviral therapy with HIV RNA and CD4 counts
- HIV genotype and phenotyping
- monitoring for chemistry abnormalities including lactate
- liver abnormalities including bilirubin
- UGT1A1 genotypes
- hematological and coagulation abnormalities
- urinalysis
- pharmacokinetic evaluation

Infants
During the study infant subjects had:

- physical exam with vital signs
- neurological (Denver II) at 4 and 6 months to screen for developmental abnormalities
- urinalysis
- monitoring for hematological and chemistry abnormalities
- monitoring total bilirubin at DOL 1, 3, 5, 7 and at 2 weeks
- monitoring for newborn hypoglycemia by obtaining glucose level following delivery
- examining lymphocyte subsets
- evaluating the possibility of HIV transmission using HIV DNA PCR and HIV RNA PCR at various time points

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

Adverse events observed with PIs include new onset diabetes, hyperglycemia, hepatotoxicity, rash, lipodystrophy, hypertriglyceridemia, hypercholesterolemia, hemolytic anemia, increased bleeding episodes in subjects with hemophilia, and fat redistribution. In study, AI424182 clinical concerns monitored in mothers included events during pregnancy, hyperbilirubinemia, ECG abnormalities including P-R interval prolongation, glucose intolerance and lipid abnormalities. For infants, clinical concerns monitored included hyperbilirubinemia, hematological abnormalities, glucose abnormalities and HIV transmission.

7.3 Major Safety Results

7.3.1 Deaths

There were no deaths In this study.

7.3.2 Nonfatal SAEs

Maternal SAEs

SAEs were reported for 15/41 (36%) treated mothers overall. The rates of these SAEs were comparable for mothers on both ATV dosing regimens. One mother had an SAE prior to the planned start of treatment and did not receive ATV/RTV (see Table 9). Of the 15 mothers treated with ATV/RTV, seven treated with 300/100mg and eight treated with 400/100mg had at least one SAE reported. The majority of maternal SAEs were pregnancy related including pre-eclampsia, pregnancy induced hypertension, premature rupture of membranes, amniotic fluid leak, post-partum bleeding, post-partum endometritis, and post-partum abdominal hernia occurred in nine of the 41 mothers. There were four out of 41 mothers (three treated with ATV/RTV 300/100mg and one treated with ATV/RTV 400/100mg) who had SAEs that may have been therapy-related including anemia (zidovudine), sinus node dysfunction (atazanavir) and hyperbilirubinemia (atazanavir).

The most commonly reported SAEs (reported in more than 1 subject) were anemia (3/41, 7.3%), endometritis decidual (2/41, 4.8%), subjects, and pre-eclampsia (2/41, 4.8%). One SAE (in Subject 5-00050) led to study drug discontinuation. Subject 0050 who was treated with ATV/RTV 400/100 developed an ALT of 564 and AST of 340 four days prior to delivery. The subject subsequently developed increased BP of 140/102, proteinuria, and pedal edema. This subject was diagnosed with pre-eclampsia three days prior to delivery and was hospitalized. The subject had two eclamptic seizures and had a laceration to the forehead when she fell during a seizure. The subject had an emergency C-section and the newborn had mild respiratory distress at birth and required brief ventilation as part of the newborn resuscitation. Study therapy was discontinued secondary to increased transaminases. See Appendix 1 for further details on this case.

Table 9: SAEs - Enrolled Mothers

	NUMBER OF SUBJECTS (%)		
	3rd Trimester Treatment		
SYSTEM ORGAN CLASS PREFERRED TERM	NOT TREATED (N= 28)	ATV300/RTV (N= 20)	ATV400/RTV (N= 21)
ANY ADVERSE EXPERIENCE	1(4)	7(35)	8(38)
BLOOD AND LYMPHATIC SYSTEM DISORDERS	0	1(5)	2(10)
ANAEMIA	0	1(5)	2(10)
CARDIAC DISORDERS	0	1(5)	1(5)
CARDIOMYOPATHY	0	1(5)	0
SINUS ARRHYTHMIA	0	0	1(5)
GASTROINTESTINAL DISORDERS	0	0	1(5)
ABDOMINAL HERNIA	0	0	1(5)
HEPATOBILIARY DISORDERS	0	0	1(5)
HYPERBILIRUBINAEMIA	0	0	1(5)
INFECTIONS AND INFESTATIONS	0	2(10)	2(10)
ENDOMETRITIS DECIDUAL	0	2(10)	0
PNEUMONIA	0	0	1(5)
SEPSIS	0	0	1(5)
INVESTIGATIONS	0	0	1(5)
TRANSAMINASES INCREASED	0	0	1(5)
PREGNANCY, PUERPERIUM AND PERINATAL CONDITIONS	1(4)	2(10)	2(10)
AMNIORRHOEA	0	0	1(5)
PRE-ECLAMPSIA	0	1(5)	1(5)
PREGNANCY INDUCED HYPERTENSION	1(4)	0	0
PREMATURE RUPTURE OF MEMBRANES	0	1(5)	0
VASCULAR DISORDERS	0	1(5)	1(5)
HAEMORRHAGE	0	1(5)	0
HYPERTENSION	0	0	1(5)

Further details regarding the maternal SAEs reported in this study are shown in Table 10.

Table 10: Maternal SAEs

PID	ATV/RTV Cohort	Timing of SAE	Preferred Term	AE Grade	Intervention	Action taken regarding study drug	Comments
4-0007	300/100mg	post-partum	endometritis decidual	3	hospitalization	None	
4-0009	300/100mg	post-partum	endometritis decidual	3	hospitalization	None	
4-00022	300/100mg	pre-partum	anemia (severe)	3	hospitalization	None	33 weeks of gestation
4-00043	400/100mg	pre-partum	Aminorrhea (amniotic fluid leak)	2	hospitalization	None	
4-00069	400/100mg	post-partum	abdominal hernia	3	hospitalization	None	Rx Cipro/Naproxen
5-00023	300/100mg	pre-partum	cardiomyopathy	3	hospitalization	None	hx of prior peripartum cardiomyopathy
5-00034	300/100mg	pre-partum	pre-eclampsia	2	hospitalization	None	
5-00050	400/100mg	prior to delivery	transaminitis and pre-eclampsia	4	hospitalization	Discontinued	transaminitis with BP 140/102, pedal edema, 2+ proteinuria subsequently diagnosed with eclampsia
5-00050	400/100mg	post-partum	pneumonia	4	hospitalization	None	
5-00052	400/100mg	post-partum	sepsis	3	hospitalization	None	
5-00059	400/100mg	post-partum	anemia	3	hospitalization	Interrupted for 2 days	pre-partum Hgb 13, at delivery Hgb 11.2, 4-5 weeks post-partum Hgb 7.0, transfused with PRBC

5-00067	400/100mg	post-partum	sinus arrhythmia	1	important medical event requiring cardiologist evaluation	None	subsequent ECG evaluation showed non-specific ST/T wave abnormality
8-00019	n/a	pre-partum	pregnancy induced hypertension (PIH)	2	hospitalization	Not dosed with atazanavir	PIH diagnosed during screening- not dosed with atazanavir
8-00027	300/100mg	pre-partum	premature rupture of membranes	1	hospitalization	None	event resolved
12-00025	300/100mg	post-partum	hemorrhage	3	important medical event requiring evaluation	None	occurring after delivery did not result in prolongation of hospitalization
12-00054	400/100mg	day of delivery	hypertension	3	hospitalization	None	Subject also had increased LFTs and pre-eclampsia mentioned in narrative
12-00065	400/100mg	pre-partum	hyperbilirubinemia	3	important medical event requiring evaluation	None	
12-00065	400/100mg	pre-partum	anemia	2	hospitalization	None	Received transfusion

Infants-SAEs
SAEs were reported for 14 enrolled infants (35%) and the incidence rates of these SAEs were comparable for infants whose mothers were on either ATV dosing regimen (see Table 11) Of the 14 infants of mothers treated with ATV/RTV, 10 treated with 300/100mg and four treated with 400/100mg had at least one SAE.The most commonly reported SAEs (reported for more than 1 subject) were anemia and bronchiolitis (each reported in 2/40 (5%) subjects.

There was one infant whose mother received ATV/RTV 300/100mg during pregnancy who had a cardiorespiratory arrest at three days of life believed to be due to a restrictive cardiomyopathy (see Appendix 2 for full narrative). As a result of this event, the subject had a seizure with cerebral ischemia and had subsequent developmental abnormalities on Denver Screening. The narratives and CRFs for subjects with SAEs were reviewed in detail. Further details of these SAEs are shown in Table 12

Table 11: SAEs - Enrolled Infants

SYSTEM ORGAN CLASS PREFERRED TERM	NUMBER OF SUBJECTS (%) Mothers 3rd Trimester Treatment ATV300/RTV (N= 20)	 ATV400/RTV (N= 20)
ANY ADVERSE EXPERIENCE	10(50)	4(20)
BLOOD AND LYMPHATIC SYSTEM DISORDERS	1(5)	1(5)
ANAEMIA	1(5)	1(5)
CARDIAC DISORDERS	1(5)	0
CARDIO-RESPIRATORY ARREST	1(5)	0
RESTRICTIVE CARDIOMYOPATHY	1(5)	0
CONGENITAL, FAMILIAL AND GENETIC DISORDERS	0	1(5)
ATRIAL SEPTAL DEFECT	0	1(5)
GASTROINTESTINAL DISORDERS	1(5)	0
CONSTIPATION	1(5)	0
VOMITING	1(5)	0
HEPATOBILIARY DISORDERS	1(5)	1(5)
HYPERBILIRUBINAEMIA	0	1(5)
JAUNDICE	1(5)	0
INFECTIONS AND INFESTATIONS	4(20)	2(10)
BRONCHIOLITIS	0	2(10)
GASTROENTERITIS	1(5)	0
MENINGITIS	1(5)	0
PNEUMONIA	0	1(5)
SEPSIS	1(5)	0
SYPHILIS	1(5)	0
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	1(5)	0
OVERDOSE	1(5)	0
METABOLISM AND NUTRITION DISORDERS	1(5)	1(5)
HYPERKALAEMIA	1(5)	0
HYPOGLYCAEMIA	0	1(5)
NERVOUS SYSTEM DISORDERS	1(5)	0
CEREBRAL ISCHAEMIA	1(5)	0
CONVULSION	1(5)	0
PREGNANCY, PUERPERIUM AND PERINATAL CONDITIONS	1(5)	1(5)
PREMATURE BABY	1(5)	1(5)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	2(10)	0
NEONATAL RESPIRATORY DISTRESS SYNDROME	1(5)	0
RESPIRATORY DISTRESS	1(5)	0

Table 12: Infant SAEs

PID	ATV/RTV Cohort	Timing of SAE (age)	Preferred Term	AE Grade	Intervention	Action taken regarding postnatal prophylaxis
4-01007	300/100mg	2 days	SYPHILIS	1	HOSPITALIZATION/PROLONGATION	NONE
4-01022	300/100mg	0 days	SEPSIS	2	HOSPITALIZATION/PROLONGATION	NONE
4-01035	300/100mg	0 days	RESPIRATORY DISTRESS	2	HOSPITALIZATION/PROLONGATION	NONE
4-01035	300/100mg	3 days	RESTRICTIVE CARDIOMYOPATHY	2	PERSISTENT/SIGNIFICANT DISABILITY	NONE
4-01035	300/100mg	3 days	CARDIO-RESPIRATORY ARREST	4	LIFE THREATENING	NONE
4-01035	300/100mg	3 days	CONVULSION	2	PERSISTENT/SIGNIFICANT DISABILITY	NONE
4-01035	300/100mg	3 days	CEREBRAL ISCHAEMIA	2	PERSISTENT/SIGNIFICANT DISABILITY	NONE
4-01043	400/100mg	2 days	HYPERBILIRUBINAEMIA	2	HOSPITALIZATION/PROLONGATION	NONE
4-01043	400/100mg	3 months	BRONCHIOLITIS	2	HOSPITALIZATION/PROLONGATION	NONE
4-01069	400/100mg	0 days	PNEUMONIA	3	HOSPITALIZATION/PROLONGATION	NONE
4-01069	400/100mg	1 month	ANAEMIA	3	IMPORTANT MEDICAL EVENT	NONE
4-01069	400/100mg	4 months	BRONCHIOLITIS	3	HOSPITALIZATION/PROLONGATION	NONE
5-01010	300/100mg	9 days	CONSTIPATION	1	HOSPITALIZATION/PROLONGATION	NONE
5-01010	300/100mg	10 days	VOMITING	1	HOSPITALIZATION/PROLONGATION	NONE

5-01015	300/100mg	3 months	GASTROENTERITIS	3	HOSPITALIZATION/PROLONGATION	NONE
5-01023	300/100mg	0 days	PREMATURE BABY	2	IMPORTANT MEDICAL EVENT	NONE
5-01023	300/100mg	0 days	NEONATAL RESPIRATORY DISTRESS SYNDROME	4	HOSPITALIZATION/PROLONGATION	NONE
5-01023	300/100mg	15 days	ANAEMIA	3	HOSPITALIZATION/PROLONGATION	ZIDOVUDINE WAS DISCONTINUED
5-01061	400/100mg	0 days	HYPOGLYCAEMIA	3	HOSPITALIZATION/PROLONGATION	NONE
8-01018	300/100mg	0 days	OVERDOSE OF ZIDOVUDINE	2	OTHER	DOSE WAS REDUCED
8-01024	300/100mg	4 months	MENINGITIS	3	HOSPITALIZATION/PROLONGATION	NONE
8-01027	300/100mg	2 days	JAUNDICE	1	HOSPITALIZATION/PROLONGATION	NONE
8-01030	300/100mg	14 days	HYPERKALAEMIA	4	OTHER	NONE
12-01054	400/100mg	0 days	PREMATURE BABY	1	HOSPITALIZATION/PROLONGATION	NONE
12-01054	400/100mg	3 days	ATRIAL SEPTAL DEFECT	2	CONGENITAL ANOMALY	NONE

7.3.3 Dropouts and/or Discontinuations

Two mothers (one treated with ATV/RTV 300/100mg and one treated with 400/100mg) were discontinued from ATV treatment due to an adverse event. There was one mother who discontinued by her request due to inability to attend study visits. One discontinuation was due to an adverse event of transaminitis that occurred together with eclampsia (see Narrative for 5-0050 in Appendix 1) and the other subject 4-0022 was discontinued due to her second episode of anemia.. Subject 4-0022 had an earlier episode of severe anemia during her third trimester characterized as a SAE (see Table 10 above) which was treated with oral and intramuscular hemantics. Both episodes of anemia were considered related to "study drug" but the investigators. Two of the 40 infants (one exposed to ATV/RTV 300/100mg and the other exposed to ATV/RTV 400/100mg) treated with post-partum antiretroviral prophylaxis (which did not include atazanavir) were discontinued due to anemia which was likely due to the zidovudine.

Reviewer Comment: For subject 4-0022 it is likely that the zidovudine component of Combivir was the causative agent for the anemia given the association of zidovudine with this AE.

7.3.4 Significant Adverse Events

Grade 3 to 4 AEs

Grade 3 to Grade 4 AEs were reported for 12/41 (29.3%) treated mothers on both regimens The most commonly reported Grade 3 to Grade 4 AEs (reported for more than 1 subject) were anemia, endometritis decidual, and pre-eclampsia (2 subjects, 4.9%). The most commonly reported Grade 3 to Grade 4 AE related to study drug (ATV/RTV and/or ZDV/LMV) was anemia (2 subjects, 4.9%).

Grade 3 to Grade 4 AEs were reported for 8/40 (20%) treated infants whose mothers were on either on either ATV/RTV 300/100mg or ATV/RTV 400/100mg. The only Grade 3 to Grade 4 AE reported for more than 1 infant was anemia (2 subjects, 4.9%).

7.3.5 Submission Specific Primary Safety Concerns

The safety profile of ATV was taken into consideration for this detailed review of specific safety concerns such as hyperbilirubinemia/jaundice, rash, hepatotoxicity, hyperglycemia, nephrolithiasis, and fat redistribution. Overall, no new safety signals or unexpected toxicities were observed.

Jaundice/Hyperbilirubinemia/Ocular Icterus

Neonatal hyperbilirubinemia, an elevation of unconjugated bilirubin, occurs in essentially all newborn infants secondary to increased bilirubin formation, mainly due to the shorter life of the newborn's red blood cells and a decrease in bilirubin elimination related to a transiently limited ability of the newborn liver to conjugate bilirubin due to the immaturity of UDP-glucuronosyl transferase 1A1(UGT1A1)(Bhutani and Johnson 2009). The condition is recognized as jaundice in about 60% of healthy term newborns in the United States (Bhutani and Johnson 2009), is usually benign, and has been termed "physiologic jaundice". Clinical observation of jaundice can be made in the majority of infants with a bilirubin level of greater than 5 mg/dL(Davidson, Merritt and Weech 1941) and term, healthy, North American, formula-fed infants have mean peak total serum bilirubin (TSB) levels between 5 and 6 mg/dL(Maisels 2006). Bilirubin levels usually peak at age 72-120 hours, and resolve by age 2-3 weeks[3].

Although neonatal jaundice is usually physiologic, unconjugated bilirubin is neurotoxic and at high levels can cause acute and chronic bilirubin encephalopathy. Kernicterus, the chronic form of bilirubin encephalopathy, is associated with significant mortality and morbidity and characterized by choreoathetoid cerebral palsy, paralysis of upward gaze, sensorineural hearing loss, dental enamel dysplasia, and intellectual handicaps(Burke et al. 2009). Although investigators have unsuccessfully attempted to correlate the occurrence of kernicterus to a specific or threshold TSB level (Bhutani and Johnson 2009), in general agreement exists that TSB levels greater than 30 mg/dL in healthy term and near-term infants increase the risk of developing kernicterus (Burke et al. 2009), and Bhutani and Johnson estimate that one in seven patients with a TSB greater than 30 mg/dL develops kernicterus (Bhutani and Johnson 2009). Bilirubin encephalopathy is rare: in the US, the incidence of acute bilirubin encephalopathy is estimated at 1 in 40,000 live births (Bhutani and Johnson 2009) and the incidence of kernicterus is approximately 1.5 per 100,000 newborns with a higher incidence in preterm infants (4 per 100 000 births) (Burke et al. 2009).

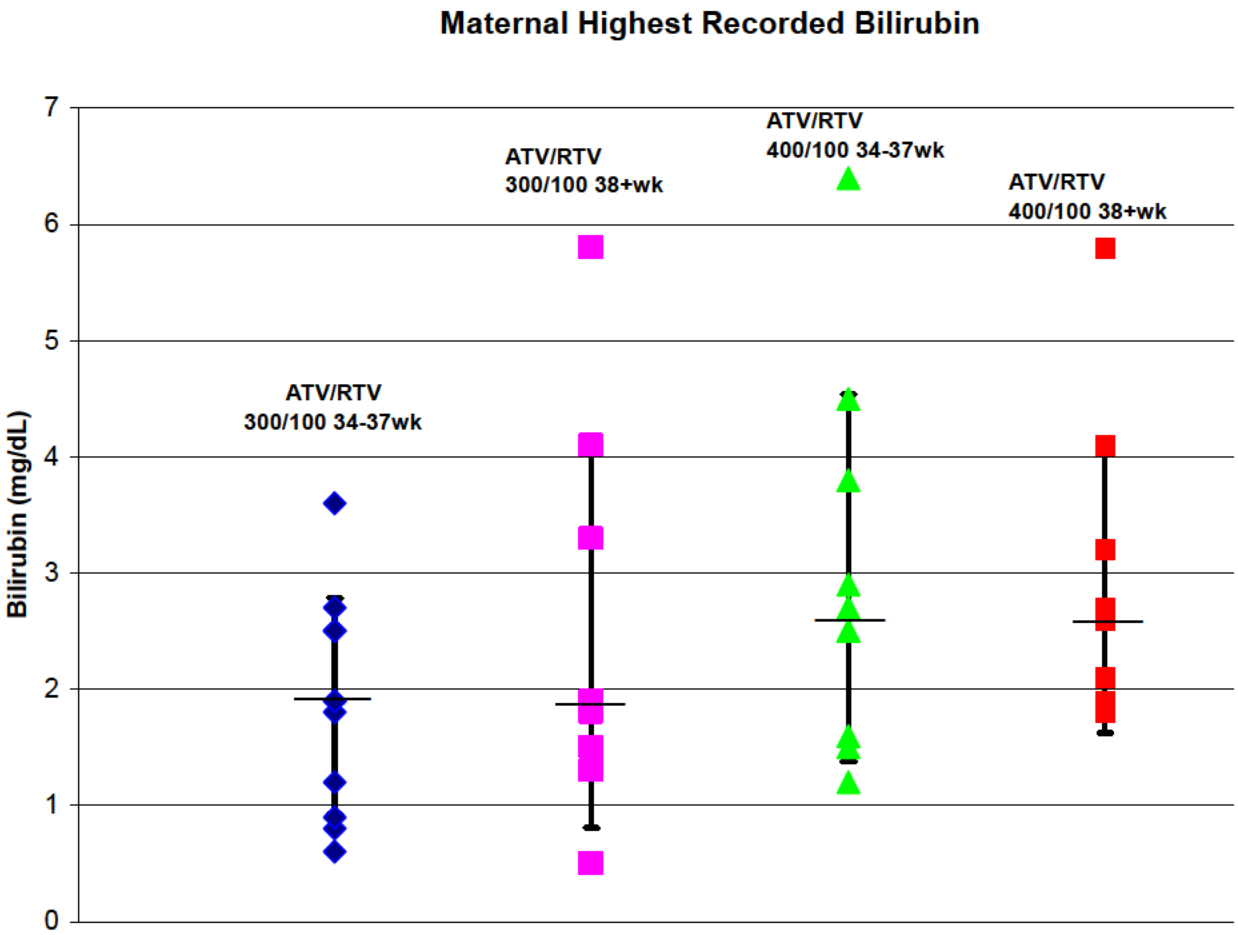
ATV and Hyperbilirubinemia

Due to UDP-glucuronosyl transferase 1A1 (UGT1A1) inhibition, most patients treated with atazanavir (ATV) experience asymptomatic elevations in unconjugated bilirubin that are reversible upon discontinuation of the drug. The incidence of hyperbilirubinemia is dose-dependent and a clinical study reported grade 3-4 bilirubin levels (greater than 2.6X upper limit of normal) in 44% of adult patients exposed to 300 mg ATV.

Maternal Hyperbilirubinemia (see Figure 3)

Maternal subjects receiving ATV/RTV had total bilirubin values ranging from 0.1 to 6.4mg/dL. Maternal subjects receiving ATV/RTV 400/100mg had a median total bilirubin value of 2.4 versus 1.9 for maternal subjects receiving ATV/RTV 300/100mg (see Figure 3). In the study, the upper limit of normal for bilirubin varied from 1.1 – 1.3 depending on the laboratory. Six of 20 (30%) women on ATV/RTV 300/100 mg and 13 of 21 (62%) women on ATV/RTV 400/100 mg experienced Grade 3-4 hyperbilirubinemia. (total bilirubin (Grade 3 is 2.6 to 5 times the upper limit of normal and Grade 4 is >5 times the upper limit of normal)). Four out of the 20 (20%) maternal subjects treated with ATV/RTV 300/100mg and six out of the 21 (29%) had a clinical AE of jaundice reported (all Grades). As shown in the following figure (Figure 3), the highest recorded total bilirubin for each maternal subject was plotted. The median value for each sub-cohort was indicated by a horizonatal bar and the one standard deviation error for each sub-cohort by vertical bars. There was no difference in the median total bilirubin within each dosing cohort (ATV/RTV 300/100mg or 400/100mg) comparing maternal subjects who had premature (35-37 weeks gestation at birth) infants with maternal subjects who had term infants (38+ weeks gestation at birth). Thus, maternal subjects treated with ATV/RTV 400/100mg had a higher median total bilirubin (2.4) than maternal subjects treated with ATV/RTV 300/100mg (1.9); however the difference between the cohorts is well within the error bar of one standard deviation.

Figure 3: Maternal Bilirubin (showing median and one standard deviation error bar)



Each diamond, square, and triangle represents the highest recorded total bilirubin for each subject

Infant Hyperbilirubinemia

The differences in the degree of hyperbilirubinemia in the first week of life in ATV exposed infants appears to be more related to prematurity (35-37 weeks versus 38+ weeks) rather than to increased ATV exposure in-utero (ATV/RTV 400/100mg vs. 300/100mg) (see Figures 4-7). Four premature infants and two term infants received phototherapy (see Phototherapy List below). Three of these infants had been exposed to ATV/RTV 300/100mg and three to 400/100mg cohort in-utero. . In examining the risk of severe hyperbilirubinemia (>95th percentile for age in hours), the Pediatric and Maternal Health Staff (PMHS) reviewer Dr. Elizabeth Durmowicz concluded that the risks were similar for infants exposed to ATV/RTV 300/100mg versus the 400/100mg dosing regimen.

To evaluate the severity of the hyperbilirubinemia in exposed infants, the PMHS reviewer plotted the bilirubin levels for each subject on the nomogram developed by the American Academy of Pediatrics (AAP) as a guideline for the initiation of phototherapy (see Table 13)(American Academy of Pediatrics Subcommittee on Hyperbilirubinemia 2004). Two subjects in the 300 mg ATV exposed cohort exceeded the PT threshold compared to no subjects in the 400 mg ATV exposure cohort.

List of Infant Subjects Who Received Phototherapy

Six infants had phototherapy performed within days of delivery:

• Subject 5-1023 (300/100) had an AE of jaundice reported on Day 2. The bilirubin level was 8.2 mg/dL on Day 3 and the infant received phototherapy on Days 5 and 7.On Days 5, 7, 14, and 43, bilirubin levels were 11.2 mg/dL, 12.7 mg/dL, 11.5 mg/dL, and 1.1, respectively (with the last recorded bilirubin on Day 43) .

• Subject 8-1027 (300/100) had a SAE of jaundice reported on Day 3. The bilirubin level was 13 mg/dL and the infant received phototherapy on Days 5 and 7 (with bilirubin of 9.9 mg/dL and 9.8 mg/dL on Days 5 and 7. The event of jaundice clinically resolved on Day 15).

• Subject 12-1025 (300/100) had an AE of jaundice reported on Day 3. The bilirubin level was 12.2 mg/dL and the infant received phototherapy on Day 3. On Days 5, 7, 15, and 46, bilirubin levels were 13.2 mg/dL, 15.3 mg/dL, 4.6 mg/dL, and 0.8 mg/dL, respectively.

• Subject 4-1043 (400/100) had a SAE of hyperbilirubinemia reported on Day 3. The bilirubin level was 13 mg/dL and the infant received phototherapy on Day 5 (bilirubin 8.6 mg/dL. The event of hyperbilirubinemia resolved on Day 5.

• Subject 12-1044 (400/100) had an AE of jaundice reported on Day 4. The bilirubin level was 9.4 mg/dL and the infant received phototherapy on Day 5. On Days 5 and 8, bilirubin levels were 8.1 mg/dL and 8.0 mg/dL, respectively (with the last recorded bilirubin on Day 8).

• Subject 12-1054 (400/100) had an AE of jaundice reported on Day 3. The bilirubin level was 9.6 mg/dL and the infant received phototherapy on Day 3, 5, 7 (with the last recorded bilirubin on Day 18).

Table 13: Study Infants and Bilirubin Levels Related to AAP Guidelines for Phototherapy (PT)

Dosing Exposure Cohort	Number of subjects that surpassed the PT threshold
300 mg ATV	2
400 mg ATV	0

Reviewer Comment: It is apparent that the decision to start phototherapy in infants was subjective and that more infants could have potentially been treated with phototherapy. Therefore, the frequency of phototherapy use is not a reliable indicator for the severity of hyperbilirubinemia.

Figure 4: Premature Neonates ATV/RTV 300/100mg Cohort

This figure describes the total bilirubin values in the first week of life of premature infants (35-37 weeks gestation at birth) of infants exposed to ATV/RTV 300/100mg. None of the premature infants in the 300/100mg cohort had a total bilirubin greater than 13mg/dL and only two infants received phototherapy (see List of Infants Who Received Phototherapy for details).

Figure 5: Term Neonates ATV/RTV 300/100mg Cohort

This figure describes the total bilirubin values in the first week of life of term infants (38+ weeks gestation at birth) of infants exposed to ATV/RTV 300/100mg. One of the term infants in the 300/100mg cohort had a total bilirubin of 15.3 mg/dLand received phototherapy. This infant's total bilirubin subsequently decreased down to 0.8mg/dL on Day 46 (see List of Infants Who Received Phototherapy for details).

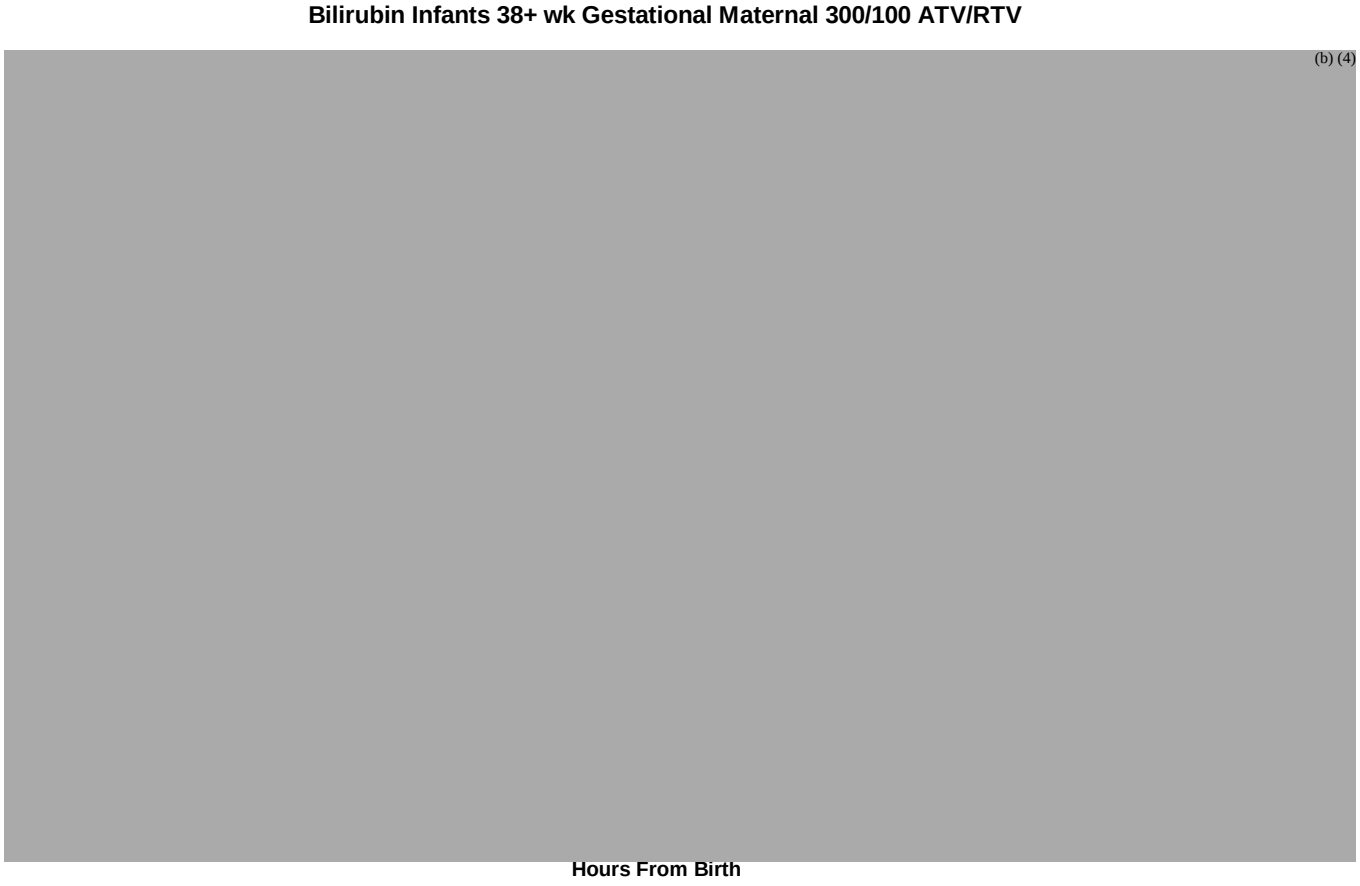


Figure 6: Premature Neonates ATV/RTV 400/100mg Cohort

This figure describes the total bilirubin values in the first week of life of premature infants (35-37 weeks gestation at birth) of infants exposed to ATV/RTV 400/100mg. None of the premature infants in the 400/100mg cohort had a total bilirubin greater than 11.7 mg/dL and only two infants received phototherapy (see List of Infants Who Received Phototherapy for details).

Figure 7: Term Neonates ATV/RTV 400/100mg Cohort

This figure describes the total bilirubin values in the first week of life of term infants (38+ weeks gestation at birth) of infants exposed to ATV/RTV 400/100mg. One of the term infants in the 400/100mg cohort had a total bilirubin of 14.2 mg/dLand received phototherapy (see List of Infants Who Received Phototherapy for details).

Based on this information above and their analysis, the PMHS reviewer concluded that infants in the ATV/RTV 300/100 mg exposure dosing cohort (n= 20) did not experience an increased incidence or degree of neonatal hyperbilirubinemia compared to healthy infants. From their analysis, the PMHS reviewer also concluded that the ATV/RTV 400/100 mg exposure dosing cohort (n=20) may have a slightly increased incidence and severity of hyperbilirubinemia compared to the ATV/RTV 300/100 mg exposure cohort and to healthy infants. Although study infants did not develop total bilirubin values >20mg/dL and were managed without complication, the study population excluded mothers more likely to have an infant at risk for the development of severe hyperbilirubinemia. In addition, the vast majority of subjects (greater than 80%) were identified as Black/African American, a race with half the incidence of hyperbilirubinemia compared to Caucasians and a quarter of the incidence compared to Asians(Newman et al. 1999).

Reviewer Comments: Concur with PMHS conclusion that the hyperbilirubinemia observed in infants in this study was not concerning and share the concern about generalizability of results in Black/African Americans infants to non-Black infants or to those who may be at higher risk for severe hyperbilirubinemia due to factors such as ABO or Rh incompatibility. However, it would not be feasible to repeat a similar study in non-Black mothers/infants in the US given the demographics of HIV infection.

Glucose Abnormalities

New-onset diabetes mellitus, exacerbation of preexisting diabetes mellitus, and hyperglycemia have been reported during postmarketing surveillance in HIV-infected patients receiving protease inhibitor therapy. Some patients required either initiation or dose adjustments of insulin or oral hypoglycemic agents for treatment of these events. Although protease inhibitors have been associated with glucose intolerance in adult patients, this association does not appear to be an issue in pregnant women who have been studied (mostly treated with nelfinavir and/or lopinavir-ritonavir) (Hitti et al. 2007, Tang et al. 2006, Dinsmoor and Forrest 2002). However, one study of HIV positive mothers treated with the protease inhibitor nelfinavir suggested that HIV protease inhibitors could cause hypoglycemia in exposed neonates even when in the absence of clinically apparent maternal glucose intolerance (Dinsmoor and Forrest 2002).

Glucose Abnormalities in Maternal Subjects

In study AI424182, all fasting glucose abnormalities were Grade 1 or Grade 2, and were comparable for mothers on both ATV regimens. Hypoglycemia was experienced by 18 of 40 (45%) mothers, and hyperglycemia was experienced by 6 of 40 (15%). Two maternal subjects had either impaired glucose tolerance Grade 2 (subject 4-00043: ATV/RTV 400/100mg) or gestational diabetes Grade 1 (subject 4-00028: ATV/RTV 300/100mg).

Infants

A total of 16 infants in this study had laboratory diagnosed hypoglycemia, defined as glucose value < 55mg/dL, but none of these infants had clinically diagnosed hypoglycemia. One infant, 5-1061, was clinically diagnosed with hypoglycemia but did not have any laboratory values (except for a single accucheck reading of “low” glucose) consistent with hypoglycemia. This infant was worked up for sepsis and was given a course of antibiotics. Many of the infants with suspected hypoglycemia had blood samples that were not processed appropriately (i.e. samples should have been placed on ice and processed within one hour), and therefore the observed abnormality could have been artifactual. Four infants had reliable glucose laboratory measurements indicative of hypoglycemia (two infants exposed to ATV/RTV 300/100mg and two infants exposed to ATV/RTV 400/100mg); however, one of the infants, 5-1050, (exposed to ATV/RTV 400/100mg) was born to a mother with eclampsia which could have contributed to the hypoglycemia. The other three infant subjects had hypoglycemia in the first day of life that could not be explained by maternal glucose intolerance, difficult delivery or sepsis (see Table 14).

Reviewer Comment: Subject 5-1061 likely had sepsis given none of the glucose values) obtained (>55mg/dL) could explain the physical findings originally thought to be due to hypoglycemia.

Table 14: Infants With Glucose < 40 mg/dL (< 2.2 mmol/L) Unexplained by Maternal Glucose Intolerance, Difficult Delivery, or Sepsis

ATV/RTV	PID DOB Time of Birth	Date and Time of Draw	Hours from Birth	Glucose	Method of glucose collection	Time to Lab Processing	Fasting for Glucose Test	Clinical Diagnosis of Hypoglycemia	Treatment Given for Hypoglycemia	Comments
300/100	5-1011 (b) (6) 3:10 pm	(b) (6) 4:00 pm	0.83	3.1 mmol/L	Accutrend heelstick	N/A	Y	No	No	3.1 mmol = 56 mg/dL
		(b) (6) UNK	<8.83*	36 mg/dL	Venous, SST, placed on ice	Within 1 hr	Y			
300/100	5-1026 (b) (6) 7:45 am	(b) (6) 9:40 am	1.92	2.8 mmol/L	Accutrend heelstick	N/A	Y	Yes	No	2.8 mmol = 50 mg/dL Infant was fed at 10:00 am
		(b) (6) UNK	<16.25*	32 mg/dL	Venous, SST, placed on ice	Within 1 hr	Y			
400/100	5-1059 (b) (6) 11:40 pm	(b) (6) 12:12 am	0.53	4.6 mmol/L	Accutrend heelstick	N/A	Y	No	No	4.6 mmol = 83 mg/dL
		(b) (6) UNK	<24.33*	27 mg/dL	Venous, SST, placed on ice	Within 1 hr	N			

* For unknown collection times, the upperbound, i.e. hours from birth for the sample is shown.

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

Mothers

Adverse events of at least Grade 1 occurred in almost all of the treated mothers and the incidence rates for these AEs were similar for both the ATV/RTV 300/100mg and 400mg/100mg cohorts (see Table 15). The most common AEs (reported for 5 or more cumulative subjects on both regimens) were upper respiratory tract infection (12 subjects; 29.3%), jaundice (10 subjects, 24.4%), headache (9 subjects; 22%), urinary tract infection (7 subjects, 17%), vomiting (7 subjects, 17%), cough (7 subjects, 17%), anemia (6 subjects, 14.6%), hypertension (6 subjects, 14.6%), nausea (6 subjects, 14.6%), dyspepsia (5 subjects, 12.2%), premature rupture of membranes (5 subjects, 12.2%). The most common AEs related to study drugs (ATV/RTV and/or ZDV/LMV) were jaundice (10 subjects, 24.4%: 4 on ATV/RTV 300/100 mg and 6 on ATV/RTV 400/100 mg) and anemia (5 subjects, 12.2%: 1 on ATV/RTV 300/100 mg and 4 on ATV/RTV 400/100)

Infants

All infants experienced AEs of any grade on study and the incidence rates of individual AEs were comparable between infants whose mothers were on either the ATV/RTV 300/100mg or ATV/RTV 400mg/100mg (see Table 16). The most common AEs (reported for 5 or more cumulative subjects whose mothers were on either regimen) were jaundice (20 infants, 50%), upper respiratory tract infection (14 infants, 35%), nasal congestion (8 infants, 20%), rash (7 infants, 17.5%), oral candidiasis (6 infants, 15%), constipation, gastro-esophageal reflux disease, umbilical hernia, cough, eczema, and vomiting (5 infants each, 12.5%).

Table 15: Adverse Events in Mothers

		ATV-RTV 300/100	ATV-RTV 400/100	Subjects
Full name of the System Organ Class	Full name of the Preferred Term	20 (100.00%)	21 (100.00%)	41 (37.61%)
INFECTIONS AND INFESTATIONS	UPPER RESP. TRACT INF.	10 (50.00%)	4 (19.05%)	14 (12.84%)
HEPATOBILIARY DISORDERS	JAUNDICE	4 (20.00%)	6 (28.57%)	10 (9.17%)
NERVOUS SYSTEM DISORDERS	HEADACHE	7 (35.00%)	2 (9.52%)	9 (8.26%)
GASTROINTESTINAL DISORDERS	VOMITING	5 (25.00%)	2 (9.52%)	7 (6.42%)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	COUGH	4 (20.00%)	3 (14.29%)	7 (6.42%)
INFECTIONS AND INFESTATIONS	URINARY TRACT INFECTION	1 (5.00%)	6 (28.57%)	7 (6.42%)
GASTROINTESTINAL DISORDERS	NAUSEA	4 (20.00%)	2 (9.52%)	6 (5.50%)
	DYSPEPSIA	4 (20.00%)	2 (9.52%)	6 (5.50%)
VASCULAR DISORDERS	HYPERTENSION	3 (15.00%)	3 (14.29%)	6 (5.50%)
BLOOD AND LYMPHATIC DISORDERS	ANAEMIA	2 (10.00%)	4 (19.05%)	6 (5.50%)
PREGNANCY, PUERPERIUM AND PERINATAL CONDITIONS	PREMATURE RUPTURE OF MEMBRANES	4 (20.00%)	1 (4.76%)	5 (4.59%)
NERVOUS SYSTEM DISORDERS	DIZZINESS	3 (15.00%)	2 (9.52%)	5 (4.59%)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	FATIGUE	4 (20.00%)	0 (0.00%)	4 (3.67%)
PREGNANCY, PUERPERIUM AND PERINATAL CONDITIONS	PREMATURE LABOUR	3 (15.00%)	1 (4.76%)	4 (3.67%)
GASTROINTESTINAL DISORDERS	DIARRHOEA	3 (15.00%)	1 (4.76%)	4 (3.67%)
	TOOTHACHE	3 (15.00%)	1 (4.76%)	4 (3.67%)
REPRODUCTIVE SYSTEM AND BREAST DISORDERS	VAGINAL DISCHARGE	2 (10.00%)	2 (9.52%)	4 (3.67%)
GASTROINTESTINAL DISORDERS	ABDOMINAL PAIN LOWER	3 (15.00%)	0 (0.00%)	3 (2.75%)
EYE DISORDERS	OCULAR ICTERUS	2 (10.00%)	1 (4.76%)	3 (2.75%)
GASTROINTESTINAL DISORDERS	ABDOMINAL PAIN	2 (10.00%)	1 (4.76%)	3 (2.75%)
	CONSTIPATION	2 (10.00%)	1 (4.76%)	3 (2.75%)
INFECTIONS AND INFESTATIONS	NASOPHARYNGITIS	2 (10.00%)	1 (4.76%)	3 (2.75%)
	INFLUENZA	1 (5.00%)	2 (9.52%)	3 (2.75%)
INVESTIGATIONS	WHITE BLOOD CELLS URINE POSITIVE	2 (10.00%)	0 (0.00%)	2 (1.83%)
INFECTIONS AND INFESTATIONS	ENDOMETRITIS DECIDUAL	2 (10.00%)	0 (0.00%)	2 (1.83%)
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	PROCEDURAL PAIN	2 (10.00%)	0 (0.00%)	2 (1.83%)
INFECTIONS AND INFESTATIONS	ORAL CANDIDIASIS	2 (10.00%)	0 (0.00%)	2 (1.83%)

Table 16: Adverse Events in Infants

		ATV-RTV 300/100	ATV-RTV 400/100	Subjects
Full name of the System Organ Class	**Full name of the Preferred Term**	20 (100.00%)	20 (100.00%)	40 (36.70%)
HEPATOBILIARY DISORDERS	JAUNDICE	10 (50.00%)	10 (50.00%)	20 (18.35%)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	NASAL CONGESTION	7 (35.00%)	1 (5.00%)	8 (7.34%)
	COUGH	5 (25.00%)	0 (0.00%)	5 (4.59%)
INFECTIONS AND INFESTATIONS	UPPER RESPIRATORY TRACT INFECTION	4 (20.00%)	10 (50.00%)	14 (12.84%)
EYE DISORDERS	CONJUNCTIVITIS	3 (15.00%)	1 (5.00%)	4 (3.67%)
INFECTIONS AND INFESTATIONS	ORAL CANDIDIASIS	3 (15.00%)	3 (15.00%)	6 (5.50%)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	RASH	3 (15.00%)	4 (20.00%)	7 (6.42%)
INFECTIONS AND INFESTATIONS	OTITIS MEDIA	3 (15.00%)	1 (5.00%)	4 (3.67%)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	ECZEMA	2 (10.00%)	3 (15.00%)	5 (4.59%)
	DERMATITIS	2 (10.00%)	2 (10.00%)	4 (3.67%)
INFECTIONS AND INFESTATIONS	BRONCHITIS	2 (10.00%)	0 (0.00%)	2 (1.83%)
GASTROINTESTINAL DISORDERS	UMBILICAL HERNIA	2 (10.00%)	3 (15.00%)	5 (4.59%)
	VOMITING	2 (10.00%)	3 (15.00%)	5 (4.59%)
INFECTIONS AND INFESTATIONS	BRONCHIOLITIS	2 (10.00%)	2 (10.00%)	4 (3.67%)
GASTROINTESTINAL DISORDERS	CONSTIPATION	2 (10.00%)	3 (15.00%)	5 (4.59%)
	GASTROOESOPHAGEAL REFLUX DISEASE	1 (5.00%)	4 (20.00%)	5 (4.59%)

7.4.2 Laboratory Findings

Grade 3-4 Laboratory Abnormalities of Concern

Maternal Laboratory Abnormalities During Pregnancy:

One subject 00050 who received ATV/RTV 400/100mg had a Grade 4 ALT which was classified as a SAE along with a blood pressure of 140/102, pedal edema, 2+ proteinuria and a SAE of pre-eclampsia prior to delivery. At this time, this subject also had an elevated Grade 4 total bilirubin and Grade 3 AST. One subject, 00011, had Grade 4 glucosuria at time of delivery.

Two subjects, 00028 and 00020, from the ATV/RTV 300/100mg cohort had Grade 3 proteinuria. Two of 41 mothers (one who received ATV/RTV 300/100mg, and one subject who received 400/100mg ATV/RTV) had Grade 3 hemoglobin (6.5-7.9 g/dL). Ten subjects (two subjects who received ATV/RTV 300/100mg, and eight subjects who received ATV/RTV 400/100mg) had Grade 3 hypocarbia (10-14 meq/L). Six of the ten subjects had Grade 3 hypocarbia at delivery.

Reviewer Comment: Acidosis (or hypocarbia) is considered normal in the 3rd stage of labor prior to delivery.

Eleven of 41 (27%) mothers (four subjects who received ATV/RTV 300/100mg, and seven subjects who received ATV/RTV 400/100mg) had Grade 3 total bilirubin (2.6-5x ULN) laboratory AEs. Two of the 11 subjects with Grade 3 total bilirubin (one subject who received ATV/RTV 300/100mg, and one subject who received ATV/RTV 400/100mg) developed Grade 3 direct bilirubin which were both obtained at delivery. Neither of these two subjects had elevation of transaminases or alkaline phosphatase at the time of the elevated direct bilirubin.

Maternal Laboratory Abnormalities in the Post-Partum Period

Subject 0050 had a Grade 4 total bilirubin and creatinine kinase four days post-partum following the pre-eclampsia event. Subjects 000028 and 00020, who were both treated with ATV/RTV 300/100mg and had proteinuria antepartum, continued to have Grade 3 proteinuria in the post partum period. Four to five weeks post-partum, one subject 00059 who was treated with ATV/RTV 400/100mg had Grade 3 hematocrit (≥19.5 to < 24%) and hemoglobin of 7g/dL which was considered an SAE since the subject required a transfusion of packed red blood cells. Two subjects treated with ATV/RTV 400mg/100mg continued to have hypocarbia from the antepartum period into the post-partum period.

Fifteen out of 41 (27%) mothers had Grade 3 total bilirubin (2.6-5x ULN) laboratory abnormalities (six subjects ATV/RTV 300/100mg, nine subjects ATV/RTV 400/100mg).

Infants

Nine infants had Grade 3-4 hypoglycemia (four infants with mothers treated with ATV/RTV 300/100mg, and five infants with mothers treated with ATV/RTV 400/100mg). In 8 of the 9 infants with Grade 3-4 hypoglycemia, the abnormality occurred on the day of birth. Infant subject number 1061 whose mother was treated with ATV/RTV 400/100mg had Grade 3 hemoglobin. Two infants had Grade 3 neutropenia (one infant whose mother was treated with ATV/RTV 300/100mg, and one infant whose mother was treated with ATV/RTV 400/100mg). Two infants had a Grade 3 amylase reported (one infant whose mother was treated with ATV/RTV 300/100mg, and one infant whose mother was treated with ATV/RTV 400/100mg). Two infants had a Grade 3 creatinine on the day of delivery (one infant whose mother was treated with ATV/RTV 300/100mg, and one infant whose mother was treated with ATV/RTV 400/100mg). Fourteen infants had Grade 3-4 hyperkalemia (eight infants with mothers treated with ATV/RTV 300/100mg, and six infants with mothers treated with ATV/RTV 400/100mg). One of the 14 hyperkalemic infants, subject 1030 (whose mother was treated with ATV/RTV 300/100mg) had an SAE due to hyperkalemia.

Reviewer Comment: 1) Creatinine values in a newborn infants are more reflective of the mother's creatinine value in the first few days of life. 2) For all of the infants with reported hyperkalemia, the elevated potassium was thought to be due to a difficult blood collection in which hemolysis occured and therefore was considered artifactual.

Three of 20 infants (15%) born to women treated with ATV 300/100 mg and four of 20 infants (20%) born to women treated with ATV/RTV 400/100 mg experienced Grade 3–4 total bilirubin at 15-18 days of life.

Reviewer Comment: The clinical significance of hyperbilirubinemia in the third week of life relative to in utero atazanavir exposure is unclear. Atazanavir's effect on the UGT1A1 should only be present at most for the first few days of life in infants exposed in utero.

7.4.3 Vital Signs

At birth, vital signs, physical measurements, and Appearance, Pulse, Grimace, Activity, Respiration (APGAR) scores were comparable for infants whose mothers were on either the ATV/RTV 300/100 mg or ATV/RTV 400/100 mg in their third trimester. Of the 40 infants, seven had low birth weight (< 2.5 kg), but no infant weighed <1.5 kg.

7.4.4 Electrocardiograms (ECGs)

Per protocol, maternal ECGs were taken at screening, 4 to 6 weeks after the baseline visit, and at postpartum Week 4 for mothers. None of these findings were considered to be clinically significant. Overall, most subjects had ECG intervals within or near the normal range. No subject had a significant P-R prolongation, an absolute Fridericia-corrected cardiac ventricular repolarization (QTcF) interval > 450 msec after treatment with study drug, and no subject discontinued for ECG-related findings. No maternal subject was diagnosed with AV block. One subject, 5-00067, was initially diagnosed with sinus arrhythmia post-partum, but was later found to have non-specific ST/T wave abnormalities upon evaluation by a cardiologist.

7.4.5 Special Safety Studies/Clinical Trials

UGT1A1 Genotyping (see Clinical Pharmacology review by Dr. Jenny H. Zheng)

Denver II Development Screening Test

In Denver Developmental Screening tests, any noted evidence of developmental delay is considered a “suspect evaluation” which requires closer follow-up and possible referral.

Overall, 4 of 40 infants showed suspect evaluations at Month 4, and 7 of 40 infants showed suspect evaluations at Month 6. Of note, 6 infants had end of study evaluations after their Month 6 data were questioned.

The following subjects, whose mothers were on ATV/RTV 300/100 mg, showed suspect evaluations:

- Subject 12-1025 exhibited suspect evaluations of language at Months 4 and 6. A repeat assessment completed about 12 months later found language development to be normal.

- Subject 4-1035 exhibited suspect evaluations of fine-motor adaptive skills at Month 4 and suspect evaluations of personal/social, fine-motor adaptive, and gross motor skills at Month 6. This infant had suffered a cardiorespiratory arrest at Day 3 after birth with evidence of cerebral ischemic damage on magnetic resonance imaging. At the time of final database lock, this infant had remaining suspect findings on Denver testing.

- Subject 5-1023 exhibited suspect evaluations of personal/social, fine motor adaptive, and gross motor skills at Month 4 and subsequently tested normal at Month 6.

- Subjects 8-1018, had 8-1027, and 8-1030 had normal language evaluations at Month 4 followed by suspect language evaluations at Month 6. Follow-up testing beyond the 6-month point revealed that the language evaluations remained suspect. All 3 infants had SAEs reported (8-1018 had an SAE of overdose, 8-1027 had an SAE of jaundice on Day 3, and 8-1030 had an SAE of hyperkalemia on Day 15). At the time of final database lock, all 3 infants had remaining suspect findings on Denver testing.

The following subjects, whose mothers were on ATV/RTV 400/100 mg, showed suspect evaluations:

- Subject 12-1054 exhibited suspect evaluations of language, gross motor, and fine motor skills at Month 4. By Month 6, this subject had suspect evaluations of gross motor skills only. Repeat testing at 12 months revealed no suspect findings.

- Subject 12-1055 exhibited a suspect evaluation of language at Month 6.
- Repeat testing at 12 months revealed no suspect findings.

7.5.1 Dose Dependency for Adverse Events

Third trimester ATV/RTV doses of 300/100mg and 400/100mg were compared in pregnant HIV positive women. The primary difference between the two doses was in the frequency of hyperbilirubinemia. Maternal subjects receiving ATV/RTV 400/100mg had a median total bilirubin value of 2.4 mg/dL compared to 1.9 mg/dL for maternal subjects receiving ATV/RTV 300/100mg. Six of 20 (30%) women on ATV/RTV 300/100 mg and 13 of 21 (62%) women on ATV/RTV 400/100 mg experienced Grade 3-4 hyperbilirubinemia (total bilirubin 2.6 to >5 times the upper limit of normal. Four out of the 20 (20%) maternal subjects treated with ATV/RTV 300/100mg and six out of the 21 (29%) had a clinical AE of jaundice reported (all Grades). In ATV-exposed infants the difference in the frequency and severity hyperbilirubinemia was not significant between the ATV/RTV 400/100mg and 300/100mg maternal doses.

7.5.2 Time Dependency for Adverse Events

There was some concern that mothers with higher than expected ATV levels post-partum and could potentially experience dose-related ATV toxicity. On review of the adverse events of all grades in the 2nd trimester, 3rd trimester, delivery and the post-

partum period, there was no pattern that suggested increased toxicity during any of dosage periods.

Human Reproduction and Pregnancy Data

The study under review is a study of ATV in pregnant women and the effects on their exposed infants.

8 Postmarket Experience

In the applicant's safety database, all pregnancy cases received until 19 December 2008 used the following conventions to classify the information as prospective or retrospective:

- Prospective: Initial reports received by Bristol-Myers Squibb Company (BMS) during ongoing pregnancy with outcome information reported at follow-up, including all BMS CSRs and reports from Study AI424182.

- Retrospective: Initial information received after the pregnancy outcome was known, including all Women and Infant Transmission Studies study reports and literature reports.

- Unknown: Limited information that did not allow BMS to distinguish between prospective/retrospective information.

For reports provided by the Antiviral Pregnancy Registry (APR), report status was determined based on most recent follow-up information.

For pregnancy cases received after 19 December 2008, a new automated table replaced the manually generated pregnancy tables that appeared in previous periodic safety reports. The new table was generated directly from the safety database, and the following criteria were used for all pregnancy cases:

- Prospective: Data were acquired prior to the knowledge of pregnancy outcome or prior to the detection of congenital malformation at prenatal examination.

- Retrospective: Data were acquired after the outcome of pregnancy was known or after the detection of congenital malformation on prenatal test.

A cumulative search of the safety database to 19 December 2009 inclusive, identified 636 reports of ATV exposure during pregnancy. Of these, 125 were spontaneous, 6 were derived from published literature, and 505 were from study reports.

Furthermore, 218 reports were classified as "serious" (i.e. any outcome other than a normal infant or unremarkable live birth). There were 5 reports that were not confirmed by a healthcare professional. There were 500 prospective and 136 retrospective reports. Of the 500 prospective pregnancy reports, there were 315 prospective pregnancies with known outcome with exposure in the fist trimester.

The 636 reports included the following pregnancy outcomes: normal newborn (273), live birth (101), spontaneous abortion (70), induced abortion (60), premature baby (24), intrauterine death (9), stillbirth (6), small for dates baby (4), ectopic pregnancy (4), blighted ovum (4), large for dates baby (2), abortion (1), missed abortion (1), ruptured ectopic pregnancy (1) and infant (1). There were 38 congenital abnormality reports.

Antiviral Pregnancy Registry (APR) Data

According to the APR June 2010 interim report,17 prospective cases identified 9 defects per 393 live births with a 2.3% (1.0%, 4.3%) prevalence during first trimester and 5 defects per 212 live births with a 2.4% (0.8%, 5.4%) prevalence in the second and third trimester exposure to any ATV regimen. The background rate of congenital defects per the Metropolitan Atlanta Congenital Defects Program is 2.7%(Correa et al. 2007)

Overlap of Applicant Postmarketing Data with APR Data

Of the 315 prospective postmarketing cases with known pregnancy outcomes described above, 191 were confirmed to have received an APR identification number. 20 cases were submitted to the APR but APR number was not recorded, 57 cases did not meet criteria for APR submission, and 47 cases were recorded prior to atazanavir approval and were not reported to the APR. Therefore 211/315 postmarketing cases overlap with the APR cases.

OSE Review of ATV Related Neonatal Hyperbilirubinemia and Neonatal Hypoglycemia

The Office of Surveillance and Epidemiology, Division of Pharmacovigilance__ was consulted to evaluate postmarketing cases of infant hyperbilirubinemia and hypoglycemia, and the reviewer's consult is summarized below.

AERS CASES

Hyperbilirubinemia (n=6): The gestational age ranged from 31 to 42 weeks, median 36 weeks. Two cases reported bilirubin levels, the highest total bilirubin levels were 10.6 mg/dL (day 2) and 160 micromol/L [equivalent to 9.4 mg/dL] (day 3). The neonate with a total bilirubin level equivalent to 9.4 mg/dL was also reported to have jaundice. These two neonates received phototherapy, and hyperbilirubinemia resolved after 1-2 days in one neonate and was unknown in the other. None of the other four cases reported treatment for hyperbilirubinemia. Hyperbilirubinemia was reported to have occurred at < 3 days of life in five cases (unknown-1). No deaths were reported. One "case" was actually a report of two infants with hyperbilirubinemia but had very limited information. Five of six neonates reported risk factors for hyperbilirubinemia (5 were premature or borderline premature, 2 were septic with metabolic acidosis, 2 had a diabetic mother, and one reported the use of oxytocin in the mother, who also had thalassemia alpha and anemia). The remaining case reported a neonate born at 42 weeks gestation with elevated bilirubin on the day of birth requiring an ICU stay. No specific treatment for hyperbilirubinemia was reported and no levels were provided. No maternal medical problems or complications during delivery or postpartum period were reported. No other pertinent information was provided.

Hypoglycemia (n=3): All three neonates were born prematurely (33, 36 and 36 weeks gestation) and had other risk factors for hypoglycemia. Two of the neonates were twins whose mother was diabetic. They were also suspected of having sepsis. Blood glucose levels were not reported. Hypoglycemia was reported to have occurred on the day of birth and was treated with intravenous fluids and feedings. The hypoglycemia resolved the following day.

The 3rd neonate was delivered by an emergency C-section due to acute severe maternal pancreatitis and fetal cardiac arrhythmia. The infant blood glucose values were as low as 20 mg/dL at 10 and 32 hours after birth. The hypoglycemic episodes recurred despite infusions of dextrose 10 and 30% solutions, and intravenous treatment with glucagon. Hypoglycemia was reported to have resolved within a few days.

Reviewer Comments: Because of the small number of postmarketing cases which were mostly confounded by underlying conditions, the OSE review did not identify a safety concern for atazanavir in regard to neonatal jaundice or neonatal hypoglycemia.

9 Appendices

Appendix 1: Maternal SAE (and drug discontinuation) Narrative 5-0050 Clinical Summary:

The subject's last menstrual period was on [redacted] (Day -194). She was gravida 2. On 18-Feb-2008 (Day -58) urine test confirmed pregnancy. On [redacted] (Day -14) prenatal ultrasound at 19 weeks of gestation showed a singleton pregnancy. On [redacted] (Day 66), the subject was noted to have an increase in transaminases. The event of "transaminase increase" was considered by the investigator to be very severe and probably related to the study medication. Laboratory test was performed on [redacted] (Day 66) and the result showed the following.

Laboratory test results

Study Day	ALP U/L	ALT U/L	AST U/L
Baseline	106	14	16
Normal Range	40-120	5-40	5-40
[redacted] (Day 66)	241	564	340
[redacted] (Day 74)	179	281	121
[redacted] (Day 98)	128	18	20

No treatment was required for the event. On an unknown date, the subject was found to have an increased blood pressure of 140/102 mmHg and pedal edema secondary to proteinuria. On [redacted] (Day 67), the subject was diagnosed with pre-eclampsia and was hospitalized. The event of pre-eclampsia was considered by the investigator to be very severe and not likely related to the study medication. The subject had 2 eclamptic seizures and was treated with magnesium sulfate. During the first seizure, the subject fell and sustained a laceration on the forehead. It was sutured. The skull x-ray was normal. An emergency caesarian section was performed on [redacted] (Day 70) and a live baby was delivered. The infant had mild respiratory distress at birth. She received ventilation for the event and the event resolved within 2 minutes. No action was taken with regard to the study medication due to the even of pre-eclampsia; however, the study therapy was discontinued due to the event of "transaminase increased" with the last dose received on [redacted] (Day 66). The event of pre-eclampsia resolved on [redacted] (Day 70). On [redacted] (Day 80), the subject developed pneumonia. She was treated with doxycycline, hydrocortisone and piperacillin/tazobactum for the event of pneumonia. The event of pneumonia resolved on [redacted] (Day 88) and the event of "transaminase increased" resolved on [redacted] (Day 98). On the same day subject was discharged from the hospital.

Appendix 2: Infant SAE (and drug discontinuation) Narrative 4-1035 Clinical Summary:

On [redacted] (Day 1), the subject was noted to have respiratory distress. At that time, the subject had an APGAR score of 8/9. The event of respiratory distress was judged by the investigator to be moderate in intensity and not likely related to the study medication. The event of respiratory distress resolved on [redacted] (Day 3). On [redacted] (Day 4), the subject developed cardiorespiratory arrest, convulsion, cerebral ischemia and restrictive cardiomyopathy. The subject received cardio-respiratory resuscitation. He was put on assisted ventilation and oxygen and was transferred to the neonatal intensive care unit (NICU). At the NICU, the subject was found to have metabolic acidosis. Sodium bicarbonate was given to correct the acidosis. A chest x-ray was performed and the result showed bilateral infiltration. The subject was treated with ampicillin and amikacin. The event of cardiorespiratory arrest was judged by the investigator to be very severe in intensity and not likely related to the study medication. The event of convulsion and cerebral ischemia were judged by the investigator to be moderate in intensity and not likely related to the study medication; and the event of restrictive cardiomyopathy was judged by the investigator to be moderate in intensity and possibly related to the study medication. The event of cardio-respiratory arrest resolved on [redacted] (Day 4) and convulsion resolved on [redacted] (Day 5). That day (08-Sep-2007), the neonate was extubated and was placed on continuous positive airway pressure. On [redacted] (Day 7), head computed tomography (CT) scan was performed which showed no significant findings. An electro-encephalogram performed on the same day and the result revealed diffuse brain injury. On [redacted] (Day 8), the subject was still had hemodynamic instability, some cardiac dysfunction, and poor motor function. Magnetic resonance imaging (MRI) on [redacted] (Day 10), revealed ischemic brain injury. The neurologist considered that the baby suffered watershed infarctions to the brain. The injury was assessed by the investigator as secondary to the hypoxia experienced during the cardiorespiratory arrest. On [redacted] (Day 15), the right ventricular dysfunction was diagnosed as restrictive cardiomyopathy. The etiology of this remained unknown. On that same day, he was discharged home and was feeding well. No action was taken with regard to study drug for the event of respiratory distress, cardiorespiratory arrest, convulsion, cerebral ischemia, and restrictive cardiomyopathy. The event of cerebral ischemia resolved with sequela on [redacted] (Day 15) and the event of restrictive cardiomyopathy was continuing at the time of the report. Denver II testing revealed "suspect" evaluations of fine-motor adaptive skills at Month 4 and suspect evaluations of personal/social, fine-motor adaptive, and gross motor skills at Month

9.1 Literature Review/References

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9.2 Labeling Recommendations: DAVP proposed changes to Proposed Package Insert and Patient Package Insert

In the Applicant's original proposed labeling, (b) (4) The Applicant also revised Section 8.1 Pregnancy to reflect (b) (4) . The Applicant's revision also included a brief summary of the (b) (4) . The review team believed that the proposed dosing of ATV for pregnancy needed to be clarified to address situations when ATV is used with concomitant medications drugs such asH2-blockers. In addition, the review team proposed significant changes to the Applicant's proposed labeling in Section 8.1 to better reflect the results of Study AI424182 and to conform more closely to the goals of the proposed pregnancy rule. The Pharmacology-Toxicology Team updated their sub-sections in 8.1 and Section 13 to give risk information relative to boosted (+RTV) atazanavir. Finally, the review team also updated the Patient Information section to address issues of atazanavir use during pregnancy.

(b) (4)

8 Page(s) of Draft Labeling has been Withheld in Full as b4 (CCI/TS) immediately following this page

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

/s/

ALAN M SHAPIRO
02/01/2011

MARY E SINGER
02/01/2011

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

NDA/BLA Number: 21-567 **Applicant: BMS** **Stamp Date: August 6, 2010**

Drug Name: Reyataz (atazanavir) **NDA/BLA Type: NDA**

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

	Content Parameter	Yes	No	NA	Comment
FORMAT/ORGANIZATION/LEGIBILITY					
1.	Identify the general format that has been used for this application, e.g. electronic CTD.	X			
2.	On its face, is the clinical section organized in a manner to allow substantive review to begin?	X			
3.	Is the clinical section indexed (using a table of contents) and paginated in a manner to allow substantive review to begin?	X			
4.	For an electronic submission, is it possible to navigate the application in order to allow a substantive review to begin (*e.g.*, are the bookmarks adequate)?	X			
5.	Are all documents submitted in English or are English translations provided when necessary?	X			
6.	Is the clinical section legible so that substantive review can begin?	X			
LABELING					
7.	Has the applicant submitted the design of the development package and draft labeling in electronic format consistent with current regulation, divisional, and Center policies?	X			
SUMMARIES					
8.	Has the applicant submitted all the required discipline summaries (*i.e.*, Module 2 summaries)?	X			
9.	Has the applicant submitted the integrated summary of safety (ISS)?	X			Safety summary is for a single study
10.	Has the applicant submitted the integrated summary of efficacy (ISE)?	X			Efficacy summary is for a single study
11.	Has the applicant submitted a benefit-risk analysis for the product?	X			
12.	Indicate if the Application is a 505(b)(1) or a 505(b)(2). If Application is a 505(b)(2) and if appropriate, what is the reference drug?			X	
DOSE					
13.	If needed, has the applicant made an appropriate attempt to determine the correct dosage and schedule for this product (*i.e.*, appropriately designed dose-ranging studies)? Study Number: Study Title: Sample Size: Arms: Location in submission:	X			
EFFICACY					
14.	Do there appear to be the requisite number of adequate and well-controlled studies in the application? Pivotal Study #1 Indication:			X	Not an efficacy supplement

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
	Pivotal Study #2 Indication:				
15.	Do all pivotal efficacy studies appear to be adequate and well-controlled within current divisional policies (or to the extent agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling?			X	Not an efficacy supplement
16.	Do the endpoints in the pivotal studies conform to previous Agency commitments/agreements? Indicate if there were not previous Agency agreements regarding primary/secondary endpoints.			X	Not an efficacy supplement
17.	Has the application submitted a rationale for assuming the applicability of foreign data to U.S. population/practice of medicine in the submission?		X		DAVP accepts foreign HIV studies to support approval in the US
SAFETY					
18.	Has the applicant presented the safety data in a manner consistent with Center guidelines and/or in a manner previously requested by the Division?	X			
19.	Has the applicant submitted adequate information to assess the arythmogenic potential of the product (*e.g.*, QT interval studies, if needed)?	X			Atazanavir has a potential to lengthen PR interval and EKGs have been done on participants
20.	Has the applicant presented a safety assessment based on all current worldwide knowledge regarding this product?	X			
21.	For chronically administered drugs, have an adequate number of patients (based on ICH guidelines for exposure[1]) been exposed at the dose (or dose range) believed to be efficacious?		X		The small sample size is more of a review issue (safety) rather than a filing issue
22.	For drugs not chronically administered (intermittent or short course), have the requisite number of patients been exposed as requested by the Division?		X		The small sample size is more of a review issue (safety) rather than a filing issue
23.	Has the applicant submitted the coding dictionary[2] used for mapping investigator verbatim terms to preferred terms?		X		Have requested a copy from Sponsor (see below)
24.	Has the applicant adequately evaluated the safety issues that are known to occur with the drugs in the class to which the new drug belongs?	X			
25.	Have narrative summaries been submitted for all deaths and	X			

[1] For chronically administered drugs, the ICH guidelines recommend 1500 patients overall, 300-600 patients for six months, and 100 patients for one year. These exposures MUST occur at the dose or dose range believed to be efficacious.

[2] The "coding dictionary" consists of a list of all investigator verbatim terms and the preferred terms to which they were mapped. It is most helpful if this comes in as a SAS transport file so that it can be sorted as needed; however, if it is submitted as a PDF document, it should be submitted in both directions (verbatim -> preferred and preferred -> verbatim).

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
	adverse dropouts (and serious adverse events if requested by the Division)?				
OTHER STUDIES					
26.	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?			X	
27.	For Rx-to-OTC switch and direct-to-OTC applications, are the necessary consumer behavioral studies included (*e.g.*, label comprehension, self selection and/or actual use)?			X	
PEDIATRIC USE					
28.	Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral?	X			
ABUSE LIABILITY					
29.	If relevant, has the applicant submitted information to assess the abuse liability of the product?			X	
FOREIGN STUDIES					
30.	Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population?		X		DAVP accepts foreign HIV studies to support approval in the US
DATASETS					
31.	Has the applicant submitted datasets in a format to allow reasonable review of the patient data?	X			
32.	Has the applicant submitted datasets in the format agreed to previously by the Division?	X			
33.	Are all datasets for pivotal efficacy studies available and complete for all indications requested?			X	Primarily a PK study with some safety data
34.	Are all datasets to support the critical safety analyses available and complete?	X			Primarily a PK study with some safety data
35.	For the major derived or composite endpoints, are all of the raw data needed to derive these endpoints included?			X	Primarily a PK study with some safety data
CASE REPORT FORMS					
36.	Has the applicant submitted all required Case Report Forms in a legible format (deaths, serious adverse events, and adverse dropouts)?		X		Have narratives for concerning adverse events. Do not have CRFs for all SAEs. Will request CRFs (see below)
37.	Has the applicant submitted all additional Case Report Forms (beyond deaths, serious adverse events, and adverse drop-outs) as previously requested by the Division?			X	
FINANCIAL DISCLOSURE					
38.	Has the applicant submitted the required Financial Disclosure information?	X			
GOOD CLINICAL PRACTICE					
39.	Is there a statement of Good Clinical Practice; that all clinical studies were conducted under the supervision of an IRB and with adequate informed consent procedures?	X			

IS THE CLINICAL SECTION OF THE APPLICATION FILEABLE? __YES_____

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

If the Application is not fileable from the clinical perspective, state the reasons and provide comments to be sent to the Applicant. **N/A**

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

1) In addition to the narratives in the CSR, please provide the case report forms (CRFs) for all mothers and infants with SAEs. In addition, please also provide the CRFs for the following subjects (if not covered under the SAE request):
AI424182-5-23
AI424182-5-34
AI424182-5-45
AI424182-4-1007
AI424182-8-1018
AI424182-4-1043
AI424182-4-1069

2) Please either identify location of the coding dictionary used for mapping investigator verbatim terms to preferred terms in the submission or provide a copy for the review team.

The "coding dictionary" consists of a list of all investigator verbatim terms and the preferred terms to which they were mapped. It is most helpful if this comes in as a SAS transport file so that it can be sorted as needed; however, if it is submitted as a PDF document, it should be submitted in both directions (verbatim -> preferred and preferred -> verbatim).

Reviewing Medical Officer	Alan M. Shapiro, MD PhD	Date 09/22/2010
Clinical Team Leader	Mary Singer, MD PhD	Date

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

/s/

ALAN M SHAPIRO
09/23/2010

MARY E SINGER
09/23/2010

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-567/S025

CHEMISTRY REVIEW(S)

CHEMISTS REVIEW	1. ORGANIZATION	2. NDA NUMBER
	ONDQA Div II, Branch VI and HFD-530	021567

3. NAME AND ADDRESS OF APPLICANT	4. COMMUNICATION, DATE
Bristol-Meyers Squibb Company 5 Research Parkway P.O. Box 5100, Room 252A, Mailstop 2CW-506 Wallingford, CT 06492	S-025 8/6/10 Efficacy SDN069 User Fee Date is 2/6/10

5. PROPRIETARY NAME	6. NAME OF THE DRUG	7. AMENDMENTS, REPORT, DATE
REYATAZ	Atazanavir sulfate	None

8. COMMUNICATION PROVIDES FOR:

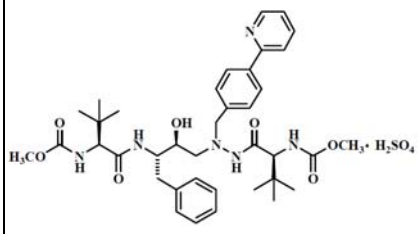
A change in labeling to incorporate data from clinical study related to ATV/RTV in HIV-infected pregnant women.

9. PHARMACOLOGICAL CATEGORY	10. HOW DISPENSED	11. RELATED IND, NDA, DMF
Antiviral	Rx	N/A
12. DOSAGE FORM	**13. POTENCY**	
Capsule	100 mg, 150 mg, 200 mg, and 300 mg	

14. CHEMICAL NAME AND STRUCTURE

Chemical Name(s): 2,5,6,10,13-Pentaazatetradecanedioic acid, 3-12-bis(1,1-dimethylethyl)-8-hydroxy-4,11-dioxo-9-(phenylmethyl)-6-[[-4-(2-pyridinyl)phenyl]methyl]-, dimethyl ester, (3*S*,8*S*,9*S*,12*S*)-, sulfate (1:1) (salt).

Molecular Formula: $C_{38}H_{52}N_6O_7 \cdot H_2O_4S$
Molecular Weight: 802.93 g/mol



BMS-232632-05

15. COMMENTS
NDA 21567/S-025 is an Efficacy Supplement supporting revised prescribing information related to ATV/RTV in HIV-infected pregnant women. There is no MOD 3 submitted. There are no proposed changes to the DESCRIPTION or *HOW SUPPLIED/STORAGE AND HANDLING* sections. There is a request for Categorical Exclusion under 21 CFR 25.31(a) since the supplement proposes no increase in active compound introduced into the environment. This request is appropriate.
16. CONCLUSION AND RECOMMENDATION
APPROVAL

17. NAME	**18. REVIEWERS SIGNATURE**	**19. DATE COMPLETED**
Brian Rogers	See appended electronic signature sheet	9/14/10

DISTRIBUTION: ORIGINAL JACKET CSO REVIEWER DIVISION FILE

AP

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-21567	SUPPL-25	BRISTOL MYERS SQUIBB CO	REYATAZ (ATAZANAVIR SULFATE)

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/s/

BRIAN D ROGERS
09/14/2010

HASMUKH B PATEL
09/14/2010

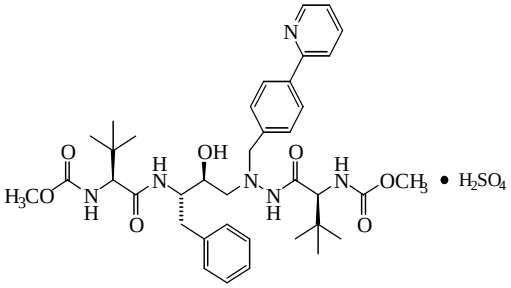
CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-567/S025

PHARMACOLOGY REVIEW(S)

PHARMACOLOGIST'S REVIEW

NDA NUMBER:	**21-567**
NUMBER/DATE/TYPE:	8/6/2010; Efficacy Supplement S-025 (Sequence #0069)
PDUFA GOAL DATE & EDR	PDUFA goal Date:2/6/2011
LOCATION:	EDR Location: \\CDSESUB1\EVSPROD\NDA021567\021567.enx
INFORMATION TO SPONSOR	Yes (x) No ()
SPONSOR	Bristol-Myer-Squibb Pharmaceutical Research Institute, Connecticut, USA
DRUG MANUFACTURER	Same as above
DIVISION NAME:	DAVDP
HFD #:	HFD-530
REVIEW COMPLETION	1/26/11
DRUG TRADE NAME:	Reyataz®
GENERIC NAME	Atazanavir
CODE NAME	BMS-232632-05; CGP-73547
CHEMICAL NAME	[3*S*-(3*R**, 8*R**, 9*R**, 12*R**)]-3,12-bis(1,1-dimethylethyl)-8-hydroxy-4,11-dioxo-9-(phenylmethyl)-6-[[4-(2-pyridinyl)phenyl]methyl]-2,5,6,10,13-pentaazatetradecanedioic acid, dimethyl ester, sulfate salt
FORMULA/MW	$C_{38}H_{52}N_6O_7XH_2SO_4$; MW=802.9 (sulfuric acid salt); 704.9 (free base)
STRUCTURE	
RELATED INDS	56,897; 60,878; (b) (4)
DRUG CLASS:	Antiviral
INDICATION:	treatment of HIV-1 infection in combination with other antiretroviral agents
CLINICAL FORMULATION:	oral capsule (100 mg, 150 mg, 200 mg, 300 mg)
ROUTE	Oral
PROPOSED USE:	HIV Infection

DISCLAIMER: Tabular and graphical information is from sponsor's submission unless stated otherwise.

INTRODUCTION

Atazanavir (BMS-232632, ATV) is a new azapeptide HIV protease inhibitor which has no apparent in vitro activities toward other human aspartyl proteases. The original NDA is originated from IND 56,897 that was initially submitted on 9/3/98 and approved for marketing in June 2003. The current approved dosage of ATV recommends co-administration with ritonavir (RTV), which provides increased exposures ATV.

This efficacy supplement (S-025) relates to a PK/safety study in HIV-infected pregnant women and showed that there was no significant difference in drug exposures between ATV/RTV 300/100 mg and ATV/RTV 400/100 mg dosing. The sponsor proposed labeling changes to reflect these results.

The preclinical data are cross-referenced to the original NDA and no new pharmacology/toxicology studies were submitted to this supplement. The only changes are pharmacology/toxicology portion of drug's labeling. Division's revision of the proposed labeling is provided below.

DIVISION'S REVISION OF SPONSOR'S LABELING CHANGES (PHARM/TOX SECTION 8 AND SECTION 13)

(b) (4)

[redacted]

2 Page(s) have been Withheld in Full as b4 (CCI/TS) immediately following this page

CONCLUSION

There is no pharmacology/toxicology concern for this supplemental NDA and from the pharmacology/toxicology's perspective, in addition to drug's labeling, no further comments will be made for the approval of this supplemental NDA.

Kuei-Meng Wu, Ph.D.
Reviewing Pharmacologist
DAVDP

Concurrences:
DAVDP/HFD-530/PTL/HGhantous
Wu/Pharm/1/26/2011

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/s/

KUEI-MENG WU
01/26/2011

HANAN N GHANTOUS
01/26/2011

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-567/S025

STATISTICAL REVIEW(S)

STATISTICS FILING CHECKLIST FOR A NEW NDA

NDA Number: 21567 **Applicant: Bristol-Myers-Squibb** **Stamp Date:** 07/24/2010

Drug Name: Atazanavir **NDA/BLA Type:** Standard Review

Reviewers: Thomas Hammerstrom

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

	Content Parameter	Yes	No	NA	Comments
1	Index is sufficient to locate necessary reports, tables, data, etc.	**X**			
2	ISS, ISE, and complete study reports are available (including original protocols, subsequent amendments, etc.)	**X**			
3	Safety and efficacy were investigated for gender, racial, and geriatric subgroups investigated (if applicable).	**X**			
4	Data sets in EDR are accessible and do they conform to applicable guidances (e.g., existence of define.pdf file for data sets).	**X**			

IS THE STATISTICAL SECTION OF THE APPLICATION FILEABLE? Yes

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

STATISTICS FILING CHECKLIST FOR A NEW NDA

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

Content Parameter (possible review concerns for 74-day letter)	**Yes**	**No**	**NA**	**Comment**
Designs utilized are appropriate for the indications requested.	X			
Endpoints and methods of analysis are specified in the protocols/statistical analysis plans.	X			
Interim analyses (if present) were pre-specified in the protocol and appropriate adjustments in significance level made. DSMB meeting minutes and data are available.			X	
Appropriate references for novel statistical methodology (if present) are included.			X	
Safety data organized to permit analyses across clinical trials in the NDA/BLA.			X	
Investigation of effect of dropouts on statistical analyses as described by applicant appears adequate.			X	

Thomas Hammerstrom 9-20-2010

Reviewing Statisticians Date

Greg Soon

Supervisor/Team Leader Date

File name: 5_Statistics Filing Checklist for NDA110207

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/s/

THOMAS S HAMMERSTROM
09/22/2010

GUOXING SOON
10/06/2010

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-567/S025

MICROBIOLOGY REVIEW(S)

DIVISION OF ANTIVIRAL PRODUCTS (HFD-530)
VIROLOGY REVIEW
NDA: 21-567 **SN**: S025 **DATE REVIEWED:** 09/20/2010
Virology Reviewer: Lisa K. Naeger, Ph.D.

Sponsor's Name and Address:
Bristol-Myers Squibb
5 Research Parkway
P.O. Box 5100
Wallingford, CT 06492-7660

Reviewer's Name: Lisa K. Naeger, Ph.D.

Initial Submission Dates:
Correspondence Date: 08/06/2010
CDER Receipt Date: 08/06/2010 (electronic)
Reviewer Receipt Date: 08/23/2010
Review Complete Date: 9/20/2010
PDUFA Date: 02/06/2011

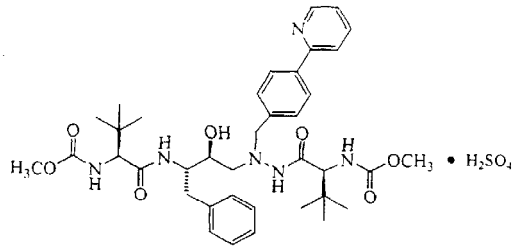
Related/Supporting Documents: IND 56,897 (BMS), NDA 21-567, NDA 21-567 B1 and B2, NDA 21-567 SE-002, IND 60,878

Product Name(s): Atazanavir (BMS-232632, ATV)
Proprietary: Reyataz™
Non-Proprietary/USAN: Atazanavir sulfate
Code Name/Number: BMS-232632

Chemical Name: Dimethyl (3S, 8S, 9S, 12S)-9-benzyl-3,12-di-tert-butyl-8-hydroxy-4,11-dioxo-6-[4-(2-pyridyl)benzyl]-2,5,6,10,13-pentaazaetradecanedioate sulfate (1:1)

Structural Formula:

Atazanavir (BMS-232632, ATV)



Molecular Formula: $C_{38}H_{52}N_6O_7 \cdot H_2SO_4$
Molecular Weight: 704.9

Dosage Form(s): 100/150/200 mg capsule
Route(s) of Administration: Oral
Pharmacological Category: Antiviral
Indication(s): Treatment of HIV-1 infection [redacted] (b) (4) in combination with other antiretroviral agents

Dispensed: Rx X OTC_____

DIVISION OF ANTIVIRAL PRODUCTS (HFD-530)
VIROLOGY REVIEW
NDA: 21-567 **SN**: S025 **DATE REVIEWED:** 09/20/2010
Virology Reviewer: Lisa K. Naeger, Ph.D.

Abbreviations: ARV, antiretroviral; ATV, atazanavir; ATV/r, atazanavir/ritonavir; BL, baseline; DC, discontinuation; EC, effective concentration; FC, fold change; FTC, emtricitabine; HAART, highly active antiretroviral therapy; HIV, human immunodeficiency virus; LPV/r, lopinavir/ritonavir; NNRTI, non-nucleoside reverse transcriptase inhibitor; NRTI, nucleoside reverse transcriptase inhibitor; PBMCs, peripheral blood mononuclear cells; PCR, polymerase chain reaction; PI, protease inhibitor; PR, protease; RNA, ribonucleic acid; RT, reverse transcriptase; RTI, reverse transcriptase inhibitor; TDF, tenofovir disoproxil fumarate; TLOVR, Time to Loss of Virologic Response; USPI, United States package insert; WT, wild-type

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TABLE OF CONTENTS

DIVISION OF ANTIVIRAL PRODUCTS (HFD-530)
VIROLOGY REVIEW
NDA: 21-567 **SN**: S025 **DATE REVIEWED:** 09/20/2010
Virology Reviewer: Lisa K. Naeger, Ph.D.

EXECUTIVE SUMMARY

Reyataz® (atazanavir sulfate) capsules received FDA approval on June 20, 2003 for the treatment of HIV-1 infection in combination with other antiretroviral agents. A supplemental NDA 21-567 was approved July 6, 2004 to support the use of the protease inhibitor, atazanavir (ATV), for the treatment of HIV infection in treatment-experienced adults, in combination with other antiretroviral agents, using an alternative "boosted" dosing regimen of Reyataz administered as 300 mg with 100 mg ritonavir (ATV/r) taken once daily (QD) with food. A pediatric supplement in support of using ATV/r in children ≥6 years was approved in March 2008. The recommended dosage of REYATAZ for pediatric patients (6 to less than 18 years of age) was based on body weight and should not exceed the recommended adult dosage. The data were insufficient to recommend dosing of REYATAZ for any of the following: (1) patients less than 6 years of age, (2) without ritonavir in patients less than 13 years of age, and (3) treatment-experienced pediatric patients with body weight less than 25 kg. In October 2008, ATV/r was approved for use in treatment-naïve HIV-1 infected patients.

This submission is a supplemental NDA (sNDA) to NDA 21-567 and is being submitted to provide data to support using ATV/r in pregnant women. Clinical Study AI424182 is entitled "Study of the Pharmacokinetics of Atazanavir (ATV)/Ritonavir (RTV) Administered as Part of highly active antiretroviral therapy (HAART) Therapy in HIV-1 Infected Pregnant Women." The primary objective of the study was to determine which dosing regimen of ATV/r produces adequate drug exposure during pregnancy compared to drug exposure in historical data in HIV-1-infected subjects. A secondary objective was to assess the virologic efficacy of an ATV/r-based HAART regimen during pregnancy. The PK and efficacy analyses were based on data from 41 treated mothers and 40 infants.

EFFICACY RESULTS

At or before delivery, all 41 mothers achieved HIV-1 RNA < 50 copies/mL. On the actual day of delivery, all mothers had HIV-1 RNA < 400 copies/mL (virologic response - observed cases [VR-OC]) and 38 of 39 mothers had HIV-1 RNA < 50 copies/mL. One mother achieved an undetectable HIV-1 RNA of < 50 copies/mL for the 3 visits prior to delivery, and again suppressed to < 50 copies/mL post delivery. Through 6 months of life, all infants were HIV-1 negative.

RESISTANCE

Resistance testing using genotypes (b) (4) was conducted at baseline on all subjects who had an HIV-1 viral load > 400 copies/mL. Resistance testing was conducted for any subject who had a virologic rebound to > 400 copies/mL while on treatment, and for subjects who discontinued ARVs postpartum and after the postpartum PK assessment was completed. In subjects who were not on HAART at enrollment, but had a history of previous ARV exposure, a genotype and phenotype sample was sent at

the Week 2 visit to determine if any pre-existing, but previously undetected resistance mutations occurred.

Baseline Genotypic Results in Mothers

Baseline genotypes and phenotypes were available for 37 of 41 mothers on either regimen (Table 1). None of the subjects who were analyzed had major IAS PI substitutions at baseline. Only one subject in the ATV/r 400/100 mg treatment group had decreased susceptibility to ATV at baseline with a fold change of 2.34.

Table 1. Baseline Genotypic Resistance Profile - Treated Mothers

		Numbers with Event/Number Evaluable	
		3rd Trimester Treatment	
		ATV/RTV 300/100 mg N = 20	ATV/RTV 400/100 mg N = 21
Baseline genotypes		17/20	20/21
Baseline phenotypes		17/20	20/21
IAS-USA major PI substitutions[a]		0	0
IAS-USA minor PI substitutions[b]		2/17	2/20
PI polymorphisms without IAS-USA major and minor		15/17	18/20
NRTI substitutions[c]	TAMS+[d]	2/17	2/20
	TAMS	1/17	0/20
	ZDV	1/17	0/20
	NNRTI[e]	4/17	3/20
	K103N	0/17	2/20
PI phenotypic resistance	Tipranavir/ritonavir (TPV/R) > 2.0	1/17	0/20
	Atazanavir (ATV) > 2.2	0/17	1/20[f]
RTI phenotypic resistance	Didanosine (ddI) > 1.3	2/17	0/20
	Delavirdine (DLV) > 6.2	1/17	2/20
	Efavirenz (EFV) > 3.0	1/17	2/20
	Nevirapine (NVP) > 4.5	1/17	2/20

Source: Supplemental Tables 5.5A and 5.5D.

[a] IAS-USA major PI substitutions are any of L24I D30N V32I L33F M46I/L I47A/V G48V I50L/V F53L/Y I54A/L/M/S/T/V L76V V82A/F/L/S/T I84V N88D/S L90M.

[b] IAS-USA minor PI substitutions are any of L10F/I/R/V V11I E35G K43T Q58E A71I/T/V G73A/C/S/T T74P N83D L89V.

[c] Any of K65N L74I/V Y115F; 69 insertion complex; 151 complex; TAMS+; TDF/FTC; ZDV.

[d] Any of M41L E44A/D D67E/G/N K70N/R V118I L210W T215F/Y K219E/N/Q/R/T/W.

[e] Any of V90I A98G L100I K101E/H/P K103N V106A/I/M V108I E138A V179D/F/T Y181C/I/V Y188C/H/L G190A/S P225H M230L.

[f] This subject was sensitive to unboosted but not boosted ATV.

On-study Phenotypic and Genotypic Resistance in Mothers

Resistance testing was conducted on study for 17 of 41 mothers. Of these 17 mothers, 16 had resistance testing conducted when they had discontinued ARVs postpartum. For Subject AI424182-5-41, a genotype was sent on Day 15 when her HIV-1 RNA level was declining but she had not yet achieved undetectability. In this case, no genotype was sent postpartum. Four subjects (AI424182-4-7, AI424182-4-8, AI424182-5-15, and

AI424182-5-51) had virologic rebound blips to > 400 copies/mL while on ARVs, but resistance testing was not performed (viral load returned to <50 copies/mL for all 4 subjects).

Of the 17 mothers who had resistance testing performed on study, 16 had baseline resistance data available while 1 mother did not (AI424182-4-9). Two subjects in each arm had minor IAS-USA PI substitutions at baseline. No major International AIDS Society (IAS)-USA PI substitutions emerged on- or off-treatment (Table 2). However, one minor IAS-USA PI substitution T74T/S emerged on- or off-treatment in Subject AI424182-12-65.

Phenotypic resistance to ATV/r emerged in an isolate from 1 subject (AI424182-5-59) on the ATV/r 400/100-mg regimen (Table 2). This subject had baseline genotypic ATV resistant substitutions [T12S I15V L19I/L K20R E35D M36I R41K H69K L89M L93L] and decreased ATV susceptibility at baseline (fold change =2.34). However, this subject achieved an HIV-1 RNA of < 50 copies/mL on Day 29 and remained undetectable through Day 140 when she was discontinued from ARVs postpartum except for one blip to 81 copies/mL on Day 57. The postpartum resistance testing of this subject on Day 167 (while off all ARVs) revealed reduced susceptibility to ATV/r (FC of 7.19) although no new PI mutations were observed.

Since Subject AI424182-4-9 did not have baseline resistance testing data available, the genotypic and phenotypic results from the on study testing are labeled as “new emergent or possibly new emergent” [K20R E35D R41K I62V L63P E65D A71T].

Table 2: Treatment-Emergent Resistance - Treated Mothers

		Numbers with Event/Number Evaluable	
		3rd Trimester Treatment	
		ATV/RTV 300/100 mg N = 20	ATV/RTV 400/100 mg N = 21
Genotypable mothers		5/20	12/21
Phenotypable mothers		5/20	12/21
IAS-USA major PI substitutions[b]		0/5	0/12
IAS-USA minor PI substitutions[b]		1/5	0
PI polymorphisms without IAS-USA major and minor		2/5	4/12
PI phenotypic resistance	ATV/RTV > 5.2	0/5	1/12
	Tipranavir/ritonavir (TPV/R) > 2.0	0/5	1/12
	Indinavir (IDV) > 2.1	0/5	1/12
	Nelfinavir (NFV) > 3.6	0/5	1/12
	Amprenavir (AMP) > 2.0	0/5	2/12
	Saquinavir (SQV) > 1.7	1/5	2/12
RTI phenotypic resistance	Didanosine (ddI) > 1.3	0	2/12

Source: Supplemental Tables 5.5C, 5.5F and Appendix 5.5F.

[a] IAS-USA major PI substitutions are any of L24I D30N V32I L33F M46I/L I47A/V G48V I50L/V F53L/Y I54A/L/M/S/T/V L76V V82A/F/L/S/T I84V N88D/S L90M.

[b] IAS-USA minor PI substitutions are any of L10F/I/R/V V11I E35G K43T Q58E A71I/T/V G73A/C/S/T T74P N83D L89V.

DIVISION OF ANTIVIRAL PRODUCTS (HFD-530)
VIROLOGY REVIEW
NDA: 21-567 **SN**: S025 **DATE REVIEWED:** 09/20/2010
Virology Reviewer: Lisa K. Naeger, Ph.D.

CONCLUSION

This study was small with 41 subjects and minimal resistance data. Baseline resistance data from 37 subjects and on-study resistance data from 17 subjects were submitted in this application. There were no major differences in genotypic and phenotypic changes to ATV between the two doses and no ATV resistance development on treatment associated with treatment failure. There are no virology label changes for this supplement.

This supplemental NDA for ATV/r is approvable with respect to virology for the treatment of pregnant. There are no virology specific Phase IV commitments that are being requested for this application.

RECOMMENDATIONS

Recommendation and Conclusion on Approvability

This supplemental NDA for ATV/r is approvable with respect to virology for the treatment of HIV-infected pregnant women.

Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable.

There are no virology specific phase IV commitments recommended for this application.

ADMINISTRATIVE

Reviewer's Signature(s)

Lisa K. Naeger
[Lisa K. Naeger, Ph.D.]
Sr. Microbiologist, HFD-530

Concurrence

HFD-530/Micro TL Signature _____ Date_____
Julian O'Rear, Ph.D.

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/s/

LISA K NAEGER
09/29/2010

JULIAN J O'REAR
09/29/2010

MICROBIOLOGY FILING CHECKLIST FOR NDA or Supplement

NDA Number: 21567 **Applicant: BMS** **Stamp Date: 08/06/2010**

Drug Name: ATV/RTV **NDA Type: S025**

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

	Content Parameter	Yes	No	Comments
1	Is the virology information (nonclinical and clinical) provided and described in different sections of the NDA organized in a manner to allow substantive review to begin?	X		
2	Is the virology information (nonclinical and clinical) indexed, paginated and/or linked in a manner to allow substantive review to begin?	X		
3	Is the virology information (nonclinical and clinical) legible so that substantive review can begin?	X		
4	On its face, has the applicant submitted cell culture data in necessary quantity, using necessary clinical and non-clinical strains/isolates, and using necessary numbers of approved current divisional standard of approvability of the submitted draft labeling?			NOT APPLICABLE
5	Has the applicant submitted any required animal model studies necessary for approvability of the product based on the submitted draft labeling?			NOT APPLICABLE
6	Has the applicant submitted all special/critical studies/data requested by the Division during pre-submission discussions?			NOT APPLICABLE
7	Has the applicant submitted the clinical virology datasets in the appropriate format as described in the relevant guidance documents and are the datasets complete?	X		
8	Has the applicant used standardized or nonstandardized methods for virologic outcome measures? If nonstandardized methods were used, has the applicant included complete details of the method, the name of the laboratory where actual testing was done and performance characteristics of the assay in the laboratory where the actual testing was done?	X		
9	Has the applicant submitted draft labeling consistent with current regulation, divisional and Center policy, and the design of the development package?	X		
10	Has the applicant submitted annotated microbiology draft labeling consistent with current divisional policy, and the design of the development package?			NOT APPLICABLE
11	Have all the study reports, published articles, and other references been included and cross-referenced in the annotated draft labeling or summary section of the submission?	X		
12	Are any study reports or published articles in a foreign language? If yes, has the translated version been included in the submission for review?		X	

IS THE MICROBIOLOGY SECTION OF THE APPLICATION FILEABLE? _YES___

If the NDA is not fileable from the microbiology 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 Microbiologist Date

Microbiology Team Leader Date

File name: 5_Microbiology Filing Checklist for a NDA or Supplement 010908

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/s/

LISA K NAEGER
09/20/2010

JULIAN J O'REAR
09/20/2010

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-567/S025

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

NDA: 21567, S025
Submission Dates: 08/06/2010
Brand Name: Reyataz®
Generic Name: Atazanavir sulfate
Formulation: 100/150/200/300 mg capsule
Applicant: Bristol-Myers Squibb Company
Reviewer: Jenny H. Zheng, Ph.D.
Team Leader: Sarah Robertson, Pharm.D.
OCP Division: DCP IV
Medical Division: DAVP

Table of Contents

1. Executive Summary

1.1 Recommendation

The clinical study submitted by the Applicant supports the approval of atazanavir (ATV)/ritonavir (RTV) use in pregnant women. The data indicated that for pregnant patients no dose adjustment is required for atazanavir (REYATAZ) with the following exceptions:

- REYATAZ without ritonavir is not recommended.
- REYATAZ should only be administered to pregnant women with HIV-1 strains susceptible to atazanavir.
- For treatment-experienced pregnant women during the second or third trimester, when REYATAZ is co-administered with either tenofovir or an H2-receptor antagonist, atazanavir 400 mg with ritonavir 100 mg once daily is recommended. There is insufficient data to recommend a REYATAZ dose for use with tenofovir *and* H_2-receptor antagonists in treatment-experienced pregnant women.

No dose adjustment is required for postpartum patients. However, adverse events should be closely monitored because atazanavir exposures could be higher during the first 2 months after delivery.

1.2 Phase IV commitment:

None.

2 Summary of Clinical Pharmacology Findings

This NDA supplement includes Study AI424182, A Study of the Pharmacokinetics of Atazanavir (ATV)/Ritonavir (RTV) administered as Part of HAART Therapy in HIV-1 Infected Pregnant Women. This is a multi-center, open-label, prospective, single-arm pharmacokinetic study in HIV-1 infected pregnant women in their second or third trimesters and postpartum. ATV/RTV 300/100 mg once daily (QD) and 400/100 mg QD (only during third trimester) in combination with ZDV/3TC (Combivir) 300/150 mg fixed dose combination (FDC) twice daily (BID) were evaluated. The study was originally evaluated based on the full data submitted by the applicant on August 8, 2010. On January 19, 2011, Division of Scientific Investigation (DSI) completed their review following inspection of the analytical site for AI424182 and indicated:

- The accuracy of protein binding data for samples analyzed in Runs 15, 16, and 26 used to quantify BMS-232632 in plasma:PBS (50:50) is not assured. Data from these samples should be excluded.
- Plasma samples analyzed in Run 20 (subject sample #s 12-44, 12-54, 12-55, 4-32, 4-43, 4-56, 5-40, 5-41, 5-50, 5-51, and 5-52) used to quantify BMS-232632 in plasma are not assured.

Therefore, the applicant was requested to exclude the affected samples from the PK and protein binding analyses and provide the reanalysis results. The reanalysis only affects ATV results. The reanalysis results indicate that only ATV PK results in the second trimester were significantly affected by the exclusion of Run 20. Protein binding results were unchanged with the excluded data from Runs 15, 16 and 26. Table 1 shows the PK comparison of the full data and the reanalysis results with exclusion of Run 20. Table 2 shows the plasma protein binding comparison of the full data and the reanalysis results with exclusion of Runs 15, 16 and 26.

Table 1: Comparison of Steady-State Pharmacokinetics of ATV in HIV-Infected Pregnant Women (Including and Excluding Run 20) with non-pregnant HIV-1 infected patients

PK Parameter	ATV/RTV 300/100 mg QD					ATV/RTV 400/100 mg QD		Reference (from label)		
	2nd Trimester		3rd Trimester	Postpartum		3rd Trimester		Non-Pregnant HIV-1 Infected Patients		
	Original (N=9)	Excluding Run 20 (N=5)	N=20 (no samples excluded)	Original (N=36)	Excluding Run 20 (N=34)	Original (N=20)	Excluding Run 20 (N=17)	ATV/RTV 300/100 mg (N=10)	ATV 400 mg (N=13)	ATV 300/100 mg + TDF (N=10)
Cmax (ng/mL) Geo.Mean (%CV)	3729.09 (39)	3078.85 (50)	3291.46 (48)	5649.10 (31)	5721.21 (31)	4210.8 (38)	4098.6 (42)	4422 (58)	2298 (71)	3190 (NR)
AUC (ng.h/mL) Geo.Mean (%CV)	34399.1 (37)	27657.1 (43)	34251.5 (43)	60532.7 (33)	61990.4 (32)	46602.4 (43)	44780.1 (47)	46073 (66)	14874 (91)	34459 (NR)
Cmin (ng/mL) Geo.Mean (%CV)	663.78 (36)	538.70 (46)	668.48 (50)	1420.64 (47)	1462.59 (45)	916.63 (60)	890.3 (65)	636 (97)	120 (109)	491 (NR)

NR = Not reported

Table 2: Plasma Protein Binding for Atazanavir by Group (Including and Excluding Runs 15, 16, and 26)

Treatment	Period		Percent Bound Mean (SD) 3h post-dose (maternal)	24h post-dose (maternal)	Cord blood
ATV/RTV 300/100 mg	2nd Trimester	Original (n=9)	87.91 (1.74)	89.06 (1.98)	
		with exclusions (n=6)	88.37 (2.02)	89.58 (2.10)	
	3rd Trimester	Original (n=20)	91.34 (2.32)	90.37 (2.58)	
		with exclusions (n=8)	91.35 (2.79)	89.61 (3.20)	
	Postpartum	Original (n=35)	87.03 (15.81) [n =34]	91.02 (3.22)	
		with exclusions (n=17)	90.71 (3.40) [n = 16]	91.74 (2.83)	
	Peripartum (Cord Blood)	Original (n=15)			77.05 (6.88)
		with exclusions (n=5)			73.22 (2.49)
ATV/RTV 400/100 mg	Peripartum (Cord Blood)	Original (n=12)			75.62 (4.34)
		with exclusions (n=7)			76.24 (4.75)

The following summarizes the study results before and after exclusion of data from Run 20 for PK analysis:

- ATV pharmacokinetics originally showed similar results between the second and the third trimesters at a dose of 300 mg in combination with 100 mg RTV once daily, while ATV exposure was doubled postpartum (mean 5.8 ± 2.1 weeks after delivery) (Table 3). The exclusion of Run 20 results in 20% lower AUC and Cmin in the second trimester as compared to the third trimester, with no significant difference in Cmax.
- Compared to historical data (pooled data from non-pregnant HIV-infected subjects receiving ATV/RTV 300/100 mg QD in Studies AI424089 and AI424137), ATV AUC(TAU), Cmax and Cmin are 26%, 40%, and 115% higher in women postpartum, respectively (Table 3).
- ATV/RTV 300/100 mg QD dosing provided 17%-27% lower Cmax and about 20% lower AUC(TAU) but similar Cmin values throughout pregnancy as compared to historical data in non-pregnant HIV-infected subjects (not on concomitant tenofovir) (Table 3).
- ATV/RTV 400/100 mg QD provided similar Cmax and AUC(TAU) in the 3rd trimester as compared with ATV/RTV 300/100 mg QD historical data in non-pregnant HIV-infected subjects, but provided a higher Cmin value (Table 3).
- ATV/RTV 300/100 mg QD dosing provided about 40% lower AUC, Cmax and Cmin in the third trimester as compared to postpartum (Table 3).
- ATV/RTV 400/100 mg QD dosing provided about 33%, 26%, and 26% lower AUC, Cmax and Cmin, respectively, in the third trimester as compared to ATV/RTV 300/100 mg QD postpartum (Table 3).

- The ratio of cord blood ATV concentrations relative to maternal peripartum concentrations was approximately 19% and 12% when mothers received ATV/RTV 300/100 mg QD and ATV/RTV 400/100 mg QD, respectively (Table 3). The exclusion of maternal peripartum data from 5 subjects in Run 20 has no effect on the ratio.
- ATV AUC, Cmax and Cmin are approximately dose-proportionally increased with the increased dose from ATV/RTV 300/100 mg QD to 400/100 mg QD during the 3rd trimester (Table 3).
- Maternal plasma protein binding (87-91%) was similar regardless of gestation time, dosing regimen, or time post-dose, and was similar to that reported for non-pregnant adults (86%). Postpartum maternal plasma protein binding was similar to that observed during pregnancy. Plasma protein binding in cord blood was lower than in maternal blood, with unbound fraction (23%) approximately twice that of maternal blood (Table 2).
- RTV exposures were similar between the 2nd and the 3rd trimester. RTV Cmax and AUC(TAU) were about 60% lower during the 2nd and the 3rd trimesters than postpartum or historical data. Therefore, low ATV exposure during pregnancy could partially be due to lower RTV exposures.

Table 3: Summary Statistics for ATV PK Parameters by Group *

Group	CMAX (NG/ML) GEO.MEAN (CV)	TMAX (H) MEDIAN (MIN-MAX)	CMIN (NG/ML) GEO.MEAN (CV)	AUC(TAU) (NG.H/ML) GEO.MEAN (CV)	T-HALF (HR) MEAN (SD)	MATERNAL CONC (NG/ML) GEO.MEAN (CV)	CORD BLOOD CONC (NG/ML) GEO.MEAN (CV)	FETAL RATIO (%) GEO.MEAN (CV)
A	3729.09	4.00	663.78	34399.13	10.63			
(N=9)	(39)	(2.0 - 6.0)	(36)	(37)	(2.38)			
B	3291.46	3.00	668.48	34251.50	15.99			
(N=20)	(48)	(1.5 - 8.0)	(50)	(43)	(22.25)			
C						1201	224 [a]	0.19 [a]
(N=19)						(63)	(67)	(41)
D	5649.10	3.00	1420.64	60532.75	17.08			
(N=36)	(31)	(0.5 - 6.0)	(47)	(33)	(7.00			
E	4210.76	4.00	916.63	46602.45	12.96			
(N=20)	(38)	(0.5 - 6.0)	(60)	(43)	(5.07)			
F						1224.20	183.52 [b]	0.12 [b]
(N=17)						(54)	(68)	(49)
H	4485.18		661.50	43388.06				
(N=23)	(32)		(67)	(42)				

Source: Table 9.1A from the sponsor's study-ai424182-csr-final.pdf

Note: Includes 8 additional subjects dosed at ATV/RTV 300/100 mg after the interim analysis datalock

Group: A - ATV/RTV 300/100 mg 2nd trimester B - ATV/RTV 300/100 mg 3rd trimester
C - ATV/RTV 300/100 mg peripartum D - ATV/RTV 300/100 mg postpartum
E - ATV/RTV 400/100 mg 3rd trimester F - ATV/RTV 400/100 mg peripartum
H - ATV/RTV 300/100 mg historical data from Studies AI424089 and AI424137, see Section 3.6.3.5 for description of pooled analysis.

[a] N=14

[b] N=15

* Original analysis (includes PK results from Run 20)

Atazanavir results from Study AI424182 are compared to the results from two other atazanavir pregnancy studies: a study conducted in Italy by D. Ripamonti et. al. (2007) and PACTG 1026s (2009). Both studies evaluated women in their 3rd trimester and postpartum only. Atazanavir exposures during pregnancy and postpartum from Study AI424182 are similar to the results from PACTG 1026s. Ripamonti's study shows in the third trimester, ATV AUC, Cmax and Cmin are about 17%, 22%, and 27% lower, respectively, as compared to Study AI424182; while during postpartum, the AUC and Cmax in Ripamonti's study are about half of the values observed in Study AI424182, and Cmin is about 64% lower. Comparing data across the three studies shows ATV's postpartum PK data are more variable relative to the 3rd trimester results, which could be partially due to differences in when PK data are collected postpartum. ATV exposures may be higher for women immediately after delivery, with levels returning slowly to the levels of pre-pregnancy over time. The postpartum evaluation was performed at 71± 45 days in the study by Ripamonti et. al., as compared to 5.8 ± 2.1 weeks (range: 3-10 weeks) in Study AI424182. The mean difference in postpartum collection time of ~30 days likely explains much of the discrepancy in postpartum results for AI424182 and the Ripamonti study. Therefore, historical data are a reasonable alternative to be used as a reference to compare the exposures during pregnancy.

The magnitude of ATV Cmin reduction in the third trimester is similar to the effect of tenofovir on ATV; coadministration of tenofovir with ATV did not decrease the efficacy of ATV when HIV-infected patients received ATV/RTV 300/100 mg QD. Results of PACTG 1026s, which included a cohort of women on concomitant TDF, indicate that the effects of TDF on ATV exposures during pregnancy and postpartum are similar to the observed magnitudes in non-pregnant healthy volunteers. In the current study, ATV Cmin in the third trimester women treated with ATV/RTV 300/100 mg QD is comparable to that of historical non-pregnant patients. The Cmin in the second trimester was originally comparable to historical non-pregnant patients using the full PK data, but is 15% lower after exclusion of Run 20 as compared to historical non-pregnant patients. This magnitude of decrease should be acceptable for pregnant women with HIV-1 strains susceptible to atazanavir, because the Cmin from all the three studies (including the 2nd and the 3rd trimesters) were all above the Cmin obtained historically for patients receiving ATV 400 mg QD. However, it could be too low for pregnant women carried atazanavir resistant HIV-1 strains. Therefore, **atazanavir should only be administered to pregnant women with HIV-1 strains susceptible to atazanavir.** Increase of ATV/RTV dose to 400/100 mg is not appropriate for the 2nd trimester because there are no safety data for women during the 2nd trimester with ATV/RTV greater than 300/100 mg QD. In addition, ATV/RTV 400/100 mg QD dosing was associated with twice as much hyperbilirubinemia (total bilirubin greater than or equal to 2.6 times the upper limit of normal) as ATV/RTV 300/100 mg QD in mothers in the current study (62% vs 30%). Therefore, **ATV/RTV 300/100 mg QD is recommended for treatment-naïve and treatment-experienced patients during pregnancy.**

However, for treatment-experienced patients who are also receiving tenofovir or H_2-receptor antagonists (which reduce ATV exposures by a similar magnitude as tenofovir), an ATV/RTV dose increase to 400/100 mg QD is recommended during the second and third trimesters to cover the possible additive decrease of exposure by tenofovir or H_2-receptor antagonists and pregnancy. The additive effect is predicted to be an 18% to 37% lower Cmin than the value obtained for non-pregnant patients at ATV/RTV doses of 300/100 mg QD. Increasing the ATV/RTV dose to 400/100 mg QD is expected to result in a Cmin similar to non-pregnant patients at ATV/RTV doses of 300/100 mg QD, but will keep Cmax lower than the value obtained for non-pregnant patients at ATV/RTV doses of 300/100 mg QD. **ATV/RTV should not be used with tenofovir *and* H_2-receptor antagonists in treatment-experienced**

pregnant women, because the predicted Cmin is expected to be 41% to 52% lower as compared to non-pregnant patients at ATV/RTV doses of 300/100 mg QD.

The pre-pregnancy dosing regimens should be resumed after delivery. However, adverse events should be closely monitored postpartum because ATV exposures could be higher during the first 2 months after delivery.

3 Question-Based Review (QBR)

A Question Based Review (QBR) section was not necessary because the submission only contains 1 study. The rationale for the labeling change is included in the Summary of Clinical Pharmacology Findings section. See the individual study review for more detail.

4. Detailed Labeling Recommendations

The following recommendations are made for Section 2, Dosage and Administration and Section 8, Use in Specific Populations:

Dosing During Pregnancy and the Postpartum Period:

- REYATAZ should not be administered without ritonavir.
- REYATAZ should only be administered to pregnant women with HIV-1 strains susceptible to atazanavir.
- For pregnant patients, no dose adjustment is required for REYATAZ with the following exceptions:
  - For treatment-experienced pregnant women during the second or third trimester, when REYATAZ is coadministered with either an H_2-receptor antagonist *or* tenofovir, REYATAZ 400 mg with ritonavir 100 mg once daily is recommended. There are insufficient data to recommend a REYATAZ dose for use with both an H_2-receptor antagonist *and* tenofovir in treatment-experienced pregnant women.
- No dose adjustment is required for postpartum patients. However, patients should be closely monitored for adverse events because atazanavir exposures could be higher during the first 2 months after delivery. [See *Use in Specific Populations (8.1) and Clinical Pharmacology (12.3)*.]

In addition, the Sponsor's proposal to add the PK results from AI424182 in Section 12.3, Pharmacokinetics is acceptable. However, the PK results should be amended to include the reanalysis, which excludes data from analytical Run 20.

5. Individual Study Report Reviews

Study AI424182: A Study of the Pharmacokinetics of Atazanavir (ATV)/Ritonavir (RTV) administered as Part of HAART Therapy in HIV-1 Infected Pregnant Women

Objectives:

Primary:

- To determine which dosing regimen of ATV/RTV produces adequate drug exposure during pregnancy compared to drug exposure in historical data in human immunodeficiency virus (HIV)-infected subjects.

Secondary:

- To compare ATV/RTV drug exposure during the 3rd trimester of pregnancy to drug exposure in the same women in the study cohort during the postpartum period
- To explore ATV/RTV drug exposure during the 2nd trimester of pregnancy (if available)
- To compare antiretroviral (ARV) drug concentrations in plasma from cord blood with those in maternal plasma at the time of delivery
- To determine the plasma protein binding of ATV during pregnancy and post partum
- To assess the safety in the neonate of maternally administered ATV
- To assess the safety and tolerability of an ATV/RTV-based HAART regimen during pregnancy
- To assess the virologic efficacy of an ATV/RTV-based HAART regimen during pregnancy
- To assess the efficacy of an ATV/RTV-based HAART regimen in preventing the mother-to-child-transmission (MTCT) of HIV-1 in formula fed infants
- To explore the relationship between UDP Glucuronosyltransferase 1A1 (UGT1A1) genotypes and bilirubin levels in pregnant women receiving ATV/RTV and in infants exposed to ATV/RTV in utero and at birth
- To evaluate the adherence to each drug and the adherence to the regimen as measured by the Multicenter AIDS Cohort Study (MACS) adherence questionnaire

Study Design:

This is a multi-center, open-label, prospective, single-arm study. Figure 1 shows the study scheme. The first 12 subjects who met inclusion/exclusion criteria received ATV/RTV 300/100 mg once daily (QD) with food + ZDV/3TC (Combivir) 300/150 mg fixed dose combination (FDC) twice daily (BID).

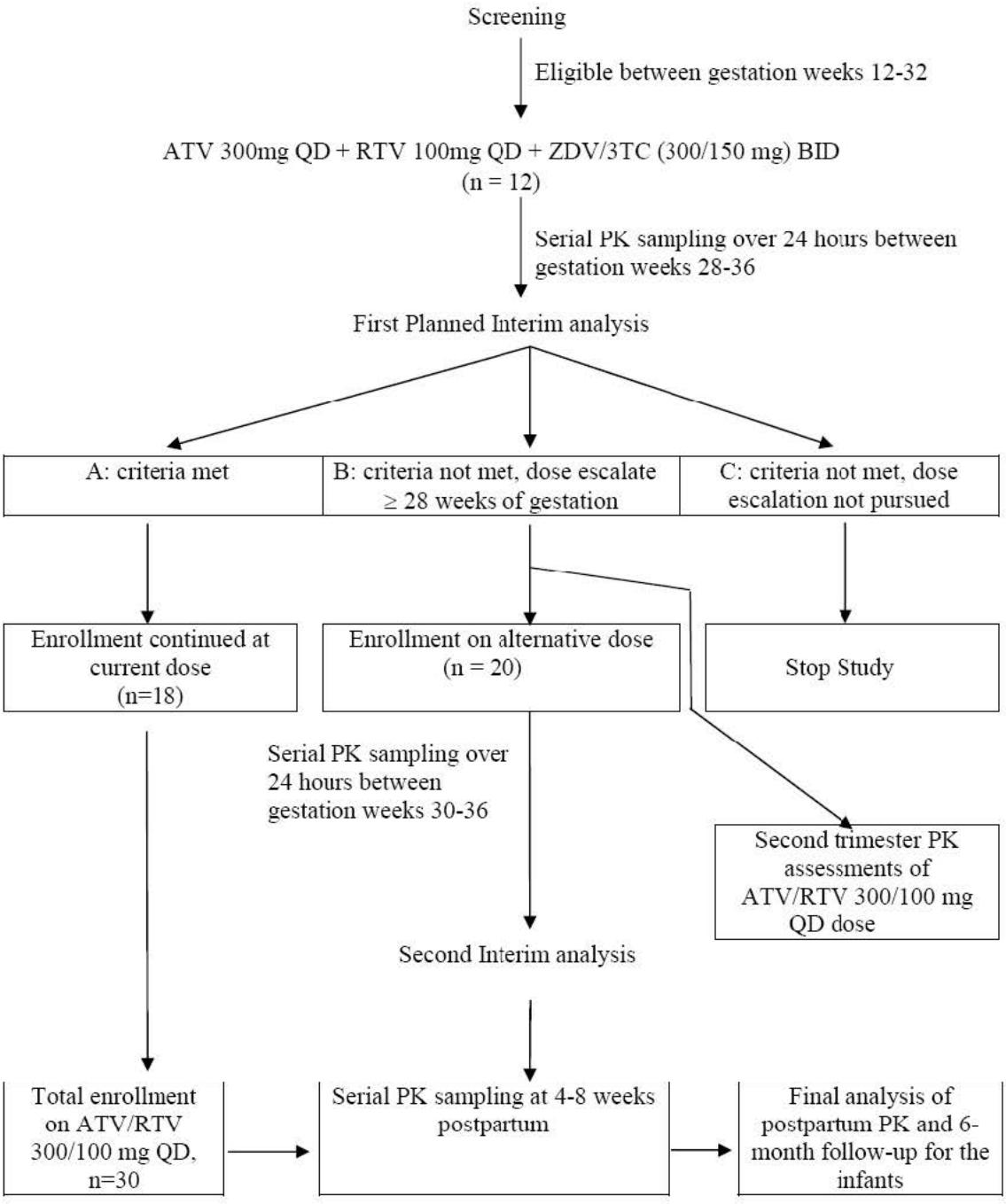
A PK interim analysis was required when 12 subjects reached steady state (2 weeks on drug) during the 3rd trimester of pregnancy to determine whether a dose adjustment would be warranted. The PK analysis was generated from an intensive PK sampling conducted over a single 24-hour period during Week 28 to Week 36 gestation. Depending on the results of this interim analysis, the study would proceed as follows:

a. If 10 of 12 of subjects have a Cmin ≥ 150 ng/mL and if the geometric mean ATV AUC(TAU) for these 12 subjects is ≥ 30,000 ng•h/mL, the dose of ATV/RTV 300/100 mg QD will be continued for an additional 18 subjects (after Amendment 05, the protocol added the following statement: if the Cmins are all ≥50 ng/mL and the geometric mean for AUC(TAU) for all 12 subjects is < 30,000 ng*h/mL but ≥ 15,000 ng*h/mL, dose escalation to ATV 400 mg QD/RTV 100 mg QD is allowed).

b. If more than 2 of 12 subjects have an ATV Cmin < 150 ng/mL, but 10 of 12 subjects have an ATV Cmin ≥ 50 ng/mL, or the geometric mean ATV AUC(TAU) for these 12 subjects is < 30,000 ng•h/mL but ≥ 15,000 ng•h/mL, there will be an increase to a dose of ATV/RTV 400/100 mg QD.

c. If more than 2 of 12 subjects have an ATV Cmin < 50 ng/mL, or the geometric mean ATV AUC(TAU) for these 12 subjects is < 15,000 ng•h/mL, the study will stop. All enrolled subjects who have not yet delivered their infants will be provided with alternative HAART to be determined by their provider.

Figure 1: Study Schematic



The targeted ATV exposure criteria were derived from previous experience with ATV with RTV in Studies AI424074 and AI424089.

The AUC criteria were not met at the interim analysis; the geometric mean AUC(TAU) was 26,600 ng•h/mL for the 12 women, which fell below the predefined cutoff of 30,000 ng•h/mL. However, all individual Cmin values exceeded the threshold of 150 ng/mL. Based on the low mean AUC, the ATV/RTV dose was increased to 400/100 mg QD in the 3rd trimester. ATV/RTV dose was kept at 300/100 mg QD in the 2nd trimester and postpartum.

The study was originally designed to compare drug exposure in HIV-1 infected pregnant women relative to HIV-1 infected non-pregnant woman using postpartum PK data. However, due to unexpectedly high postpartum ATV exposures at ATV/RTV 300/100 mg QD, the protocol was amended to make historical data (pooled data from subjects receiving ATV/RTV 300/100 mg QD in Studies AI424089 and AI424137) the reference in the primary objective. Pooled data included results only for subjects on an NRTI backbone that did not include tenofovir.

PK Sampling:

Intensive PK sampling was done between 30-36 weeks of gestation and at Week 4-8 postpartum (originally at Week 4, then amended to Week 4-8, and later extended up to 10 weeks postpartum). An additional intensive PK assessment was done between 18-24 weeks of gestation (if possible) for subjects who reached steady-state on ATV/RTV 300/100 mg QD. A random PK sample was collected at delivery. A cord blood sample was taken at delivery to determine neonatal exposure to ATV and RTV at the time of delivery.

Results

Of 69 enrolled women, 41 were treated with ATV/RTV. In the final analysis PK data were available for a total of 20 women treated with 300/100 mg in the 3rd trimester (8 additional women were enrolled after the interim analysis before the protocol amendment went into effect). In total, PK data were obtained on the following number of women:

Number of Subjects:

	ATV/RTV 300/100 2nd trimester	ATV/RTV 300/100 3rd trimester	ATV/RTV 400/100 3rd trimester	ATV/RTV 300/100 postpartum
# Subjects with PK data	9	20	20	36

PK Results:

Atazanavir PK: Summary statistics for all ATV PK parameters are presented in Tables 1 and 2. Box-plots of ATV AUC(TAU), Cmax, and Cmin vs group are shown in Figures 1, 2, and 3, respectively. The data show:

- ATV pharmacokinetics are similar between the second and third trimesters at a dose of 300/100 mg QD, while ATV exposure is doubled during postpartum.
- Compared to historical data (pooled data from non-pregnant HIV-infected subjects receiving ATV/RTV 300/100 mg QD without concomitant tenofovir in Studies AI424089 and AI424137), ATV AUC(TAU), Cmax and Cmin are 26%, 40%, and 115% higher in women during postpartum, respectively.
- ATV/RTV 300/100 mg QD dosing provided 17%-27% lower Cmax and about 20% lower AUC(TAU) but similar Cmin values throughout pregnancy as compared to historical data in non-pregnant HIV-infected subjects.

- ATV/RTV 400/100 mg QD provided similar Cmax and AUC(TAU) in the 3rd trimester as compared with ATV/RTV 300/100 mg QD historical data in non-pregnant HIV-infected subjects, but provided a higher Cmin value.
- ATV/RTV 300/100 mg QD dosing provided about 40% lower AUC, Cmax and Cmin in second and third trimesters as compared to postpartum.
- ATV/RTV 400/100 mg QD dosing provided about 33%, 26%, and 26% lower AUC, Cmax and Cmin, respectively, in third trimesters as compared to ATV/RTV 300/100 mg QD during postpartum.
- ATV AUC, Cmax and Cmin are proximately dose-proportionally increased with the increased dose from ATV/RTV 300/100 mg QD to 400/100 mg QD during the 3rd trimester.
- The ratio of fetal ATV concentration relative to maternal was approximately 19% and 12% when mothers received ATV/RTV 300/100 mg QD and ATV/RTV 400/100 mg QD, respectively (Table 1), indicating ATV does cross the placenta, but not freely.
- Maternal plasma protein binding was similar regardless of gestational age, dosing regimen, or time post-dose. Postpartum maternal plasma protein binding was similar to that observed during pregnancy. Plasma protein binding in cord blood was lower than in maternal blood with unbound fraction approximately twice that of maternal (Table 2).

Table 1: Summary Statistics for ATV PK Parameters by Group

Group	CMAX (NG/ML) GEO.MEAN (CV)	TMAX (H) MEDIAN (MIN-MAX)	CMIN (NG/ML) GEO.MEAN (CV)	AUC(TAU) (NG.H/ML) GEO.MEAN (CV)	T-HALF (HR) MEAN (SD)	MATERNAL CONC (NG/ML) GEO.MEAN (CV)	CORD BLOOD CONC (NG/ML) GEO.MEAN (CV)	FETAL RATIO (%) GEO.MEAN (CV)
A	3729.09	4.00	663.78	34399.13	10.63			
(N=9)	(39)	(2.0 - 6.0)	(36)	(37)	(2.38)			
B	3291.46	3.00	668.48	34251.50	15.99			
(N=20)	(48)	(1.5 - 8.0)	(50)	(43)	(22.25)			
C						1201	224 [a]	0.19 [a]
(N=19)						(63)	(67)	(41)
D	5649.10	3.00	1420.64	60532.75	17.08			
(N=36)	(31)	(0.5 - 6.0)	(47)	(33)	(7.00			
E	4210.76	4.00	916.63	46602.45	12.96			
(N=20)	(38)	(0.5 - 6.0)	(60)	(43)	(5.07)			
F						1224.20	183.52 [b]	0.12 [b]
(N=17)						(54)	(68)	(49)
H	4485.18		661.50	43388.06				
(N=23)	(32)		(67)	(42)				

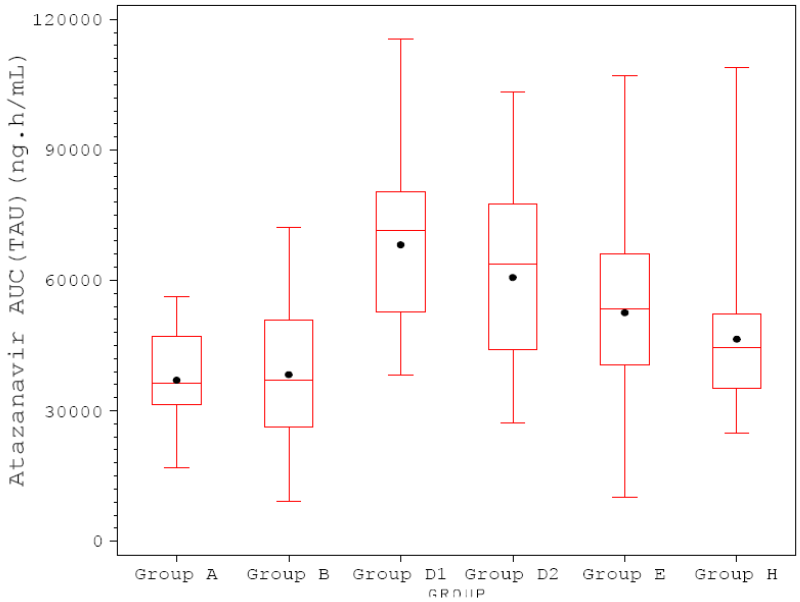
Source: Table 9.1A from the sponsor's study-ai424182-csr-final.pdf

Note: Includes 8 additional subjects dosed at ATV/RTV 300/100 mg after the interim analysis datalock

Group: A - ATV/RTV 300/100 mg 2nd trimester B - ATV/RTV 300/100 mg 3rd trimester
C - ATV/RTV 300/100 mg peripartum D - ATV/RTV 300/100 mg postpartum
E - ATV/RTV 400/100 mg 3rd trimester F - ATV/RTV 400/100 mg peripartum
H - ATV/RTV 300/100 mg historical data from Studies AI424089 and AI424137

[a] N=14
[b] N=15

Figure 1: Boxplot of Atazanavir AUC(TAU) versus Group

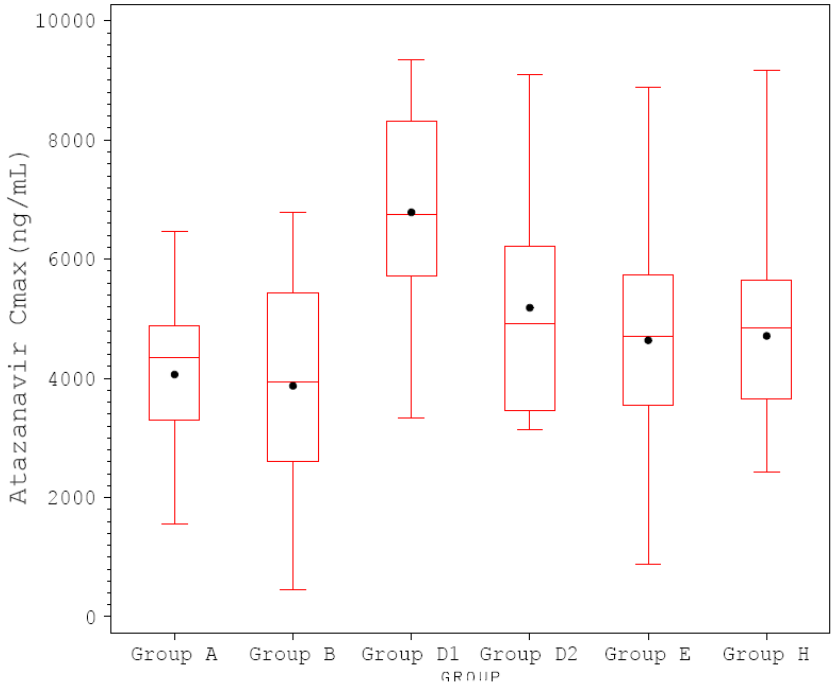


Source: Figure 9.1C from the sponsor's study-ai424182-csr-final.pdf

Note: Includes 8 additional subjects dosed at ATV/RTV 300/100 mg after the interim analysis datalock

Group A: ATV/RTV 300/100 mg 2nd Trimester
Group B: ATV/RTV 300/100 mg 3rd Trimester
Group E: ATV/RTV 400/100 mg 3rd Trimester
Group D1: ATV/RTV 300/100 mg Postpartum for Subjects on ATV/RTV 300/100 mg in 3rd Trimester
Group D2: ATV/RTV 300/100 mg Postpartum for Subjects on ATV/RTV 400/100 mg in 3rd Trimester
Group H: ATV/RTV 300/100 mg pooled HIV+ subjects from Historical Studies AI424137 and AI424089

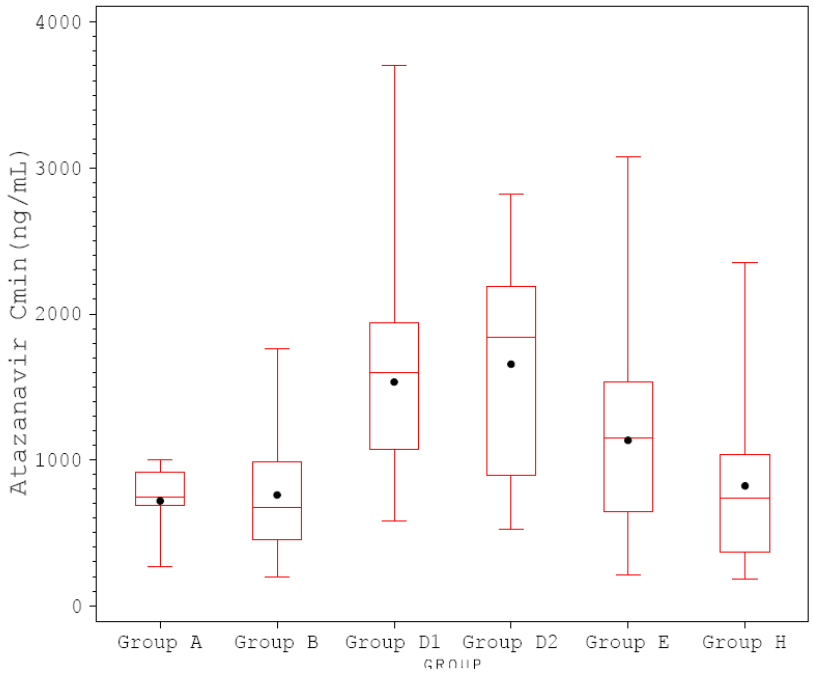
Figure 2: Boxplot of Atazanavir Cmax versus Group



Source: Figure 9.1B from the sponsor's study-ai424182-csr-final.pdf

Note: Includes 8 additional subjects dosed at ATV/RTV 300/100 mg after the interim analysis datalock

Figure 3: **Boxplot of Atazanavir Cmin versus Group**



Source: Figure 9.1D from the sponsor's study-ai424182-csr-final.pdf

Note: Includes 8 additional subjects dosed at ATV/RTV 300/100 mg after the interim analysis datalock

Group A: ATV/RTV 300/100 mg 2nd Trimester
Group B: ATV/RTV 300/100 mg 3rd Trimester
Group E: ATV/RTV 400/100 mg 3rd Trimester
Group D1: ATV/RTV 300/100 mg Postpartum for Subjects on ATV/RTV 300/100 mg in 3rd Trimester
Group D2: ATV/RTV 300/100 mg Postpartum for Subjects on ATV/RTV 400/100 mg in 3rd Trimester
Group H: ATV/RTV 300/100 mg pooled HIV+ subjects from Historical Studies AI424137 and AI424089

Table 2: Summary Statistics for ATV PK Parameters by Group (Protein Binding)

Group	PBOUND (%) MEAN (SD) AT 3 HR	PBOUND (%) MEAN (SD) AT 24 HR	PFREE (%) MEAN (SD) AT 3 HR	PFREE (%) MEAN (SD) AT 24 HR	PBOUND (%) MEAN (SD) IN CORD BLOOD	PFREE (%) MEAN (SD) IN CORD BLOOD
A (N=9)	87.91	89.06	12.09	10.94		
	(1.74)	(1.98)	(1.74)	(1.98)		
B (N=20)	91.34	90.37 [a]	8.67	9.63 [a]		
	(2.32)	(2.58)	(2.32)	(2.58)		
D (N=35)	87.03 [b]	91.02	10.03 [b]	8.98		
	(15.81)	(3.22)	(4.06)	(3.22)		
E (N=20)	87.70	88.89	12.31	11.11		
	(2.69)	(2.40)	(2.69)	(2.40)		
C (N=15)					77.05	22.95
					(6.88)	(6.88)
F (N=12)					75.62	24.38
					(4.34)	(4.34)

Source: Table 9.1B from the sponsor's study-ai424182-csr-final.pdf

Note: Includes 8 additional subjects dosed at ATV/RTV 300/100 mg after the interim analysis datalock

Group: A - ATV/RTV 300/100 mg 2nd trimester B - ATV/RTV 300/100 mg 3rd trimester
C - ATV/RTV 300/100 mg peripartum D - ATV/RTV 300/100 mg postpartum
E - ATV/RTV 400/100 mg 3rd trimester F - ATV/RTV 400/100 mg peripartum

[a] N=19

[b] N=34

ATV PK Reanalysis by excluding Run 20, 15, 16 and 26: On January 19, 2011, Division of Scientific Investigation (DSI) completed their review and indicated:

- The accuracy of protein binding data for samples analyzed in Runs 15, 16, and 26 used to quantify BMS-232632 in plasma:PBS (50:50) is not assured. Data from these samples should be excluded.
- Plasma samples analyzed in Run 20 (subject sample #s 12-44, 12-54, 12-55, 4-32, 4-43, 4-56, 5-40, 5-41, 5-50, 5-51, and 5-52) used to quantify BMS-232632 in plasma are not assured.

Therefore, the applicant was requested to exclude the affected samples from the PK and protein binding analyses and provide the reanalysis results. The reanalysis only affects ATV results. The reanalysis results indicate that only ATV PK results in the second trimester were significantly affected by the exclusion of Run 20. Protein binding results were unchanged with the excluded data from Run 15, 16 and 26. Table 1 shows the PK comparison of the full data and the reanalysis results with exclusion of Run 20. Table 2 shows the plasma protein binding comparison of the full data and the reanalysis results with exclusion of Runs 15, 16 and 26.

Table 3: Comparison of Steady-State Pharmacokinetics of ATV in HIV-Infected Pregnant Women with non-pregnant HIV-1 infected patients (Including and Excluding Run 20)

PK Parameter	ATV/RTV 300/100 mg QD					ATV/RTV 400/100 mg QD		Reference (from label)	
	2nd Trimester		3rd Trimester	Postpartum		3rd Trimester		non-pregnant HIV-1 infected patients	
	Original (N=9)	Excluding Run 20 (N=5)	N=20 (no sample was in Run 20)	Original (N=36)	Excluding Run 20 (N=34)	Original (N=20)	Excluding Run 20 (N=17)	ATV/RTV 300/100 mg (N=10)	ATV 400 mg (N=13)
Cmax (ng/mL) Geo.Mean (%CV)	3729.09 (39)	3078.85 (50)	3291.46 (48)	5649.10 (31)	5721.21 (31)	4210.8 (38)	4098.6 (42)	4422 (58)	2298 (71)
AUC (ng.h/mL) Geo.Mean (%CV)	34399.1 (37)	27657.1 (43)	34251.5 (43)	60532.7 (33)	61990.4 (32)	46602.4 (43)	44780.1 (47)	46073 (66)	14874 (91)
Cmin (ng/mL) Geo.Mean (%CV)	663.78 (36)	538.70 (46)	668.48 (50)	1420.64 (47)	1462.59 (45)	916.63 (60)	890.3 (65)	636 (97)	120 (109)

Table 4: Plasma Protein Binding for Atazanavir by Group (Including and Excluding Runs 15, 16, and 26)

Treatment	Period		Percent Bound Mean (SD) 3h post-dose (maternal)	24h post-dose (maternal)	Cord blood
ATV/RTV 300/100 mg	2nd Trimester	Original (n=9)	87.91 (1.74)	89.06 (1.98)	
		with exclusions (n=6)	88.37 (2.02)	89.58 (2.10)	
	3rd Trimester	Original (n=20)	91.34 (2.32)	90.37 (2.58)	
		with exclusions (n=8)	91.35 (2.79)	89.61 (3.20)	
	Postpartum	Original (n=35)	87.03 (15.81) [n =34]	91.02 (3.22)	
		with exclusions (n=17)	90.71 (3.40) [n = 16]	91.74 (2.83)	
	Peripartum (Cord Blood)	Original (n=15)			77.05 (6.88)
		with exclusions (n=5)			73.22 (2.49)
ATV/RTV 400/100 mg	Peripartum (Cord Blood)	Original (n=12)			75.62 (4.34)
		with exclusions (n=7)			76.24 (4.75)

Ritonavir PK: Summary statistics for all RTV PK parameters are presented in Table 3. The data show:

- RTV geometric mean Cmax, AUC(TAU) and Cmin were 62%, 54%, and 19% lower, respectively, in the 3rd trimester compared to historical data.
- RTV exposures were similar on ATV/RTV 400/100 mg QD regimen and ATV/RTV 300/100 mg QD regimen.
- RTV geometric mean Cmax and AUC(TAU) were 66% and 55% lower in the 2nd trimester compared to historical data. The Cmin in the 2nd trimester was similar to historical data.
- RTV exposures were similar between the 2nd and the 3rd trimester.
- Low ATV exposure during pregnancy could partially due to low RTV exposures.
- The RTV geometric mean Cmax was 19% lower postpartum compared to the geometric mean Cmax in the historical data. AUC(TAU) postpartum was similar to AUC(TAU) historical data. The geometric mean Cmin was 96% higher postpartum compared to historical data.
- The RTV point estimates of Cmax, AUC(TAU), and Cmin were 52% - 66% lower in the 3rd trimester relative to postpartum data.

Table 5: Summary Statistics for RTV PK Parameters by Group

Group	CMAX (NG/ML) GEO.MEAN (CV)	TMAX (H) MEDIAN (MIN-MAX)	CMIN (NG/ML) GEO.MEAN (CV)	AUC(TAU) (NG.H/ML) GEO.MEAN (CV)	T-HALF (HR) MEAN (SD)	MATERNAL CONC (NG/ML) GEO.MEAN (CV)	CORD BLOOD CONC (NG/ML) GEO.MEAN (CV)	FETAL RATIO (%) MEAN (SD)
A	530.81	6.00	50.10	4500.03	5.08[a]			
(N=9)	(62)	(1.5 - 24.0)	(110)	(43)	(0.81)			
B	587.36	4.00	41.12	4664.93	5.44[b]			
(N=20)	(61)	(1.5 - 24.0)	(92)	(51)	(1.46)			
C						134	16[c]	0.08[c]
(N=19)						(96)	(36)	(108)
D	1253.40	4.00	99.60	10461.21	6.28[d]			
(N=36)	(58)	(0.5 - 12.0)	(66)	(50)	(2.46)			
E	524.48	6.00	38.05[e]	4383.30	5.51[e]			
(N=20)	(74)	(0.5 - 12.0)	(75)	(79)	(2.65)			
F						161	12[f]	0.04[f]
(N=16)						(96)	(65)	(39)
H	1554.84		50.91	10124.09				
(N=23)	(37)		(69)	(42)				

Source: Table 9.2A from the sponsor's study -ai424182-csr-final.pdf

Note: Includes 8 additional subjects dosed at ATV/RTV 300/100 mg after the interim analysis datalock

Group: A - ATV/RTV 300/100 mg 2nd trimester B - ATV/RTV 300/100 mg 3rd trimester
C - ATV/RTV 300/100 mg peripartum D - ATV/RTV 300/100 mg postpartum
E - ATV/RTV 400/100 mg 3rd trimester F - ATV/RTV 400/100 mg peripartum
H - ATV/RTV 300/100 mg historical data from Studies AI424089 and AI424137, see Section 3.6.3.5 for description of pooled analysis

[a] N=8

[b] N=19

[c] N=9

[d] N=33

[e] N=19

[f] N=9

PK/PD Results: As shown in Figures 5 and 6, there was a lack of relationship between infant total bilirubin on delivery day vs ATV cord blood concentrations or maternal peripartum concentrations.

Figure 5: **Scatter Plot of Individual ATV Cord Blood Concentration vs Infant Total Bilirubin on Delivery Day**

Source: Figure 9.3A from the sponsor's study-ai424182-csr-final.pdf

Figure 6: **Scatter Plot of Individual ATV Maternal Concentration vs Infant Total Bilirubin on Delivery Day**

Source: Figure 9.3B from the sponsor's study-ai424182-csr-final.pdf

For mothers, ATV/RTV 400/100 mg QD was associated with twice as much Grade 3 to Grade 4 hyperbilirubinemia as ATV/RTV 300/100 mg QD (62% vs 30%).

MACS Adherence: Adherence remained stable over time for the regimens and individual drug components of the regimens. Using the non-completers as failures (NC = F) analysis, the proportion of mothers who were adherent to the regimens ranged from 67% to 100% through Week 4 postpartum (data from Visit 2 in 2nd trimester was excluded). The proportion of mothers who were adherent to ATV and RTV ranged from 83% to 100% through Week 4 postpartum (data from Visit 2 in 2nd trimester was excluded). At Visit 2, adherence to the entire regimen was as low as 38% and only 8 subjects were evaluated for MACS adherence. Of these 8 subjects, all reported adherence to ATV, 7 reported adherence to RTV, but only 4 reported adherence to ZDV/3TC. These data resulted in only 3 of 8 subjects adhering to the full regimen.
Given the high responses rates for ZDV/3TC (95% to 100%) at other visits, this is likely an anomaly due to low number of respondents and inaccurate reporting.

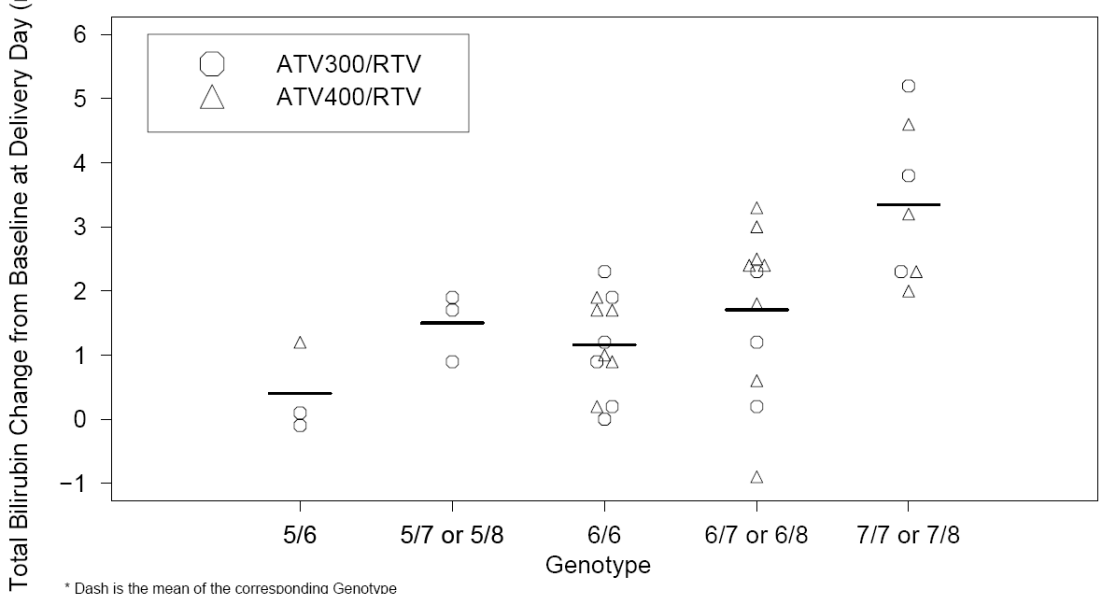
Pharmacogenomic Results: Mean total bilirubin levels were analyzed by UGT1A1 genotype and race for treated mothers and live-born infants, with small sample sizes in some categories. Table 6 and Figure 7 show that magnitude of total bilirubin increase differed for different genotype functionalities in mothers at delivery. It indicates that the mothers with decreased UGT1A1 functionality experienced greater increases in bilirubin level at delivery as compared to baseline. The results are consistent with the results previously observed in non-pregnant subjects, which showed that the magnitude of unconjugated bilirubin increase by atazanavir is higher in

subjects with UGT1A1 genotype 6/7 (moderately decreased functionality) as compared to genotype 6/6 (normal functionality).

Table 6: Total Bilirubin Change from Baseline at Delivery by Genotype Function for Treated Mothers

	Mean (SE) Total Bilirubin Change from Baseline (mg/dL)	
	Treatment Regimen in 3rd Trimester	
Genotype Function (Genotype)	ATV/RTV 300/100 mg	ATV/RTV 400/100 mg
Increased Functionality (5/6)	0.0 (0.10)	1.20 (0.00)
	(N=2)	(N = 1)
Unknown (5/7 or 5/8)	1.50 (0.31)	N/A
	(N =3)	(N=0)
Normal (6/6)	1.1 (0.37)	1.23 (0.27)
	(N =6)	(N =6)
Moderate Decreased (6/7 or 6/8)	1.23 (0.61)	1.89 (0.49)
	(N =3)	(N =8)
Major Decrease (7/7 or 7/8)	3.77 (0.84)	3.03 (0.58)
	(N =3)	(N =4)

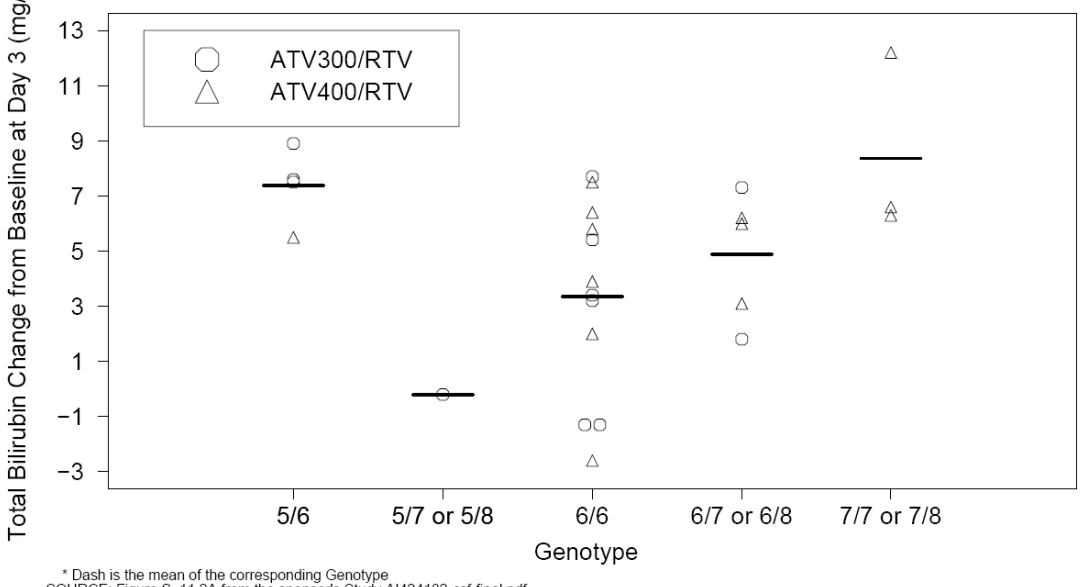
Figure 7:
Total Bilirubin Change at Delivery Day by Genotype Function − Treated Mothers



* Dash is the mean of the corresponding Genotype
Source: Figure S.11.1A from the sponsor's Study AI424182-csf-final.pdf

For live-born infants, although the overall genotype-by-visit effect was not significant, there were observed differences in increased total bilirubin changes at Day 3 compared to delivery day among different genotype functionalities. Other than Genotype 5/6 (increased functionality), live-born infants with decreased UGT1A1 functionality generally experienced greater increases in bilirubin level at Day 3 compared to at delivery. Repeated measures analysis of total bilirubin for live-born infants showed there was a significant visit effect on total bilirubin levels ($p < 0.0001$). It increased in the first several days and started to decrease in the subsequent weeks.

Figure 8:
Total Bilirubin Change at Day 3 by Genotype Function − Live−born Infants



* Dash is the mean of the corresponding Genotype
SOURCE: Figure S. 11.2A from the sponsor's Study AI424182-csf-final.pdf

The mean total bilirubin levels were similar in both races (black and other (including white and other)) categories, for both treated mothers and live-born infants.

The results of genotype effect on hyperbilirubinemia severity are consistent with the genotype effect on bilirubin levels for both mother and infants.

Discussion: Pregnancy is known to result in significant physiologic changes and the PK of many drugs are altered during pregnancy, usually most dramatically in the 3rd trimester. Reduced plasma concentrations during pregnancy have been reported for nelfinavir (750 mg three times daily), indinavir and lopinavir (with ritonavir). However, plasma concentrations equivalent to those in non-pregnant adults have been reported in pregnant women receiving nelfinavir at doses of 1250 mg twice daily. Increased lopinavir (with ritonavir) plasma concentrations in postpartum women 2 weeks after delivery have been reported as compared to non-pregnant adults.

Atazanavir Results Compared to the Preganancy Study Conducted by D. Ripamonti (Italy), et. al (2007)[1].

D. Ripamonti, et. al. conducted a pharmacokinetics and placental transfer study of atazanavir plus low-dose ritonavir (300 mg/100 mg QD) in pregnant HIV-infected women (n = 17). The postpartum evaluation was performed at 71± 45 days as compared to 5.8 ± 2.1 weeks (range: 3-10 weeks) in Study AI424182. Table 7 shows that there were no significant differences between the exposures during third trimester and postpartum. D. Ripamonti's study shows in the third trimester, ATV AUC, Cmax and Cmin are about 17%, 22%, and 27% lower as compared to Study AI424182; while during postpartum, AUC and Cmax in D. Ripamonti's study are about half of the values observed in Study AI424182, and Cmin is about 64% lower. Compared to historical data, D. Ripamonti's study provided 30%, 36%, and 23% lower ATV AUC, Cmax and Cmin during postpartum as compared to historical data in non-pregnant HIV-infected subjects. The investigators updated their PK data including 31 pregnant women in 2010 (abstract), and the data were similar to the previous report from 17 subjects. The postpartum data were generally

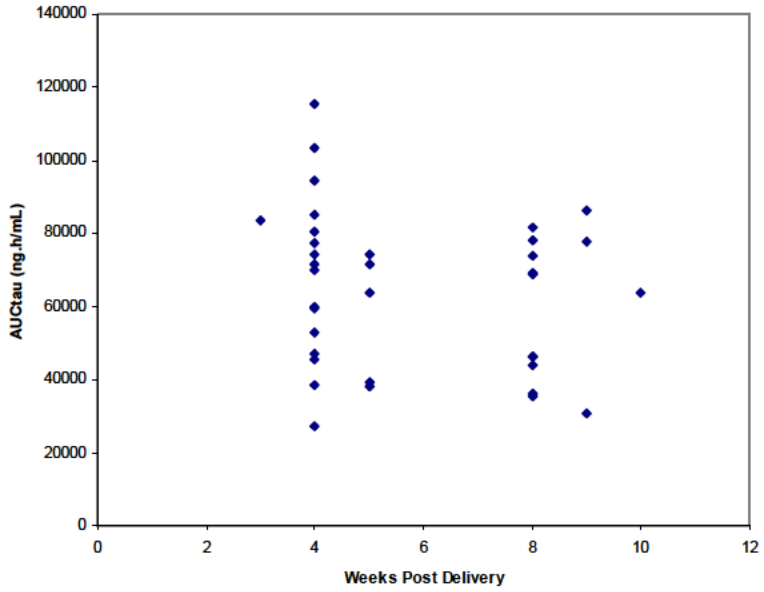
collected at later dates postpartum than in the current study, which may contribute to the differences in postpartum PK data. The analysis in Study AI424182 indicated that there is no apparent correlation between postpartum exposure and the time after delivery (Figure 9). However, most of these data were collected between 4-8 weeks. It is not clear when atazanavir PK returns to non-pregnancy level after delivery and how much inter-study variability contributes to the difference between these two studies.

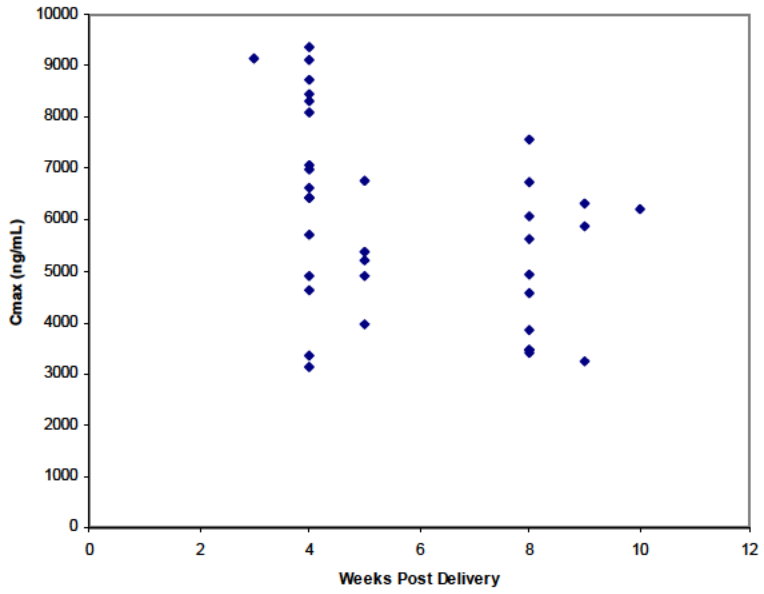
Table 7: Ante and Postpartum Atazanavir Pharmacokinetic Parameters by D. Ripamonti, et. al.

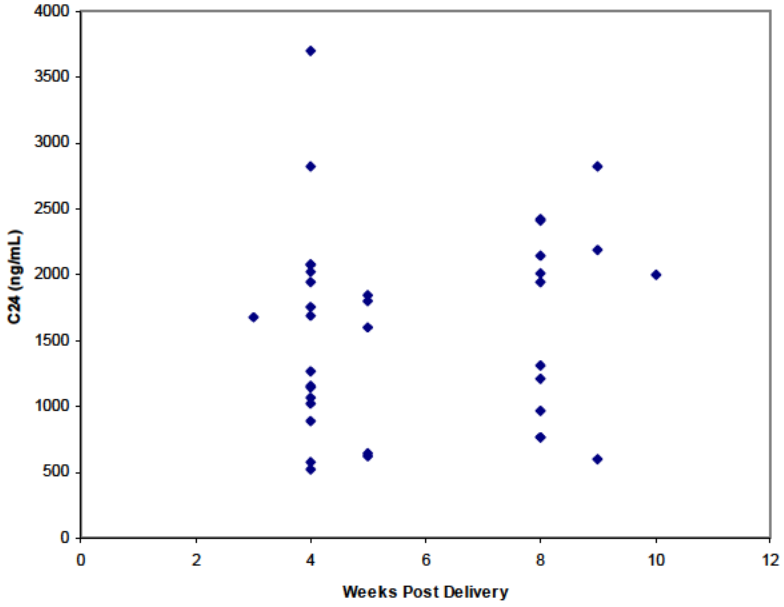
Parameters	Third trimester	Postpartum
Mean[a] AUC_{0-24}, ng h/l (95% CI)	28510 (23765–34200)	30465 (24440–37960)
Mean[a] C_{max}, ng/ml (95% CI)	2591 (2080–3224)	2878 (2164–3810)
Mean[a] C_{trough}, ng/ml (95% CI)	486 (396–597)	514 (377–699)
Mean $T_{1/2}$, h (SD)	10.0 (2.4)	10.6 (2.4)
Mean T_{max}, h (SD)	3.2 (1.6)	2.8 (0.8)

AUC_{0-24}, Area under the plasma concentration-time curve from 0 to 24 h; CI, confidence interval; C_{max}, maximum observed plasma concentration; C_{trough}, 24-h postdose concentration; $T_{1/2}$, elimination half life; T_{max}, maximum plasma concentration.
[a]Mean is the geometric least-squares mean.
Source: Table 1 in D. Ripamonti, et. al (AIDS, 2007):Atazanavir plus Low-Dose Ritonavir in Pregnancy: Pharmacokinetics and Placental Transfer.

Figure 9: Postpartum Exposure vs Time after Delivery in Study AI424182







The ratio of cord blood concentrations versus maternal peripartum concentrations was also assessed in the study by Ripamonti et. al. The mean ratio was 0.13, consistent with the results in the current study.

Atazanavir Results Compared to PACTG 1026s Study[2]

Atazanavir pharmacokinetics with and without tenofovir were evaluated during pregnancy in PACTG study 1026s. The postpartum data were collected between 6 to 12 weeks after delivery (no detailed information regarding the mean time). ATV exposure was reduced during the third trimester both with and without concomitant TDF use as compared to the values obtained postpartum.

The ATV PK data in the presence of RTV (without TDF) are comparable to the results obtained from Study AI424182.

The effects of TDF on ATV exposures during pregnancy and postpartum are similar to the observed magnitudes in non-pregnant healthy volunteers (~25% lower AUC and Cmin).

Figure 5: PK data from PACTG 1026s

	ATV, no TDF		ATV + TDF	
	3rd trimester (n=14)	PP (n=9)	3rd trimester (n=13)	PP (n=12)
AUC (mcg*hr/mL)	37.5 (21.3-75.8)*	57.9 (37.5-90.3)	32.7 (8.9-64.0)	41.9 (8.4-80.7)
Met AUC target/Total	9/14	9/9	8/13	8/12
C24h (mcg/mL)	0.72 (0.36-1.54)*	1.20 (0.73-2.98)	0.59 (0.14-1.58)*	0.95 (0.16-2.09)
Met C24 target/Total	14/14	9/9	12/13	12/12

ATV/RTV Dose Regimen

It seems to be reasonable to use the historical data as a reference rather than the post-partum results as originally intended, with the caveat that possible between-study variability may impact the comparison. The postpartum data are quite different between D. Ripamonti's study and Study AI424182 as well as PACTG study, but the 3rd trimester data are relatively similar across all three studies. The Cmin values obtained during pregnancy from the Current and PACTG studies are similar as compared to the historical data in non-pregnant adults. However, D. Ripamonti's study shows in the third trimester, ATV Cmin was about 27% lower as compared to Study AI424182. This magnitude of ATV Cmin reduction in the third trimester is similar to the effect of tenofovir on ATV; while coadministration of tenofovir with ATV did not decrease the efficacy of ATV when HIV-infected patients received ATV/RTV 300/100 mg QD. The effects of TDF on ATV exposures during pregnancy and postpartum in the PACTG study are similar to the observed magnitudes in non-pregnant healthy volunteers. The Cmin in the third trimester is comparable to the historical non-pregnant patients. The Cmin in the second trimester was originally comparable to the historical non-pregnant patients using the full data, but is 15% lower after exclusion of Run 20 as compared to the historical non-pregnant patients. This magnitude of decrease should be acceptable for pregnant women with HIV-1 strains susceptible to atazanavir because the Cmin from all the three studies (including the 2nd and the 3rd trimesters) were all above the Cmin obtained historically for patients receiving ATV 400 mg QD. However, exposure could be too low for pregnant women carried atazanavir resistant HIV-1 strains. Therefore, **atazanavir should only be administered to pregnant women with HIV-1 strains susceptible to atazanavir.** Increased ATV/RTV dose is not appropriate because there are no safety data for women during the 2nd trimester with ATV/RTV doses greater than 300/100 mg. In addition, ATV/RTV 400/100 mg dosing was associated with twice as much hyperbilirubinemia (total bilirubin greater than or equal to 2.6 times the upper limit of normal) as ATV/RTV 300/100 mg in the current study (62% vs 30%). Therefore, **ATV/RTV 300/100 mg QD is recommended for treatment-naïve and treatment-experienced patients during pregnancy.**

However, for treatment-experienced patients also receiving tenofovir or H_2-receptor antagonists (which reduce ATV exposures by a similar magnitude as tenofovir), ATV/RTV dose increase to 400/100 mg QD is recommended during the third trimester to cover the possible additive decrease of exposure by tenofovir or H_2-receptor antagonists and pregnancy (predicted to be 18% to 37% lower in Cmin than the value obtained for non-pregnant patients at ATV/RTV doses of 300/100 mg QD). Increase ATV/RTV dose to 400/100 mg is expected to bring Cmin similar to 18% lower as compared to non-pregnant patients at ATV/RTV doses of 300/100 mg QD, but will keep Cmax still lower than the value obtained for non-pregnant patients at ATV/RTV doses of 300/100 mg QD. **ATV/RTV should not be used with tenofovir *and* H_2-receptor antagonists in treatment-experienced pregnant women,** because the predicted Cmin is expected to be 41% to 52% lower as compared to non-pregnant patients at ATV/RTV doses of 300/100 mg QD.

Conclusion:

- For treatment-naïve patients during pregnancy, ATV/RTV 300/100 mg QD is recommended; ATV without RTV should not be recommended.
- Atazanavir should only be administered to pregnant women with HIV-1 strains susceptible to atazanavir.
- For treatment-experienced patients without H_2-receptor antagonist or concomitant tenofovir: ATV/RTV 300/100 mg QD is recommended.
- For treatment-experienced patients taking H_2-receptor antagonist or tenofovir: increasing the dose to ATV/RTV 400/100 mg QD is recommended during the second or third trimester.
- The pre-pregnancy dosing regimens should be reassumed after delivery. However, adverse events should be closely monitored postpartum because ATV exposures could be higher during the first 2 months after delivery.

---

[1] Ripamonti D, Cattaneo D, Maggiolo F, et al. Atazanavir plus low-dose ritonavir in pregnancy: pharmacokinetics and placental transfer. AIDS 2007, 21:2409–2415.

[2] Mirochnick M, Stek A, Capparelli E, et. al. and the PACTG 1026s Protocol Team. Atazanavir pharmacokinetics with and without tenofovir during pregnancy [abstract 941]. 16th Conferendce on Retrovirus and Opportunistic Infections; 2009 February 8-11; Montreal, Canada.

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/s/

HUIMIN H ZHENG
01/31/2011

SARAH M ROBERTSON
02/01/2011

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

Office of Clinical Pharmacology

New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA/BLA Number	**21567**	**Brand Name**	**Reyataz**
OCP Division (I, II, III, IV, V)	**IV**	**Generic Name**	**Atazanavir**
Medical Division	**DAVP**	**Drug Class**	**Protease Inhibitor**
OCP Reviewer	**Jenny H Zheng**	**Indication(s)**	**HIV** (b) (4)
OCP Team Leader	**Sarah Robertson**	**Dosage Form**	**Capsules**
Pharmacometrics Reviewer/TL	**N/A**	**Dosing Regimen**	(b) (4)
Date of Submission	**8/6/2010**	**Route of Administration**	**Oral**
Estimated Due Date of OCP Review	**1/16/2011**	**Sponsor**	**Bristol-Myers Squibb Company**
Medical Division Due Date	**2/06/2011**	**Priority Classification**	**Priority**
PDUFA Due Date	**2/06/2011**		

Clin. Pharm. and Biopharm. Information

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	**X**			
Tabular Listing of All Human Studies	**X**			
HPK Summary	**X**			
Labeling	**X**			
Reference Bioanalytical and Analytical Methods	**X**	**1**	**1**	
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:				
multiple dose:				
Patients-				
single dose:				
multiple dose:				
Dose proportionality -				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:				

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geriatrics:				
renal impairment:				
hepatic impairment:				
Pregnancy	**X**	**1**	**1**	**AI-424182**
PD -				
Phase 2:				
Phase 3:				
PK/PD -				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
Population Analyses -				
Data rich:				
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies				
Bio-waiver request based on BCS				
BCS class				
Dissolution study to evaluate alcohol induced dose-dumping				
Comparability				
III. Other CPB Studies				
Immunogenicity				
Genotype/phenotype studies				
Chronopharmacokinetics				
Pediatric development plan				
Literature References				
Total Number of Studies		**2**	**2**	

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

	Content Parameter	Yes	No	N/A	Comment
Criteria for Refusal to File (RTF)					
1	Has the applicant submitted bioequivalence/comparability data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?			x	
2	Has the applicant provided metabolism and drug-drug interaction information?			x	
3	Has the sponsor submitted bioavailability data satisfying the CFR requirements?			x	
4	Did the sponsor submit data to allow the evaluation of the validity of the analytical assay?	x			
5	Has a rationale for dose selection been submitted?	x			
6	Is the clinical pharmacology and biopharmaceutics section of the NDA organized, indexed and paginated in a manner to allow substantive review to begin?	x			
7	Is the clinical pharmacology and biopharmaceutics section of the NDA legible so that a substantive review can begin?	x			

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

8	Is the electronic submission searchable, does it have appropriate hyperlinks and do the hyperlinks work?	X			
Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality)					
	Data				
9	Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)?	X			
10	If applicable, are the pharmacogenomic data sets submitted in the appropriate format?			X	
	Studies and Analyses				
11	Is the appropriate pharmacokinetic information submitted?	X			
12	Has the applicant made an appropriate attempt to determine reasonable dose individualization strategies for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)?	X			
13	Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance?			x	
14	Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics?			x	
15	Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?			x	
16	Did the applicant submit all the pediatric exclusivity data, as described in the WR?			X	
17	Is there adequate information on the pharmacokinetics and exposure-response in the clinical pharmacology section of the label?			X	
	General				
18	Are the clinical pharmacology and biopharmaceutics studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?	X			
19	Was the translation (of study reports or other study information) from another language needed and provided in this submission?			X	

IS THE CLINICAL PHARMACOLOGY SECTION OF THE APPLICATION FILEABLE?
_Yes_____

If the NDA/BLA is not fileable from the clinical pharmacology 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.

The submitted .csv, .ctl, and .lst files used and generated from the population PK and exposure-response analyses in Module 5.3.3.5 were submitted in PDF format with a .txt extension. Please resubmit these files in ASCII format.

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

Reviewing Clinical Pharmacologist	Date
Team Leader/Supervisor	Date

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/s/

HUIMIN H ZHENG
09/27/2010

SARAH M ROBERTSON
09/27/2010

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-567/S025

OTHER REVIEW(S)

Filing Meeting Agenda
NDA 21-567 Reyataz ® atazanavir sulfate

1. Team Introductions

2. Introduction of application, including important dates

Summary Description of Product:

NDA 21-567/S-025- Reyataz/Atazanavir is a protease inhibitor for the treatment of HIV infection. This protocol was submitted to provide data from study AI424182, a study of atazanavir and ritonavir in HIV infected pregnant women with corresponding labeling revisions. The protocol is to expand the population; however there are no new dosing regiments. The application was submitted on August 6, 2010 and is a priority review. The filing date is October 5, 2010 and the PDUFA goal date is February 6, 2011. The midcycle meeting is November 8, 2010 and the wrap up meeting is January 10, 2011.

Stamp Date: 8.6.10

Filing Date: 10.5.10

Day 74 Letter Date: 10.5.10

Review Completion Goal Date according to GRMP: 2.4.11

PDUFA Goal Date: 2.6.11

3. Overview of Application by Discipline: Studies/info submitted; identification of Info Requests; Day 74 letter items
   a. CMC – Brian Rogers/1 minute
   b. P/T – KM Wu/1 minute
   c. Clin Pharm/Biopharm – Jenny Zheng/5 minutes
   d. Clinical – Alan Shapiro/10 minutes
   e. Clinical Micro – Lisa Naeger/1 minute
   f. Stats – Thomas Hammerstrom/1 minute
   g. Labeling – Lori Cantin/1 minute

4. Identification of RTF Issues by Discipline
   a. CMC – Brian Rogers/1 minute
   b. P/T – KM Wu/1 minute
   c. Clin Pharm/Biopharm – Jenny Zheng/5 minutes
   d. Clinical – Alan Shapiro/10 minutes
   e. Clinical Micro – Lisa Naeger/1 minutes
   f. Stats – Thomas Hammerstrom/1 minute

g. Labeling – Lori Cantin/1 minute

5. Reach agreement on filing decision

Mid-Cycle Meeting Description and Agenda Template

Mid-Cycle Meeting Agenda Template

1. Important Goal Dates

   Review Completion Goal Date according to GRMP: February 4, 2011

   Primary reviews due: **January 13, 2011**

   Secondary Reviews due: **January 16, 2011**

   CDTL review due: **January 23, 2011**

   DD review due: **February 4, 2011**

   PDUFA Goal Date: **February 6, 2011 Action Date: February 4, 2011**

2. Discipline Specific Reviews of Application (handouts provided)

   Clin Pharm/Biopharm – Jenny Zheng, 30 minutes

   Clinical – Alan Shapiro, 30 minutes

3. Pending Consults
   - MHT - due date: 12.13.10, Leyla Sahin -5 minutes
   - DSI Inspection- Martin Yau-5 minutes

4. Issues Requiring Resolution -

5. Labeling Issues -

6. PMC and Risk Management Plan Issues -

7. Scheduled Meetings

Team Meetings: **December 8, 2010 10 am**

Wrap-Up: **January 10, 2011, 3-4:30 pm**

Labeling: **December 15, 2010, 3 pm**

January 5, 2011, 3 pm

January 19, 2011, 9 am

NDA 21-567, Reyataz Wrap-Up Meeting Agenda

1. Important Goal Dates

   PDUFA Goal Date: February 4, 2011

2. Discipline Specific Reviews of Application
   - Conclusions of the studies/information submitted
   - Expected review completion date – review finalized with full sign off
   - Outstanding issues
     a. P/T – KM Wu-1 minute
     b. Clin Pharm/Biopharm – Jenny Zheng
     c. Clinical – Alan Shapiro
3. Pending Consults
   - DSI Inspection- Due 1.20.11, Martin Yau, Sripal Mada
   - DRISK/DMEPA-Due 1.13.11
4. Discussion of Proposed Action To Be Taken – Jenny Zheng

   Labeling Discussion-Sent to sponsor 1.11.11
5. Discussion of sign-off procedure and schedule

   Internal briefing for DD-TBD

   CDTL review- 1.24.11

   Action letter and package-1.24.11

   DD signoff and review -2.1.11

REGULATORY PROJECT MANAGER LABELING REVIEW (PHYSICIAN LABELING RULE)

Division of Antiviral Products

Application Number: NDA 21-567/S-025

Name of Drug: Reyataz ® (atazanavir sulfate, ATV, BMS-232632) capsules 100 mg, 150 mg, 200 mg, 300 mg

Applicant: Bristol Myers Squibb

Material Reviewed:

Submission Date: August 6, 2010

Receipt Date: August 6, 2010

Type of Labeling Reviewed: WORD

Background and Summary

Bristol Myers Squibb submitted prior approval supplemental new drug applications with updates to the following:

- The DOSAGE AND ADMINISTRATION section was updated with pregnancy recommendations
- The USE IN SPECIFIC POPULATIONS section was updated with pregnancy recommendations
- The PI was updated in "What should I tell my healthcare provider before I take REYATAZ?"

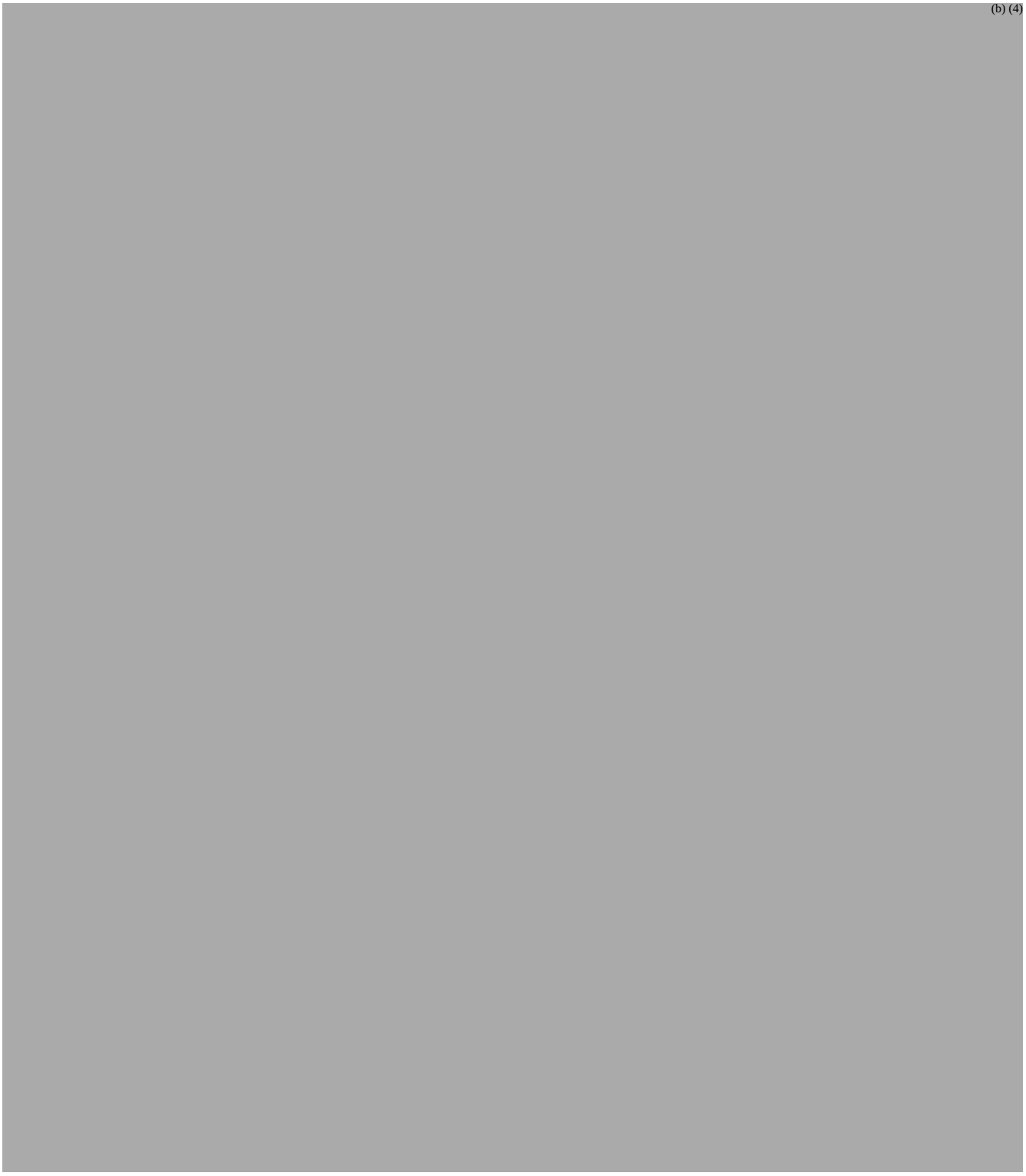
PROPOSED LABELING (Sponsor proposed text in highlighted)

HIGHLIGHTS OF PRESCRIBING INFORMATION

RECENT MAJOR CHANGES

Deleted Indication and Usage 11/2009

(b) (4)



6 Page(s) of Draft Labeling has been Withheld in Full as b4 (CCI/TS) immediately following this page

(b) (4)

[redacted]

Recommendations

The August 6, 2010 version of the label was reviewed by the review team and reflects the following agreements made by FDA and Bristol Myers Squibb. This version was compared to the labeling approved on April 26, 2010 and should be approved.

Venessa M Perry, MPH
REGULATORY PROJECT MANAGER

Supervisory Comment/Concurrence:

Victoria S Tyson
Chief, Project Management Staff

Drafted: VMP
Revised/Initialed:
Finalized:
Filename: CSO Labeling Review Template (updated 1-16-07).doc
CSO LABELING REVIEW OF PLR FORMAT

APPEARS THIS WAY ON ORIGINAL

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/s/

VENESSA M PERRY
02/04/2011

VICTORIA L TYSON
02/04/2011

Department of Health and Human Services

Public Health Service

Food and Drug Administration

Center for Drug Evaluation and Research

Office of Surveillance and Epidemiology

Date:	January 31, 2011
Application Type/Number:	NDA 021567/S-025
To:	Debra Birnkrant, MD, Division Director Division of Anti-Viral Products
Through:	Kellie Taylor, PharmD, MPH, Associate Director Carol Holquist, RPh, Director Division of Medication Error Prevention and Analysis
From:	Kristina A. Toliver, PharmD, Team Leader Division of Medication Error Prevention and Analysis
Subject:	Labeling Review
Drug Name(s):	Reyataz (Atazanavir) Capsules, 100 mg, 150 mg, 200 mg, and 300 mg
Applicant/sponsor:	Bristol-Myers Squibb Company
OSE RCM #:	2010-1833

CONTENTS

1 INTRODUCTION

This review evaluates efficacy supplement S-025 which provides for information on pregnancy to the dosage and administration section and specific populations sections of the package insert labeling. We find the proposed additions to the package insert labeling acceptable.

2. METHODS AND MATERIALS

For this review, DMEPA searched the FDA Adverse Event Reporting System (AERS) database to identify any medication errors with Reyataz. Additionally, we evaluated the proposed insert labeling submitted by the Applicant on December 22, 2010.

2.1. ADVERSE EVENT REPORTING SYSTEM (AERS) SELECTION OF CASES

An AERS search was conducted on January 5, 2011 using the search terms: tradename "Reyataz," active ingredient "Atazanavir" and verbatim terms "Reyat%" and "atazana%." The MedDRA High Level Terms (HLT) 'Maladministration', 'Medication Exposure due to Accidental Overdose' 'Medication Errors NEC', and the Preferred Terms 'Accidental Overdose', 'Multiple Drug Overdose', 'Overdose' and 'Product Quality Issues' were used in the search.

Reports were manually reviewed to determine if a medication error occurred. Reports that did not describe a medication error or did not describe an error applicable to this review were excluded from further analysis [i.e. adverse events with no medication error identified (n=20), errors involving concomitant medications unrelated to Reyataz (n=12), intentional under/overdoses (n=3), overdoses with no causality stated (n=9), overdose associated with a clinical trial protocol (n=2), wrong patient medication error with no causality stated (n=1), overdoses caused by improper transcription (n=2), wrong product strength in sealed bottle from manufacturer (n=2), wrong drug error due to counterfeit medication (n=1),wrong drug error with no causality stated (n=1), wrong strength error with no causality stated (n=1), and not enough information available to describe an error (n=3)]. If an error occurred, the reports were categorized by type of error and evaluated for contributing factors to the medication errors. Duplicate reports were combined into cases.

2.2 LABELS AND LABELING

Using Failure Mode and Effects Analysis (FMEA),[1] the Division of Medication Error Prevention and Analysis (DMEPA) evaluated the insert labeling.

3. RESULTS AND DISCUSSION

The following sections describe our findings from AERS and evaluation of the labeling.

3.1 AERS RESULTS AND DISCUSSION

The AERS search yielded a total of 60 cases. Following exclusion of reports as described in section 2.1, three cases remained relevant.

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

The three medication error cases are described below:

- Improper storage where a patient stored Reyataz in the refrigerator instead of at room temperature (ISR#6906264-7)
- Drug-Drug Interactions (n=2)
    - A patient taking Reyataz took Simvastatin. Concomitant administration of these products is contraindicated (ISR# 6939044-4)
    - A patient taking Reyataz was also prescribed Nevirapine, which is a labeled drug-drug interaction (ISR# 6313777-5)

The package insert labeling clearly states storage conditions in the How Supplied/Storage and Handling sections as well as in the Patient Labeling section of the insert labeling. With regard to the drug-drug interaction medication errors we note that the interactions listed above are clearly described in the Drug Interaction section of the insert labeling and thus the labeling should not have contributed to the error. Additionally, we do not believe that the errors noted above will be exacerbated by the addition of information on dosing during pregnancy to the package insert labeling.

3.2 LABELING

The changes introduced with this efficacy supplement do not pose any new safety concerns which may result in medication errors.

Our assessment of the insert labeling noted the following deficiencies:

- The units of measure are not presented with dosing information in the Dosage and Administration section.
- Dosing in pregnancy is not included in the Highlights section. We provide recommendations in Section 5.

4 CONCLUSION AND RECOMMENDATIONS

We do not have any safety concerns with regard to the addition of dosing in pregnant women to the Dosage and Administration and Specific Populations sections of the insert labeling associated with this efficacy supplement. However, we have identified areas of improvement in the insert labeling that will help with the presentation of dosing information so that it is less error prone and to ensure it accurately reflects the changes to the insert labeling. We provide recommendations in Section 4.1 below and we request the recommendations be communicated to the Applicant prior to approval of these supplements.

Please copy the Division of Medication Error Prevention and Analysis on any communication to the Applicant with regard to this review. If you have further questions or need clarifications on this review, please contact the OSE Regulatory Project Manager, Brantley Dorch at 301-796-0150.

4.1 COMMENTS TO THE DIVISION:

1. Full Prescribing Information, Dosage and Administration Section – Table 2 and Table 3: Include the unit of measure with each notation of strength. For example, revise "200" to read "200 mg."
2. Highlights Section, Dosage and Administration Subsection: Include information on dosing in pregnancy as all other categories are currently listed (e.g. treatment-naïve patients, treatment-experienced patients, pediatric patients, etc).

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/s/

KRISTINA C ARNWINE
01/31/2011

KELLIE A TAYLOR
01/31/2011

CAROL A HOLQUIST
01/31/2011

M E M O R A N D U M

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

DATE: January 19, 2011

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

FROM: Sripal R. Mada, Ph.D.
Division of Scientific Investigations (HFD-45)

THROUGH: Sam H. Haidar, Ph.D., R.Ph.
Branch Chief
GLP and Bioequivalence Branch
Division of Scientific Investigations (HFD-45)

SUBJECT: Review of EIRs Covering NDA 21-567, Reyataz® Capsules (Atazanavir), from Bristol-Myers Squibb Company

At the request of the Division of Antiviral Products (DAVP), the Division of Scientific Investigations (DSI) conducted inspections of clinical and analytical portions of the following study:

AI424182: "A Study of the Pharmacokinetics of Atazanavir (ATV)/ Ritonavir (RTV) Administered as Part of HAART Therapy in HIV-1 Infected Pregnant Women"

CLINICAL INSPECTIONS:

Inspections of clinical portions were conducted at the following sites:

Site-1: University of Puerto Rico, Rio Piedras, Puerto Rico

Site-2A: Helen Joseph Hospital, Gauteng, South Africa

Site-2B: Johannesburg Hospital, Gauteng, South Africa

Site-2C: Coronation Hospital, Gauteng, South Africa

Following the inspection at the University of Puerto Rico (November 29 to December 21, 2010), no Form FDA-483 was issued.

Following the inspection at Helen Joseph Hospital, Johannesburg Hospital, and Coronation Hospital (December 13-17, 2010), Form FDA-483 was issued (**Attachment SL1**). The firm's response, dated December 21, 2010, was received on January 12, 2011 (see **Attachment SL2**).

Note: The inspection for studies conducted at Helen Joseph Hospital, Johannesburg Hospital and Coronation Hospital was conducted and Form FDA-483 was issued at Helen Joseph Hospital in Gauteng, South Africa.

Our evaluation of the Form FDA-483 observations and the written response follow:

1. **Failure to prepare or maintain accurate case histories with respect to observations and data pertaining to the clinical investigation. (For the study conducted at Helen Joseph Hospital)**

Two subjects (initials (b)(6) and (b)(6)) were consented, did not meet all inclusion criteria. These two subjects were not identified as screening failures. This resulted in inaccuracies of the total number of subjects screened and screening failures as reported to the Ethics Committee and appearing in Final Reports. Total of 33 screened vs. 31 reported.

DSI recommends that this observation has no significant impact on data integrity or subject safety.

2. **An investigation was not conducted in accordance with the investigational plan. (For the study conducted at Helen Joseph Hospital)**

Specifically, there were no records of PK blood processing to document that the samples were handled and processed according to protocol section 7.3.11.1: There were no records of the times between collection and centrifugation; times and temperatures of centrifugation; times between centrifugation and storage; and storage temperatures until shipment to the laboratory.

In their response, the Helen Joseph Hospital acknowledged that these records were not maintained.

Although the Helen Joseph Hospital's documentation was incomplete, the analytical site (b)(4)

(b) (4) In view of these stability data, the observation is unlikely to have effects on data integrity.

ANALYTICAL INSPECTION:

The inspection of the analytical portion was conducted at (b) (4)

(b) (4)

(b) (4)

DSI finds the firm's response to be sufficient.

Conclusions:

Following the inspections, DSI recommends the following:

(b) (4) **Audit**:

- (b) (4)
-

- (b) (4) [redacted]

The clinical data and other analytical data are acceptable for your review.

After you have reviewed this transmittal memo, please append it to the original NDA submission.

Sripal R. Mada, Ph.D.

Final Classifications:
NAI – University of Puerto Rico, Rio Piedras, PR
FEI: 3008729417
VAI – Helen Joseph Hospital, Gauteng, South Africa
FEI: 3005192648
VAI – Johannesburg Hospital, Gauteng, South Africa
FEI: 3005192648
VAI – Coronation Hospital, Gauteng, South Africa
FEI: 3005192648
VAI – (b) (4) [redacted]
FEI: (b) (4) [redacted]

cc:
DSI/Ball
DSI/GLPBB/Mada/Dejernett/Yau/Haidar/CF
OCP/DCP4/Robertson/Zheng
ODE4/DAP/Birnkrant/Perry
HFR-CE3560/Mangalindan
HFR-CE8585/Laufenberg
HFR-SE500/Melendez
Draft: SRM 01/10/2011
Edit: JAK 01/17/2011; MFS 01/18/2011
DSI: 6121; O:\Bioequiv\EIRCover\21567bri.ata.doc
FACTS: 1226498

Email: DSI/CDER DSI PM TRACK

Attachment - SL1

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

DISTRICT OFFICE ADDRESS AND PHONE NUMBER	DATE(S) OF INSPECTION
CDER - BIMO 7520 Standish Place Rockville, MD 20855-2773 Industry Information: www.fda.gov/oc/industry (301) 594-0020	Dec. 13-17, 2010
	FEI NUMBER 3005192648

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT IS ISSUED

TO: Dr. Francesca Conradie - Clinical Investigator

FIRM NAME	STREET ADDRESS
University of Witwatersrand, Clinical HIV Research Unit (CHRU)	Helen Joseph Hospital Perth Road, Westdene
CITY, STATE AND ZIP CODE	TYPE OF ESTABLISHMENT INSPECTED
Johannesburg, South Africa 2041	Clinical Investigator

THIS DOCUMENT LISTS OBSERVATIONS MADE BY THE FDA REPRESENTATIVE(S) DURING THE INSPECTION OF YOUR FACILITY. THEY ARE INSPECTIONAL OBSERVATIONS; AND DO NOT REPRESENT A FINAL AGENCY DETERMINATION REGARDING YOUR COMPLIANCE. IF YOU HAVE AN OBJECTION REGARDING AN OBSERVATION, OR HAVE IMPLEMENTED, OR PLAN TO IMPLEMENT CORRECTIVE ACTION IN RESPONSE TO AN OBSERVATION, YOU MAY DISCUSS THE OBJECTION OR ACTION WITH THE FDA REPRESENTATIVE(S) DURING THE INSPECTION OR SUBMIT THIS INFORMATION TO FDA AT THE ADDRESS ABOVE. IF YOU HAVE ANY QUESTIONS, PLEASE CONTACT FDA AT THE PHONE NUMBER AND ADDRESS ABOVE.

DURING AN INSPECTION OF YOUR FIRM (I) ~~(WE)~~ OBSERVED:

1) Failure to prepare or maintain accurate case histories with respect to observations and data pertaining to the investigation.

Specifically, two subjects (initials (b) (6) and (b) (6)) were consented and during screening it was determined they did not meet all inclusion criteria. These two subjects were not identified as screen failures. This resulted in inaccuracies of the total number of subjects screened and screen failures as reported to the Ethics Committee and appearing in Final Reports. Total of 33 screened vs. 31 reported.

2) An investigation was not conducted in accordance with the investigational plan.

Specifically, there were no records of PK blood processing to document the samples were handled and processed per protocol section 7.3.11.1. This includes no record of the time between collection and centrifugation; time and temperature of centrifugation; time between centrifugation and storage; and storage temperature until shipment to the laboratory.

SEE REVERSE OF THIS PAGE	EMPLOYEE(S) SIGNATURE	EMPLOYEE(S) NAME AND TITLE (Print or Type)	DATE ISSUED
	Scott B. Laufenberg	Scott B. Laufenberg Investigator	Dec. 17, 2010

Attachment – SL 2

A syndicate of the Wits Health Consortium
Helen Joseph Hospital, Perth Road, Johannesburg, South Africa, 2042
Postnet Suite 176, Private Bag X2600, Houghton, Johannesburg, South Africa, 2041
Tel: +27 11 276-8800; Fax: +27 11 482-2130

Dr Sam H. Haidar
Acting Branch Chief
GLP and Bioequivalence Investigations Branch
Division of Scientific Investigations
Office of Compliance
CDER

21 December 2010

Re FDA GCP inspection FEI 3005192648 conducted 13-17th December 2010- study AI424-182- Dr Conradie

Dear Dr Haidar,

This letter is in response to the FDA site inspection conducted at my site during the period 13-17 December 2010

The findings and comments presented in your report have been reviewed by me and my team and BMS. The site is committed to fully resolving all FDA findings relative to the conduct of the above study supporting the Application for atazanavir and, as such hereby responds to the inspector's findings and comments. I trust that you will find this response and the actions taken satisfactory to resolve the concerns noted during the inspection.

We are committed to conducting clinical research in compliance with Good Clinical Practice and with all regulatory requirements. We appreciate the professional conduct of the inspector Mr Scott Laufenberg and the additional constructive suggestions he provided during the inspection. I would be grateful to receive the final inspection report. Please contact us if you require any further information.

Yours sincerely,

Doctor Francesca Conradie

Copy: *Willem Kriel, BMS Site monitors Manager*

Inspection Description: A Pilot Study Of Atazanavir (ATV)/Ritonavir (RTV) Administered As Part Of HAART Therapy In HIV-1 Infected Pregnant Women: Exploring The Pharmacokinetics In Pregnant Women, Safety In Their Neonates, Efficacy And Tolerability In Pregnant Women, And Prevention Of Mother-To-Child Transmission (MTCT) of HIV-1

Inspected Entity: FDA inspection conducted on the 13-17th December 2010 at the Clinical HIV Research Unit (CHRU), University of Witwatersrand, South Africa

Response submitted by: Dr Francesca Conradie **Date:** 6 Jan 2011

Finding (#) 1	**Finding Description:** Failure to prepare or maintain accurate case histories with respect to observations and data pertaining to the investigation. Specifically, two patients (initials (b)(6) and (b)(6)) were consented and during screening it was determined they did not meet the inclusion criteria. These two subjects were not identified as screen failures. This resulted in inaccuracies as reported to the Ethics Committed and appearing on the Final Reports. Total of 33 screened vs. 31 as reported.

Analysis of finding:

1. Dr Conradie acknowledges that two subjects were not entered onto the screening log as screening failures. The first patient ((b)(6)) early in the visit admitted to a significant intake of alcohol which rendered her ineligible for the study. The second ((b)(6)) was determined ineligible once a full history was taken, and the patient was found on examination to be more that 32

weeks pregnant, falling outside the window for enrolment.
At the time these patients were determined as screen failures, no protocol specific procedures had been done e.g. ECG, protocol mandated bloods tests.

2. While I am aware that these should still have been reported as screen failures (based on signing of informed consent), the omissions did not impact the results of the study from our site as they were true screen failures and not subjectively excluded from the trial. Patient safety was not compromised, and the integrity of the study data and the study findings were not affected in any way.

Corrective Action:	***Responsible:***	***Implementation Date:***
Corrective action that will be undertaken is that both the Human Research Ethics Committee (HREC) of the University of Witwatersrand and the Medical Control Council (MCC) will be made aware of the omission of two screen failures not previously reported for the study.	Dr Conradie	***13 January 2011***
Preventive Action:	***Responsible:***	***Implementation Date:***
In addition, there will be re-training of the staff with regard to the importance of maintenance of an accurate screening log (to include all patients who are screened for clinical trials), and to update the enrollment/randomization (IVRS) system.. An attendance register will be filled in and any absent study staff members will be trained at a later date.	Dr Conradie and BMS monitor	This will be done in early January 2011

Finding (#)2	***Finding Description:***
	An investigation was not conducted in accordance with the investigational plan. Specifically, there were not records of PK bloods processing to document that the samples were handled and processed per protocol 7.3.11.1. This includes no record of the time between collection, centrifugation: time and temperature of the centrifugation; time between the

centrifugation and storage: and storage temperature until shipment to the laboratory.

Analysis of finding:

We acknowledge that our documentation supporting the processing of the PK blood sample processing is not sufficiently detailed in all instances to demonstrate our compliance with all aspects of the protocol (section 7.3.11.1). Nonetheless, samples were processed according to [redacted] (b) (4) Standard Operating Procedure issued at study initiation (attachment 1) and following guidelines provided by [redacted] (b) (4) (attachment 3). Processing the samples according to these requirements is consistent with the process required by the protocol.

When considering the undertaking of this study, much attention was given to the challenges of ensuring that the PK bloods were processed in a timely fashion.

a. For 24-hour PK measurements (third/second trimester, post partum), subjects were admitted to the Folateng Ward of the Johannesburg Hospital, 3 stories above where the laboratory was situated. This was done so that there could be as short a time between obtaining the specimen and preparation.
For the 2 hours apart 2 PK measurements (labor and delivery), subjects were admitted at Rahima Moosa Mother and Child Hospital (was Coronation Women and Children's Hospital), 5 km from [redacted] (b) (4) lab. When a subject was admitted in labor, the [redacted] (b) (4) project Manager, [redacted] (b) (4) was alerted. He collected blood samples when they were obtained and took them to the laboratory. Time of sampling & receipt time are noted on the requisition form. The Req form is date & time stamped as it is clocked in on receipt into the laboratory. [redacted] (b) (4) was selected for this task as he lives within 5 minutes of the Rahima Moosa Mother and Child Hospital. he was on call throughout the study.

b. The [redacted] (b) (4) Project Manager, [redacted] (b) (4) was solely responsible for the collection and processing of all PK specimens. There was a dedicated bench in the laboratory and only one laboratory staff member assigned to this task. He personally undertook the preparation of the specimens. Also attached, please find a sworn affidavit that [redacted] (b) (4)

(b) (4) adhered to the (b) (4) SOP. (Attachment 2).

c. As per normal lab practice the laboratory staff followed the SOP & Lab Manual guidelines. The sample is logged into the LIS (laboratory information System) upon receipt & a shipping log / waybill is available at time of shipment to ensure the 24 hour period of time of collection to shipping for PK samples was met. Shipments to (b) (4) were sent on a daily basis from (b) (4)

Corrective Action:	***Responsible:***	***Implementation Date:***
The Standard Operating Procedure issued to the laboratory at the time of the initiation of the study (Attachment 1) and the confirmation that (b) (4) adhered to the SOP (Attachment 2) will be added to the study file.	***Dr Conradie and BMS monitor***	***January 2011***
Preventive Action: Centrifugation time and temperature are not normally logged for routine blood samples. However, for future studies, the (b) (4) SOP will require to document PK blood sample processing specific steps. A log will be developed according to the protocol specific requirements and all concerned staff will be trained on its completion. (b) (4) will be implementing a PK Processing form which will encompass times of collection, centrifugation, storage and shipment of specimens. At study start the monitor will discuss in more detail the sample path and document this discussion in the monitoring report.	***Responsible:*** ***Head of (b) (4) Lab*** ***BMS monitor***	***Implementation Date:*** ***1st February 2011***

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/s/

SRIPAL R MADA
01/19/2011
Original signed documents are available in the DSI file.

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications

PRE-DECISIONAL AGENCY MEMO

Date: January 14, 2011

To: Venessa Perry, MPH, DAVP

From: Lynn Panholzer, PharmD, DDMAC
Michelle Safarik, PA-C, DDMAC

Re: NDA# 021567/S-025
Reyataz (atazanavir sulfate) Capsules

As requested in your consult dated August 18, 2010, DDMAC has reviewed the draft labeling for Reyataz (atazanavir sulfate) Capsules. DDMAC's comments are based on the proposed, substantially complete, marked-up version of the labeling sent to DDMAC via e-mail by DAVP on January 5, 2011.

DDMAC's comments are provided directly in the attached, marked-up copy of the labeling.

If you have any questions about DDMAC's comments on the PI please contact Lynn Panholzer at 6-0616 or at Lynn.Panholzer@fda.hhs.gov. If you have any questions about our comments on the PPI please contact Michelle Safarik at 6-0620 or at Michelle.Safarik@fda.hhs.gov.

82 Page(s) of Draft Labeling has been Withheld in Full as b4 (CCI/TS) immediately following this page

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

/s/

LYNN M PANHOLZER
01/18/2011

MICHELLE L SAFARIK
01/18/2011

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Office of New Drugs - Immediate Office
Pediatric and Maternal Health Staff
Silver Spring, MD 20993
Telephone 301-796-2200
FAX 301-796-9744

M E M O R A N D U M

DATE: January 12, 2011

FROM: Elizabeth L. Durmowicz, MD, Medical Officer
Leyla Sahin, MD, Medical Officer
Pediatric and Maternal Health Staff

THROUGH: Karen Feibus, MD, Medical Team Leader
Hari Cheryl Sachs, MD, Medical Team Leader
Lisa Mathis, MD, OND Associate Director
Pediatric and Maternal Health Staff

TO: Alan Shapiro, MD, PhD, Medical Reviewer
Mary Singer, MD, PhD, Medical Team Leader
Vanessa M. Perry, MPH, Regulatory Project Manager
Division of Antiviral Products (DAVP)

RE: •In utero exposed neonates with hyperbilirubinemia
•Pregnancy Labeling

Drug: Reyataz® (atazanavir)

Application: NDA 21-567

Supplement: Efficacy: S-025 (Sequence #0069): New Pharmacokinetic (PK) data to support dosing in pregnant women

Dosage form (strength): oral capsule (100 mg, 150 mg, 200 mg, 300 mg)

Sponsor: Bristol-Myers Squibb

Indication (approved): treatment of HIV-1 infection in combination with other antiretroviral agents
(No change in indication sought)

Division Consult Request:
The Division has requested PMHS comment regarding the risks of hyperbilirubinemia in atazanavir (ATV) exposed infants, the appropriate monitoring of these patients and recommendations for risk management. Specific comment is requested on whether in utero ATV exposure results in a higher incidence of hyperbilirubinemia, if ATV exposed neonates are at higher risk of bilirubin related complications, and if additional data are needed to better characterize this risk. The Division also requested input on how to best convey new PK, efficacy and safety data in Pregnancy Labeling.

Materials Reviewed:

- Reyataz® labeling (April 26, 2010)
- Sponsor submission/efficacy supplement S-025: Sequence # 0069 (August 6, 2010)
- Sponsor Submission: Sequence # 0077(November 12, 2010)
- Protocol AI424182 (November 3, 2008)
- Medical Review, atazanavir, NDA 21-567 Kendall Marcus, MD (June 20, 2003)

Background:
Atazanavir, originally approved in June 2003, is a protease inhibitor indicated for use in combination with other antiretroviral agents for the treatment of HIV-1 infection in patients 6 years of age and older. The current approved dosage of atazanavir recommends co-administration with ritonavir (RTV), which provides increased plasma levels of atazanavir.

The sponsor's efficacy supplement, S-025 provides data from a PK and safety study in HIV infected pregnant women evaluating the approved adult dose of 300mg ATV + 100mg RTV (300/100) to an increased dose of 400mg ATV + 100mg RTV (400/100) to determine if an increased dose of ATV is needed in the third trimester. Please see the medical officer review by Dr. Alan Shapiro for a detailed analysis of the safety and efficacy data submitted by the sponsor. The sponsor did not observe significant differences in PK, and is requesting changes in pregnancy labeling to reflect these results; a change in dosing and/or indication is not requested. Please see discussion of PK data (later in this review).

Overview of Study Drugs

Atazanavir
Atazanavir is labeled pregnancy category B, based on negative reproductive and developmental toxicology data. The Antiretroviral Pregnancy Registry report from May 2010 concludes that sufficient numbers of first trimester exposures have been monitored to detect at least a two-fold increase in risk of overall birth defects. No such increases have been detected to date.

Atazanavir is approved in pediatric patients 6 years and older. PREA required studies of atazanavir for use in the treatment of HIV were waived in pediatric patients less than 3

months in 2004 due to the criterion that evidence strongly suggests that the drug product would be unsafe in this pediatric age group. Thus, the Pediatric Use section was revised in 2008 to state that REYATAZ should not be administered to pediatric patients below the age of 3 months due to the risk of kernicterus.

Ritonavir (Norvir®)

Ritonavir is a protease inhibitor initially approved by FDA in 1991 for the treatment of HIV-infection in combination with other antiretroviral agents. It is Pregnancy Category B, based on negative reproductive and developmental toxicology data. The Antiretroviral Pregnancy Registry report from May 2010 concludes that sufficient numbers of first trimester exposures have been monitored to detect at least a two-fold increase in risk of overall birth defects. No such increases have been detected to date. A phase I/II study in pregnancy showed lower levels during pregnancy compared to postpartum[31]. Given low levels in pregnancy when used alone, ritonavir is recommended in low dose for use in combination with another protease inhibitor to increase levels of the other protease inhibitor[7].

Ritonavir is approved in pediatric patients 1 month and older. The adverse event profile seen during clinical trials and through postmarketing experience is similar to that for adult patients.

Management of the HIV Infected Pregnant Woman

The use of antiretroviral agents for HIV-infected women during pregnancy must take into account two separate but related issues:

1. Antiretroviral treatment of maternal HIV infection; and
2. Antiretroviral chemoprophylaxis to reduce the risk of perinatal HIV transmission.

The benefits of antiretroviral therapy for a pregnant woman must be weighed against the risk of adverse events to the woman, fetus, and newborn. According to the Department of Health and Human Services Panel on Treatment of HIV-Infected Pregnant Women and Prevention of Perinatal Transmission Recommendations for Use of Antiretroviral Drugs in Pregnant HIV-Infected Women for Maternal Health and Interventions to Reduce Perinatal HIV Transmission in the United States (May 24, 2010), general principles for treatment of HIV infected women during pregnancy include the following:

- HIV infected pregnant women should receive standard potent combination antiretroviral therapy as recommended for nonpregnant adults, taking into account what is known about use of specific drugs in pregnancy

- For women who require immediate initiation of therapy for their own health, treatment should be initiated as soon as possible, including in the first trimester

- HIV-infected pregnant women who do not require treatment for their own health should also receive three-drug combination antiretroviral regimens for prophylaxis of perinatal transmission

- For women who are receiving antiretroviral drugs solely for prevention of perinatal transmission, delaying initiation of prophylaxis until after the first trimester can be considered

- Use of ZDV as a component of the antiretroviral regimen is recommended when feasible

- Intrapartum intravenous ZDV is recommended for all HIV-infected pregnant women, regardless of their antepartum regimen, to reduce perinatal HIV transmission.

RECOMMENDATIONS FOR USE OF ANTIRETROVIRAL DRUGS DURING PREGNANCY[7]

All women who receive antiretroviral drugs during pregnancy, either for treatment or prophylaxis, should receive a combination regimen including two nucleoside reverse transcriptase inhibitors (NRTIs) and either a non-nucleoside reverse transcriptase inhibitor (NNRTI) or a protease inhibitor (PI) (with or without low-dose ritonavir). The preferred NRTI regimen in pregnancy, based on efficacy studies in preventing perinatal transmission and large experience with use in pregnancy, is zidovudine/lamivudine. Use of zidovudine, both antepartum and intrapartum, is important due to its excellent transplacental passage, unlike many other antiretroviral drugs. Additional mechanisms by which antiretroviral treatment can reduce perinatal transmission include decreasing maternal viral load and post-exposure infant prophylaxis. However, combination antiretroviral drug therapy has been shown to reduce the risk of transmission even among women with low viral load[35].

Lopinavir/ritonavir is the preferred protease inhibitor regimen for pregnant women because of efficacy studies in adults and experience with use in pregnancy. Alternative protease inhibitors include ritonavir-boosted atazanavir, saquinavir, or indinavir, although experience with these regimens in pregnancy is more limited and the latter two may be less well tolerated. Data on use in pregnancy for other PIs are too limited to recommend routine use in pregnancy, although they may be considered if other agents are not tolerated. The DHHS Guidelines list increased unconjugated bilirubin levels exacerbating physiologic hyperbilirubinemia in the neonate as a theoretical concern for atazanavir and indinavir.

Hyperbilirubinemia in Neonates:

Neonatal hyperbilirubinemia, an elevation of unconjugated bilirubin, occurs in essentially all newborn infants secondary to increased bilirubin formation, mainly due to the shorter life of the newborn's red blood cells and a decrease in bilirubin elimination related to a transiently limited ability of the newborn liver to conjugate bilirubin due to the immaturity of UDP-glucuronosyl transferase 1A1(UGT1A1)[3]. The condition is recognized as jaundice in about 60% of healthy term newborns in the United States[3], is usually benign, and has been termed "physiologic jaundice" [1]. Clinical observation of jaundice can be appreciated in the majority of infants with a bilirubin level of greater than

5 mg/dL[6]. Term, healthy, North American, formula-fed infants have mean peak total serum bilirubin (TSB) levels between 5 and 6 mg/dL[19]. Bilirubin levels usually peak at age 72-120 hours, and resolve by age 2-3 weeks[3]. However, per some experts, because more neonates are now breast fed than in previous decades, "normal" bilirubin levels are higher than they were several decades ago and the time to resolution may be more prolonged. Normal values in pediatric patients after infancy and in adults are considered <1.2 mg/dL[27].

Although neonatal jaundice is usually physiologic, unconjugated bilirubin is neurotoxic and at high levels can cause acute and chronic bilirubin encephalopathy[1]. Kernicterus, the chronic form of bilirubin encephalopathy, is associated with significant mortality and morbidity and characterized by choreoathetoid cerebral palsy, paralysis of upward gaze, sensorineural hearing loss, dental enamel dysplasia, and intellectual handicaps[5]. Although investigators have unsuccessfully attempted to correlate the occurrence of kernicterus to a specific or threshold TSB level[3], in general agreement exists that TSB levels greater than 30 mg/dL in healthy term and near-term infants increase the risk of developing kernicterus[5]. Bhutani and Johnson estimate that one in seven patients with a TSB greater than 30 mg/dL develops kernicterus[3]. Bilirubin encephalopathy is rare: in the US, the incidence of acute bilirubin encephalopathy is estimated at 1 in 40,000 live births[3] and the incidence of kernicterus is approximately 1.5 per 100,000 newborns with a higher incidence in preterm infants (4 per 100 000 births) [5].

Defining a normal total serum bilirubin is problematic as the range of normal levels varies widely depending on race, the incidence of breastfeeding, and other genetic and epidemiologic factors[19]. Major risk factors for the development of severe hyperbilirubinemia include jaundice observed in the first 24 hours of life, blood group incompatibility with positive direct antiglobulin test, other known hemolytic disease such as G6PD deficiency, previous sibling received phototherapy, cephalohematoma or significant bruising and exclusive breastfeeding (see Appendix I: Risk Factors for Development of Severe Hyperbilirubinemia in Infants of 35 or More Weeks' Gestation) [1]. Compared with Caucasians, rates of identified hyperbilirubinemia are about twice as high in Asians, half as high in Blacks, and the same in Latinos[23] and "East Asian race" is considered a major risk factor for the development of severe hyperbilirubinemia[1].

Furthermore, the risks of developing bilirubin toxicity may be higher in conditions that affect albumin binding of bilirubin, the blood-brain barrier, and the susceptibility of the brain cells to damage by bilirubin. Hence, premature infants (defined as less than 38 weeks gestation by the American Academy of Pediatrics (AAP) in the Guideline for Management of Hyperbilirubinemia) and patients with asphyxia, significant lethargy, temperature instability, sepsis, acidosis or albumin less than 3.0 g/dL are considered higher risk for bilirubin toxicity[1].

Hyperbilirubinemia in preterm infants is more prevalent, more severe, and the course is more protracted than in term neonates[38]. In a series of studies published from 1958 to 1972, kernicterus was described in premature infants at TSB levels ranging from 10 to 18 mg/dl [38,39]. However, kernicterus is currently a very rare event in premature infants in

neonatal intensive care units. The literature notes that the available data on bilirubin induced neurological injury in preterm infants is complex and additional data are needed to define the risk of elevated bilirubin in premature infants [38,39]. Normative data that are available for term and near-term infants do not appear to be available for preterm infants.

An additional difficulty in determining a normal TSB, is that the TSB is an imprecise indicator of long-term neurodevelopmental outcome unless levels are extremely high and associated with signs and symptoms of bilirubin encephalopathy [1]. Data are inadequate to determine if severe hyperbilirubinemia or prolonged moderate hyperbilirubinemia in the absence of signs and symptoms of acute bilirubin encephalopathy are associated with sequelae [3].

"Significant" hyperbilirubinemia has been defined as greater than the 95th percentile for age in hours [3] based on data obtained from over 17,000 healthy, near term infants born at a Pennsylvania Hospital from 1993 to 1997 [4]. Defined numeric values used commonly are TSB levels greater than 10 mg/dL, greater than 14 mg/dL, and greater than 17 mg/dL on days of life 2, 3 and 4-5, respectively[30]. TSB levels greater than 20 mg/dL are often considered "severe hyperbilirubinemia" and those greater than 25 or 30 mg/dL, "extreme hyperbilirubinemia" [19]. Per Bhutani and Johnson, significant hyperbilirubinemia, i.e. greater than the 95% for age in hours, occurs in 8 to 11% of infants, and approximately 1 in 650-1000 infants greater than 35 weeks gestation can develop serum bilirubin values greater than 25 mg/dL and approximately 1 in 10,000 have levels exceed 30 mg/dL [3].

Management:
Although the development of bilirubin encephalopathy is rare[5], given the seriousness of the condition, newborn infants are monitored to identify those at risk for the development of severe hyperbilirubinemia, and therefore at potential risk for bilirubin encephalopathy. If indicated, infants are treated to avoid potentially toxic levels of serum bilirubin [1]. A nomogram for designation of risk based on the infant's hour-specific serum bilirubin is available and used by practitioners to assess the risk of developing severe hyperbilirubinemia and to establish a monitoring plan based on the assessed level of risk (Appendix II)[1]. In addition, the AAP has established guidelines on when to initiate phototherapy (PT) (Appendix III: Guidelines for phototherapy in hospitalized infants of 35 or more weeks' gestation.) and when to perform an exchange transfusion based on hour-specific serum bilirubin measurements and other risk factors[1]. Phototherapy is used to reduce the risk that the TSB level will reach a level at which exchange transfusion is recommended, and the goal of both procedures is to keep TSB levels below those at which bilirubin encephalopathy has been reported[1].

Atazanavir and Hyperbilirubinemia:
Due to UDP-glucuronosyl transferase 1A1 (UGT1A1) inhibition, most patients treated with atazanavir (ATV) experience asymptomatic elevations in unconjugated bilirubin that are reversible upon discontinuation of the drug. The incidence of hyperbilirubinemia is dose-dependent and a clinical study reported grade 3-4 bilirubin levels (greater than 2.6X upper limit of normal) in 44% of patients exposed to 300 mg ATV. The mean total serum bilirubin (TSB) in patients from study A1424034 (034), one of the two phase 3

pivotal studies, was 6.3 mg/dL (SD 1.4). Per the medical officer review of the original NDA, the occurrence of TSB levels 10 mg/dL or greater occurred in 5 patients without additional associated liver function abnormalities. Based on clinical trials and post-marketing experience, ATV-associated hyperbilirubinemia does not appear to increase the risk for hepatic injury or hepatic enzyme abnormalities.

Reviewer Comment:
Data regarding the time to resolution of the hyperbilirubinemia seen in adults after ATV discontinuation do not appear to be included in the original medical officer review; however, Nettles et al state that hyperbilirubinemia associated with protease inhibitors resolves completely days after the medication is discontinued[22].

The Sponsor notes that data are not available to determine if ATV administration during pregnancy will exacerbate physiological hyperbilirubinemia or increase the risk of kernicterus in neonates and young infants. Per the Sponsor, the placenta allows only unidirectional transport of bilirubin from the fetus to the mother and not from mother to fetus. In contrast, published case reports of Crigler-Najjar syndrome show neonatal hyperbilirubinemia and corresponding high maternal bilirubin levels at the time of delivery (this is discussed later in this review). High maternal bilirubin levels due to ATV administration during pregnancy might theoretically disrupt the normal transplacental transport of fetal bilirubin, and lead to intrauterine hyperbilirubinemia.

Reviewer Comment:
Studies have demonstrated that unconjugated bilirubin in the fetus normally crosses the placenta to reach the maternal circulation as the fetal liver has limited UGT1A1 activity[17]. Per Holstein et al, high levels of maternally derived unconjugated bilirubin may lead to neuronal and astrocytal degeneration in the fetus[12]. Given that the fetus is considered to be at risk from the neurotoxic effects of unconjugated bilirubin[9,12], the risk of intrauterine exposure to elevated levels of unconjugated bilirubin secondary to maternal ATV inhibition should be considered.

The familial unconjugated hyperbilirubinemias, Crigler-Najjar syndromes type I and II and Gilbert syndrome, are caused by genetic lesions encoding for UGT1A1 and result in a spectrum of unconjugated hyperbilirubinemias. The clinical spectrum of these disorders range from the clinically negligible Gilbert syndrome to the severe and often fatal Crigler-Najjar type I syndrome[30], which is characterized by the complete absence of UGT1A1. Information about patients with these syndromes may be useful in understanding the risk of elevated maternal unconjugated bilirubin in the fetus. Gilbert syndrome occurs in 3%–10% of the general population[15] and is considered a benign condition. In most patients, the hyperbilirubinemia of Gilbert syndrome becomes manifest in adolescence or early adulthood[36], and serum bilirubin levels are usually less than 3 mg/dL, although fluctuations may occur especially with illness[11,29]. Review of the literature for reports of pregnancy outcomes in women with Gilbert syndrome did not identify any articles. Although Gilbert syndrome is reported to be more common in males (4:1)[11], given that the occurrence of this condition is common and the literature provides a paucity of information regarding infants born to women with Gilbert

syndrome, the bilirubin levels seen in women with Gilbert syndrome may not be problematic to the fetus.

Crigler-Najjar type I (CN-I) is associated with a progressive and severe neurologic syndrome resembling kernicterus, usually resulting in death within the first two years of life. Total plasma bilirubin levels have been reported in a wide range from 15 to over 50 mg/dL. In Crigler-Najjar type II (CN-II) bilirubin levels are lower than in CN-I and typically range from 10-20 mg/dL. Central nervous system damage is rare, and the majority of patients survive into adulthood without complications[29]. Both CN syndromes are considered rare and pregnancy in CN patients is considered an "exceptional" event[9]; however, of note, patients with CNI have historically been advised to terminate pregnancy due to the risk of bilirubin toxicity. The literature has a few case reports of pregnancy and pregnancy outcome for patients with CNI and CNII[2,9,10,12,13,32]. Pregnancy outcomes were reported in four patients with CNI exposed in utero to TSB levels 12-25 mg/dL[9,10]. Normal neurological outcomes were reported in three patients but quadriplegia was reported at age 18 months in one patient[34]. Of note, one of the three infants with reported normal neurologic outcomes initially had MRI findings consistent with bilirubin deposition and developmental concerns were raised, but by age 4 years the MRI and neurologic and developmental exams were reported to be within normal limits[10]. The other two infants were reported to have normal exams at 18 months and 4 months. For all patients, maternal and infant TSB levels were similar at birth, and all infants were treated aggressively, i.e. two infants were treated with phototherapy and double-volume exchange transfusion and one infant was treated solely with phototherapy. Among the six case reports of pregnancy outcomes in patients with CNII identified by the reviewers[2,12,13,32], all mothers maintained bilirubin levels less than 10 mg/dL, and neonatal bilirubin levels were between 5.1-13.2. Arora and Choudhary observed (based on two case reports in the literature and their own case) that maternal serum bilirubin levels of 9 mg/dl or less before delivery were associated with good neonatal outcomes[2]. Smith and Baker conclude that CN II seems to pose no unique maternal risk during pregnancy and note that the fetus seems to be resistant to elevated maternal unconjugated bilirubin[32].

Per ATV labeling, animal reproduction and pre and post-natal development studies did not identify evidence of adverse fetal effects or teratogenicity with ATV exposure. Per the literature, a paucity of animal data exists.

In summary, although the Sponsor states that the placenta allows only unidirectional transport of bilirubin from the fetus to the mother, the literature suggests that the placenta allows bidirectional passage of bilirubin between mother and fetus, and levels of unconjugated bilirubin in infants with CNI and II were similar to maternal levels. The limited data from patients with familial unconjugated hyperbilirubinemias suggest that bilirubin levels in the range of adult patients treated with ATV in clinical trials may not represent an unacceptable risk to the fetus.

The Sponsor also notes that fetal exposure to ATV that has crossed the placenta has the potential to inhibit infant UGT1A1, hence exaggerating physiologic jaundice and potentially contributing to the development of significant hyperbilirubinemia.

Reviewer Comment:
*Although the Sponsor states the concern that ATV may inhibit **infant** UGT1A1, they do not appear to have discussed the potential impact of ATV on **fetal** UGT1A1. Although inhibition of the UGT1A1 enzyme may occur, studies in rats[16] suggest that elevated unconjugated bilirubin could also potentially stimulate fetal UGT1A1 activity thereby, theoretically, protecting the fetus from exposure to elevated maternal levels of bilirubin. Hence, bilirubin metabolism is complex and a number of unknowns exist regarding the effects of ATV and bilirubin levels on fetal UGT1A1 activity and in utero bilirubin metabolism.*

Labeling lists no contraindications; however the Pediatric Use section states that REYATAZ should not be administered to pediatric patients below the age of 3 months due to the risk of kernicterus.

Reviewer Comment:
Per personal correspondence Alan Shapiro, MD (December 6, 2010), given that other products with well-characterized safety profiles are available to treat HIV infection in infants less than 3 months, studies of ATV were waived in this pediatric subpopulation because the unknown risk of prolonged exposure of young infants to unconjugated bilirubin as well as the risk of PR prolongation outweighed the potential benefits of the drug.

Study AI424182
Protocol Summary:
Study AI424182 was a multi-center, open-label, prospective, single-arm study designed to determine which dosing regimen of ATV/RTV produces adequate drug exposure during pregnancy compared to drug exposure of HIV-infected subjects from historical data. PK and efficacy analyses were based on data from 41 treated mothers and 40 infants. Safety variables included the frequency and duration of hyperbilirubinemia in the neonate at study days 1, 3, 5, and 7 postpartum, the frequency and severity of adverse events (AEs) in the neonates, the frequency and severity of AEs in pregnant women, and the frequency and occurrence of adverse pregnancy or neonatal outcomes. Of note, bilirubin levels were to be evaluated at study days 1, 3, 5, 7, and 14, with additional monitoring as clinically indicated. Cord samples were drawn at delivery for neonatal ATV and RTV exposure testing.

Women with risk factors known to increase the risk of "pathologic jaundice" in neonates were excluded from the study: the exclusion criteria included patients with Rhesus antibody positive, a previous infant who developed hemolytic disease as a newborn and/or had neonatal pathologic jaundice that required phototherapy and a history of glucose-6-phosphate dehydrogenase (G6PD) deficiency. Testing to determine infant

blood type and/or antiglobulin testing to assess for the potential for ABO incompatibility and/or hemolysis was not performed. Breast feeding was not permitted.

Reviewer Comment:
Although the exclusion of women with risk factors known to increase the risk for hyperbilirubinemia in neonates may have been considered an appropriate safety consideration to limit exposure to those infants at lower risk for the development of severe hyperbilirubinemia, the criteria appear to limit the ability to adequately assess the potential for developing hyperbilirubinemia in all infants exposed to ATV as the data are likely to not be applicable to the general population of potentially exposed infants.

Blood samples were to be obtained by venipuncture or from an indwelling catheter (with discard of 0.5 ml of blood). Laboratory tests were to be performed by a central laboratory that is licensed and meets Clinical Laboratory Improvement Amendments (CLIA) regulations or equivalent by country. Blood samples for analysis of ATV and RTV were to be performed at a central analytical laboratory.

Reviewer Comment:
Although blood sampling for bilirubin assessment appears to have been correctly collected, bilirubin analysis appears to have been performed at the local site and the method of analysis does not appear to be specified. Given that inaccuracy of bilirubin determinations has been a long-term concern and that interlaboratory variability of bilirubin measurements is well documented[8,37], the Division should be satisfied that the methods used to assess bilirubin levels were sufficiently similar and carefully evaluated to insure comparability of the reported values.

Maternal adverse events were graded according to the WHO recommendations for Grading Acute and Subacute Toxic Effects and infant adverse events were graded according to criteria adapted from toxicity grading tables for pediatric and infant adverse events from the National Institutes of Health Division of AIDS, DAIDS (see Appendix IV: Grading of Maternal and Infant Adverse Events). For both mother and infants greater than 14 days, Grade 3 and Grade 4 bilirubin toxicity were defined as 2.6-5X and greater than 5 X the upper limit of normal, respectively. For infants 14 days or younger, the definitions for Grade 3 and Grade 4 toxicity were as follows:

PARAMETER	GRADE 1 Mild	GRADE 2 Moderate	GRADE 3 Severe	GRADE 4 Potentially Life-Threatening
Bilirubin (Total)				
Pediatric > 14 days	1.1 - 1.5 x ULN	1.6 - 2.5 x ULN	2.6 - 5.0 x ULN	> 5.0 x ULN
Infant ≤ 14 days (non-hemolytic)	NA	20.0 - 25.0 mg/dL *342 - 428 µmol/L*	25.1 - 30.0 mg/dL *429 - 513 µmol/L*	> 30.0 mg/dL *> 513.0 µmol/L*
Infant ≤ 14 days (hemolytic)	NA	NA	20.0 - 25.0 mg/dL *342 - 428 µmol/L*	> 25.0 mg/dL > 428 µmol/L

Reviewer Comment:
Although the Sponsor does not appear to have provided the upper limit of normal for pediatric patients greater than 14 days or for adult patients and the standard normal ranges of laboratory values may vary between laboratories, total bilirubin levels are generally defined as less than 1.2 mg/dL[27] after the neonatal period. Hence, Grades 2, 3 and 4 toxicities would be considered total bilirubin values of approximately 1.9-3 mg/dL, >3-< 6 mg/dL and ≥ 6 mg/dL respectively.

Per the study protocol, the AAP Clinical Practice Guideline on the management of neonatal hyperbilirubinemia was recommended to guide management of neonates with hyperbilirubinemia in the study and was provided to investigators. However, given that the Guideline has not been validated in populations outside the US or in neonates exposed to antiretroviral drugs in-utero, other than the monitoring mandated by the protocol, the management and monitoring of South African neonates was ultimately at the discretion of the local investigators and clinicians. Although study sites were required to have the ability to perform phototherapy (PT), specific guidance regarding how PT was performed do not appear to be provided, i.e. continuous vs. intermittent, high vs. low intensity.

Reviewer Comment:
South African patients represented the vast majority of study patients, n=28 (40%). However, as discussed below, the variability in management of hyperbilirubinemia is unlikely to have affected the interpretability of the results.

Study Results:
Forty one mothers were treated and 40 in utero exposed infants were followed. Twenty infants were exposed to each dosing cohort, i.e. ATV/RTV 300/100 mg n=20 infants, ATV/RTV 400/100 mg n=20 infants. One mother withdrew consent and her infant was not followed. Race was identified as "Black/African American" in 33 patients, "White" in 6 patients and as "Other: Mixed Race" in 1 patient. Twenty eight patients were treated in sites in South Africa, 10 patients in Puerto Rico and 2 patients in the US (see Appendix V: Demographics and Disease Characteristics of Enrolled Infants).

Reviewer Comment:
As discussed above, the range of normal bilirubin levels varies widely depending on racial composition, and the rate of hyperbilirubinemia in Black patients is reported to be half as high as that in Caucasian patients, and the rate in Asian patients is considered to be twice as high as that in Caucasians[23]. Hence, given that 33/40 (82.5%) patients were identified as Black/African American and no Asian patients were enrolled in this study, the ability of the data to determine the incidence of hyperbilirubinemia in the general population of infants exposed to ATV is limited, especially in Asian patients.

Atazanavir Levels in Maternal vs. Cord Blood**:**
The Sponsor states that relative to the corresponding maternal ATV concentrations at the time of delivery, the ATV concentrations in cord blood were approximately 12% and 19% at ATV/RTV 300/100 mg and ATV/RTV 400/100 mg, respectively. The Sponsor

concluded that the ratio of ATV concentrations in maternal and umbilical cord blood indicates that ATV does not freely cross the placenta; however, the levels observed may be enough to inhibit the infant's UGT1A1 enzyme until the drug is cleared by the infant.

Reviewer Comment:
The sponsor's finding of low transplacental passage of atazanavir at the time of delivery is consistent with the literature regarding other protease inhibitors[20, 21,26]. Per the pediatric reviewer's correspondence with the Clinical Pharmacology Reviewer, Jenny Zheng, PhD (December 10, 2010), the ATV cord blood concentration was about 200 mg/ml, a level that could potentially inhibit the infant's UGT1A1. Thus, given that UGT1A1 is known to be immature at birth, ATV inhibition of UGT1A1 could theoretically further decrease the infant's ability to conjugate bilirubin, possibly increasing the infant's risk for the development of severe and/or prolonged unconjugated hyperbilirubinemia (more below). If the half life of ATV in neonates is similar to that in adults (t½ in healthy adults is 18 hours), the neonate would be expected to clear the ATV within four days. However, as previously noted, from animal data, exposure to high levels of unconjugated bilirubin in utero could potentially stimulate UGT1A1. Thus, the relationship between in-utero drug exposure and bilirubin metabolism is likely to be dependent on a complex interplay of a number of factors, and PK data are not available in infants to determine if enzyme inhibition occurs and/or if enzyme inhibition could be prolonged or delayed

Maternal Bilirubin Levels:
Per the Sponsor, ATV/RTV 400/100 mg dosing was associated with twice as much Grade 3 to Grade 4 hyperbilirubinemia as ATV/RTV 300/100 mg in mothers, i.e. 6 of 20 mothers on ATV/RTV 300/100 mg and 13 of 21 mothers on ATV/RTV 400/100 mg. The maximum maternal bilirubin level reported in mothers exposed to 300 mg ATV and 400 mg ATV was 5.8 mg/dL and 6.4 mg/dL, respectively.

Reviewer Comment:
Although a comparison of bilirubin levels between trials is deferred to the clinical reviewer, the maternal bilirubin level results appear to be consistent with the findings from the adult clinical trials and do not appear to be unexpected. Of importance, the levels do not appear to be higher than those identified in previous trials. If the higher levels of unconjugated bilirubin elevation observed in mothers in this trial and in the adult clinical trials, i.e. 6.3 mg/dL (SD 1.4) are observed in infants within the first 24 hours of life, the levels would likely be considered elevated and may place infants at higher risk for the development of severe hyperbilirubinemia (more below). However, these bilirubin levels are markedly below those at which kernicterus is of concern, specifically 25mg/dL or greater in term infants.

Comparison of Maternal and Infant Bilirubin Levels:
The Sponsor concluded that the correlation between maternal bilirubin, both on the date of delivery and the mean level in the 4 weeks prior to delivery, with that of the infant on the day of delivery was low, and scatterplots of the data were provided:

Scatterplot and Fitted Line of Infant vs. Mother's Total Bilirubin at Delivery Day:
(From the Sponsor)

Reviewer Comment:
At lower maternal bilirubin levels, i.e. less than 2-3 mg/dL, a correlation between maternal and infant bilirubin levels does not appear to exist, and many infants have TSB levels higher than those reported in their mothers. However, per the pediatric reviewers' interpretation of the scatterplot, the data are insufficient to rule out a correlation between higher maternal serum bilirubin measurements at the time of birth and infant bilirubin level measurements, and this correlation may be consistent with the literature reports from patients with CN syndrome discussed above. Specifically, two mothers had bilirubin levels 5 mg/dL or greater at the time of delivery and their infants also had bilirubin levels greater than 5 mg/dL during the first day of life. In addition, one cannot rule out a correlation between mothers with bilirubin levels of 3-4 mg/dL and their infants based on the data. Review by the statistical reviewer could be considered; however, given the limited numbers of mothers with bilirubin levels 5 mg/dL or greater at the time of delivery, definitive conclusions cannot be made from the available data.

Although debate exists, jaundice appearing in neonates within the first 24 hours of life is generally of concern[1,2,25,30] (more below). Given the possibility that elevated maternal bilirubin levels may result in elevated neonatal bilirubin levels at birth or within the first 24 hours of life, a review was performed of infants born to mothers with TSB values 3 mg/dL or greater at any time during pregnancy.

Eight mothers in the study (8/40, 20%) had bilirubin elevations of 3 mg/dL or greater during pregnancy. Three mothers (3/40, 7.5%) had bilirubin levels greater than 5 mg/dL at some point during pregnancy and two mothers (2/40, 5%) had bilirubin levels 5 mg/dL or greater at birth. TSB levels greater than 3 mg/dL during pregnancy were more common in mothers treated with 400 mg ATV.

Table I: Comparison of Maternal and Infant Bilirubin Values in Mothers with Bilirubin Levels 3 mg/dL or greater During Pregnancy:

ATV Dose Cohort	Preterm (P) or Term (T)	Patient #	Maximum maternal TSB value (mg/dL)	Mean/Median maternal TSB values over last 4 weeks (mg/dL)	Maternal TSB at Birth	Infant's first TSB (Time in hours) Percentile Level based on data for term infants and on age in hours*	Infant Course/ Comments
300 mg	P	1022	3.9	3.4/3.6	3.6	4.3 (24.8) <40%	Uneventful
	T	1009	4.1	2.7/2.9	4.1	10.2 (70.8) <40%	TSB 3.0 mg/dL at DOL: 13 (LRV)
		1018	5.8	4.1/4.3	5.7	7.6 (1.5) >>95%	TSB 1.3 mg/dL at DOL: 13, then WNL.
400 mg	P	1032	4.5	2.8/2.9	3.8	4.4 (4.2) >95%	TSB 3.4 mg/dL at DOL: 13, then WNL.
		1050	6.4	3.9/4.4	0.6	3.2 (1.8) >95%	TSB 2.3 mg/dL at DOL: 15 (>1.5-2.5X ULN), then WNL.
		1054	3.8	2.7/2.8	2.7	4.4 (0) >95%	Received PT. TSB 11.4 mg/dL at DOL: 6, 8.5 mg/dL DOL 17 >5X ULN) (LRV).
	T	1043	4.1	1.5/1.2	3.5	2 (5.9) <95%	TSB elevated to within 1 mg/dL of the PT threshold. Patient received PT. Remainder of course uneventful with LRV WNL.
		1064	6.0	4.3/5.0	5.0	6.2 (0.7) >95%	Uneventful

*Percentile Based on Age: Normative data for bilirubin levels in patients less than 24 hours of age are based on data from Bhutani et al[4]. Data are available identifying the 40%, 75% and 95% TSB level for age in hours for term or near term healthy infants 12 hours of age and older. Newman et al, assuming a linear increase in the 95% for TSB levels from birth (2 mg/dL) to 24 hours (8 mg/dL), provide the approximate 95% bilirubin levels for term infants from birth to 24 hours[25].

DOL= Day of Life
LRV = Last Reported Value
WNL = Within Normal Limits

Infants 1018 (300 mg ATV cohort) and 1064 (400 mg ATV cohort), term infants born to mothers with bilirubin levels 5 mg/dL or greater at birth, reported bilirubin levels greater than the 95% for age in hours within the first 24 hours of life. Infant 1018's TSB was greater than the PT threshold and infant 1064's TSB was approximately 1 mg/dL below

the PT threshold. However, these infants did not receive PT and their hyperbilirubinemia resolved without complications.

Three additional infants of mothers with TSB levels greater than 3 mg/dL and less than 5 mg/dL, preterm infants in the 400 mg ATV exposure cohort, had bilirubin levels >95% for age in hours within the first 24 hours of life, i.e., infants 1032, 1050 and 1054. Infant 1032 had TSB of 3.4 mg/dL on DOL 13 and normal TSB levels on study days 41 and 130. Infant 1050 had a TSB 1.5-2.5X ULN for a term infant at DOL 15 and a normal TSB level on study day 43. Infant 1054 received PT and had a last reported bilirubin value of 8.5 mg/dL (>5X ULN) on DOL 17. Given that these patients were premature and normative data do not appear to be available for premature infants, the level of hyperbilirubinemia in the first 24 hours is difficult to interpret. In addition, although infant 1054 had an abnormal bilirubin level on DOL 17, the TSB levels of infants 1032 and 1050 on DOL 13 and DOL 15, respectively, may not be elevated.

Two infants of mothers with TSB levels greater than 3 mg/dL and less than 5 mg/dL (patients 1009 and 1022) did not have bilirubin levels drawn within the first 24 hours of life and although resolution of hyperbilirubinemia was not documented in infant 1009, the course of hyperbilirubinemia for both infants appears unremarkable.

The remaining infant (patient 1043), a term infant in the 400 mg exposure cohort did not have a bilirubin level greater than the 95% at birth. The infant's TSB reached within 1 mg/dL of the PT threshold, the infant received PT and the bilirubinemia resolved. This infant's mother's bilirubin was 3.5 mg/dL at birth, maximum bilirubin during pregnancy was 4.1 mg/dL and the mother's mean and median bilirubin levels during the last 4 weeks of pregnancy were 1.5 mg/dL and 1.2 mg/dL, respectively, which may suggest that the infant did not have prolonged exposure to maternal TSB values greater than 3 mg/dL.

In summary, bilirubin data from the first 24 hours of life are available for six of eight infants of mothers with TSB levels greater than 3 mg/dL at some point during pregnancy. Of these six patients, five had a bilirubin greater than the 95% for age in hours for term infants in the first day of life based on the interpretation of normative data from term infants used by Newman et al (of note, using this method, 31 infants, 77.5% of study infants, were identified as having a TSB level greater than the 95% for age in the first 24 hours of life[25], more below). Four of five infants were in the 400 mg exposure cohort and three of five were premature. None of the patients had complicated courses. Of particular interest, the infants born to mothers with TSB levels 5 mg/dL or greater at birth who also had TSB levels 5 mg/dL or greater within the first 24 hours of life had uneventful resolution of the bilirubinemia without intervention. While there is a theoretical concern that maternal ATV in the infant circulation could inhibit UGT1A1 enzyme activity, it is also possible that chronic elevated unconjugated bilirubin may somehow protect the fetus/neonate through stimulation of fetal UGT1A1 activity or through another placental or fetal mechanism. Based on the relatively small sample size, incomplete data collection, incomplete information about potential confounding factors such as ABO blood group incompatibility and the paucity of normative data on bilirubin levels in the first 24 hours of life in term and preterm infants, determining whether a

correlation exists between maternal and infant serum total bilirubin levels at birth does not appear possible.

Infant Bilirubin Levels:
The Sponsor concluded that the bilirubin elevations were most likely physiologic and reported that jaundice occurred in 20/40 patients (50%). Per the Sponsor, increased total bilirubin was the only Grade 3 to Grade 4 liver function abnormality and observed in 7 of 40 infants (3 infants whose mothers were on ATV/RTV 300/100 mg and 4 infants whose mothers were on ATV/RTV 400/100 mg). Six of 40 infants had phototherapy (PT) performed and two patients, 8-1027 and 4-1043, had an SAE of hyperbilirubinemia or jaundice reported.

1. Incidence of Hyperbilirubinemia in Neonates:
To evaluate the incidence of hyperbilirubinemia in the study patients, the pediatric reviewer plotted the highest bilirubin level obtained at 12 hours of age or older for each patient on the Nomogram to Assess the Risk of Developing Severe Hyperbilirubinemia which provides the normative serum bilirubin values for healthy term and near term infants as determined by Bhutani et al (see Appendix II)[4].

Table 2: Number of Infants per Risk Zone per the Bhutani Nomogram to Assess Risk of Developing Severe Hyperbilirubinemia

Risk Zone	**Number of patients** (% total n=40)	**300 mg** (% total n=20)	**400 mg** (% total n=20)
Low Risk bilirubin level (0-<40%)*	21 (52.5)	12 (60)	9 (45)
Low Intermediate Risk (40-<75%)*	11 (27.5)	2 (10)	9 (45)
High Intermediate Risk (75-<95%)*	5 (12.5)	5 (25)	0
High Risk (≥ 95%)*	3 (7.5)	1 (5)	2 (10)

Note: The percentile ranking is based on age in hours

Reviewer Comment:
The distribution of the data appear to indicate that study infants did not have a markedly increased incidence and severity of hyperbilirubinemia than would be expected based on normative data from Bhutani et al[4]. Of note, of the three patients categorized as High Risk for developing severe hyperbilirubinemia, only one patient met the criteria established by the AAP for the initiation of PT based on gestational age and hour-specific bilirubin measurement (patient 8-1027) and two of the patients received phototherapy (patients 8-1027 and 4-1043). The patients who received phototherapy were those for which hyperbilirubinemia was reported as an SAE.

2. Incidence of Hyperbilirubinemia in the First 24 Hours of Life:
As noted earlier, jaundice appearing in the first 24 hours of life is generally of concern[1,2,25,30], and is considered a risk factor for the development of severe hyperbilirubinemia[1]. Newman et al concluded from a retrospective review of over 700 newborns that jaundice at less than 24 hours was uncommon, occurring in only 6.7% of newborns[25]. Normative data from Bhutani et al are available to identify the 40%, 75% and 95% TSB level for age in hours for term or near term healthy infants 12 hours of age and older[4]; however, normative data do not appear to be available for preterm infants or patients less than 12 hours of age. Hence, Newman et al assumed a linear increase in the 95% for TSB levels from birth (2 mg/dL) to 24 hours (8 mg/dL) to provide the approximate 95% TSB levels for term infants from birth to 24 hours[25].

To estimate the incidence of severe bilirubinemia in the first 24 hours of life, the line used by Newman et al to identify infants with bilirubin levels greater than the 95% was used:

Table 3: Incidence of Hyperbilirubinemia within the first 24 hours based on normative data from term or near term healthy infants:

	Dosing Exposure Cohort	Preterm	Term
No bilirubin level in the first 24 hours	300 mg	1	1
	400 mg	0	2
Bilirubin level <95% for age in hours	300 mg	2	1
	400 mg	1	1
Bilirubin level >95% for age in hours	300 mg	6	9
	400 mg	9	7

Reviewer Comment:
Using the line developed by Newman et al to identify infants with bilirubin levels greater than the 95% for age in hours identified 31 infants (77.5% of study patients) as having a TSB level greater than the 95% for age in the first 24 hours of life. However, this method of determining the 95% TSB for age in hours relies on the assumption that the rise in bilirubin is linear, and plotting the data on the graph provided by Newman et al may be prone to some degree of inaccuracy due to the small scale of the graph. In addition, the line developed by Newman et al is based on normative data from term infants, and therefore may not be relevant to preterm infants.

Ten infants (25% of study patients) 4 in the 300 mg exposure cohort and 6 in the 400 mg exposure cohort (4 premature and 6 term), were identified with bilirubin levels 4 mg/dL or greater within the first day of life. Six infants (15% of study patients), 3 in each study exposure cohort (2 premature and 1 term), were identified with bilirubin levels of 5 mg/dL in the first 24 hours of life (see Appendix VI: Infants with TSB greater than 4 mg/dL in the first 24 hours of life). When plotted on the line used by Newman et al to identify infants with bilirubin levels greater than the 95%, all 6 infants with bilirubin

levels greater than 5mg/dL within the first 24 hours of life had TSB levels greater than the 95%.

Reviewer Comment:
Although the data may suggest that the presence of hyperbilirubinemia may be increased in the first 24 hours, none of the patients had bilirubin related complications and few qualified for phototherapy (see below). Hence, the implications of these findings are unclear. Given that the interpretation of TSB levels is based upon age in hours and other clinical and epidemiologic factors[19], the reviewers defer to the Division to determine if including the number of patients with TSB levels greater than 4 mg/dL or 5 mg/dL in the first 24 hours of life would be helpful information for providers and therefore should be included in labeling.

3. Incidence of Hyperbilirubinemia Potentially Requiring Treatment in Neonates:
As discussed above, the threshold for the initiation of PT as recommended by the AAP is based on gestational age and additional risk factors that may put an infant at higher risk for bilirubin toxicity, such as isoimmune hemolytic disease and systemic illness. Although information was not provided regarding maternal or infant blood type, or direct antiglobulin testing, i.e. Coombs testing, no concerns or signs/symptoms of isoimmune hemolytic disease appear to be documented for any patient. Review of the final clinical study report data did not identify additional risk factors for the development of severe hyperbilirubinemia, such as cephalohematoma or significant bruising, or identify that patients were considered at higher risk for bilirubin toxicity secondary to conditions such as low albumin or sepsis.

Reviewer comment:
Data on maternal and infant blood type, and Coombs testing would have provided important information on the contribution of hemolysis to any elevated bilirubin levels in the infants.

To evaluate the severity of the hyperbilirubinemia in exposed infants, the pediatric reviewer plotted the bilirubin levels for each patient on the nomogram developed by the AAP as a guideline for the initiation of phototherapy (Appendix III). In the cohort exposed to 300 mg ATV and 400 mg ATV, the bilirubin levels remained 2 mg/dL or more below the phototherapy (PT) threshold in 17/20 (85%) and 9/20 (45%) patients, respectively. Two patients in the 300 mg ATV exposed cohort exceeded the PT threshold compared to no patients in the 400 mg ATV exposure cohort; however, 4 patients in the 400 mg ATV exposed cohort came within 1 mg/dL of the PT threshold compared to no patients in the 300 mg ATV exposed cohort:

Table 4: Location of the Infants on the Nomogram for the Guideline for the Initiation of Phototherapy

Dosing Exposure Cohort	Number of patients that surpassed the PT threshold	Number of patients that were within 1 mg/dL of the PT threshold	Number of patients within 1-2 mg/dL of the PT threshold	Number of patients 2 mg/dL or more below the PT threshold.
300 mg ATV	2	0	1	17
400 mg ATV	0	4	7	9

Reviewer Comment:
The patients in the 400 mg ATV exposure group appear to have had TSB levels that were closer to the threshold identified for the initiation of PT. Hence, patients in the 400 mg ATV dosing exposure cohort may have a slightly increased incidence and severity of hyperbilirubinemia compared to the 300 mg exposure cohort.

4. Phototherapy (PT):
As noted by the Sponsor, six patients received phototherapy, three patients from each dosing exposure cohort. All patients were identified as Black/African American. Five patients were treated at a South African site and one patient was treated at the Puerto Rico site.

Reviewer Comment:
The courses of the patients that received PT do not appear to be remarkable, and no patient developed severe hyperbilirubinemia. Although two patients, 8-1027 (35.6 week gestation, 300 mg ATV exposure cohort) and 12-1054 (35 week, 400 mg ATV exposure cohort), met the PT threshold established by the AAP, the other 4 patients do not appear to have met the "strict" threshold level based on the available data. However, the Guideline notes that PT may be initiated at TSB levels 2-3 mg/dL below the recommended threshold level, and these 4 patients met the less stringent criteria. Three of the four patients had an uneventful course, though complete resolution of hyperbilirubinemia was not documented in a 37.7 week, 400 mg ATV exposure cohort patient (12-1044), i.e. last TSB level was 8 mg/dL at day of life 7. Patient 12-1025, a term infant in the 300 mg ATV exposure cohort, may have had a more prolonged course than expected. Despite PT, the patient's serum bilirubin level peaked on day of life 6 (15.3 mg/dL), and on day of life 14, the level remained 4.6 mg/dL or 2.6-5X the upper limit of normal. TSB level was normal on study day 46 (more below). Although some patients may have been managed more conservatively than the AAP Guideline recommends, the variability in management of hyperbilirubinemia is unlikely to have affected the interpretability of the results.

Prolonged Jaundice:
Per the Sponsor, in the third week of life (15-18 days), three of 20 infants (15%) born to women treated with REYATAZ/ritonavir 300/100 mg and four of 20 infants (20%) born to women treated with REYATAZ/ritonavir 400/100 mg experienced Grade 3–4 bilirubin toxicity (>3 mg/dL). As discussed above, physiologic jaundice generally resolves in the first 2- 3 weeks of life to normal values of less than 1.2 mg/dL[27]. Causes of prolonged

jaundice include hemolytic disease, breast milk jaundice, prematurity, Gilbert syndrome. Crigler-Najjar syndrome, bowel obstruction, congenital hypothyroidism and galactosemia[11,14].

Reviewer Comment:
ATV drug concentrations in cord blood were approximately 12-19% of maternal concentrations, and ATV clearance is expected in the first few days of life based on the half life of ATV in adult patients. Therefore, prolonged UGT1A1 suppression or prolonged hyperbilirubinemia secondary to ATV would not be anticipated (per Dr. Zheng, the clinical pharmacology reviewer); however, initial scan of the infant bilirubin data at time points 14 days and greater appeared to identify elevated levels. Consequently, the number of infants with elevated bilirubin levels at age 14 days was examined:

Table 5: Infants with elevated bilirubin measurements at age 14 days or older (Normal bilirubin considered 1.2 mg/dL)

Patient Age (Day of Life)	Dosing Exposure Cohort	TSB level >1.5- 2.5 x ULN (>1.92-3.12 mg/dL)		TSB level > 2.5 - 5 x ULN (>3.12-6 mg/dL)		TSB level >5 x ULN (>6.0 mg/dL)		Total number of patients with TSB > 1.5 x ULN per cohort	Total number of patients with TSB > 1.5 x ULN
		Preterm	Term	Preterm	Term	Preterm	Term		
≥14-21 days	300 mg	-	-	-	1008, 1025	1027	-	3	9
	400 mg	1050, 1055,	-	1049	1065	1054*	1067	6	
> 21 days	300 mg	-	-	1027	-	-	-	1	1
	400 mg	-	-	-	-	-	-	0	
> 42 days	300 mg	-	-	1027	-	-	-	1	4
	400 mg	1056, 1068	1067	-	-	-	-	3	

Note: Patient 12-1054 had a bilirubin level of 8.5 mg/dL at day of life 17 and did not have further TSB levels reported.

Reviewer Comment:
Given that hyperbilirubinemia usually resolves within the first 2-3 weeks of life, the patients with elevated TSB levels after 21 days are of interest. Four patients had an elevated TSB 1.5 X ULN at a time point greater than 42 days of age (See Appendix VII: Bilirubin values in patients with elevated bilirubin levels at greater than 42 days).

Three patients were premature, three patients were in the 400 mg exposure cohort and only one had a documented return of TSB to normal. Although two patients were treated with trimethoprim sulfamethoxazole (SMX/TMP), the medication was started on the day the bilirubin level was performed (for patient 1027, November 27, 2007) or after the bilirubin level was evaluated (for patient 1056, bilirubin was assessed on October 27, 2008 and SMX/TMP treatment started on November 3, 2008). Maternal bilirubin levels

were unremarkable in all 4 patients, i.e. maximum maternal TSB value of the four patients was 2.5 mg/dL and the range of mean and median maternal bilirubin values were 0.7-1.9 mg/dL and 0.8-2.1 mg/dL.

Although premature infants may have a more protracted course of hyperbilirubinemia and normative data are not available, elevated bilirubin levels at 6-7 weeks of age appears unusual, and the reason for elevated bilirubin levels at this time point is unclear to the PMHS reviewers. Although low levels of unconjugated bilirubin levels are unlikely to have clinical significance, data are not available to assess the safety of a prolonged course of hyperbilirubinemia and hence a longer period of exposure to low levels of unconjugated bilirubin in infants.

Consult Questions:

1) Do neonates with in utero exposure to ATV have a higher incidence of neonatal hyperbilirubinemia as compared to healthy neonates? If yes, does the increased incidence and/or degree of neonatal hyperbilirubinemia place the ATV exposed neonates at higher risk of bilirubin related complications?

In the small group of study patients exposed to ATV when compared to the normative data of the incidence of hyperbilirubinemia in term infants from Bhutani et al[4] and analyzed based on the Guideline from the AAP on TSB levels for which phototherapy is recommended[1], the data suggest that study infants do not experience an increased incidence or degree of neonatal hyperbilirubinemia compared to healthy infants. The cumulative data from the 400 mg exposure dosing cohort (n=20) may suggest that these patients may have a slightly increased incidence and severity of hyperbilirubinemia compared to the 300 mg exposure cohort, but the data are inconclusive.

Study infants did not develop severe hyperbilirubinemia and were managed without complication; however, the study population excluded mothers more likely to have an infant at risk for the development of severe hyperbilirubinemia. In addition, the vast majority of patients (greater than 80%) were identified as Black/African American, a race with half the incidence of hyperbilirubinemia compared to Caucasians and a quarter of the incidence compared to Asians[23]. Therefore, the study data are not likely to be applicable to the general population of infants that may be exposed to ATV.

The study data and the literature raise the question whether infants of mothers treated with ATV could be at risk for the development of more severe hyperbilirubinemia secondary to two factors: the risk of an increased bilirubin load and/or the risk of decreased bilirubin clearance. As noted in the literature, passive placental transfer of unconjugated bilirubin to the fetus appears to occur at higher maternal bilirubin levels although a threshold level has not been identified. Hence, if an infant born to a mother treated with ATV develops hemolysis and/or has a condition that results in an increased red blood cell load, such as significant bruising or cephalohematoma, the combination of both increased unconjugated bilirubin from transplacental acquisition and from increased production as well as decreased bilirubin clearance secondary to UGT1A1

inhibition could hypothetically result in more severe and/or prolonged hyperbilirubinemia. Data are insufficient to determine whether prolonged low levels of hyperbilirubinemia either in-utero or during the neonatal period result in adverse effects.

In summary, ATV exposed infants in the study did not appear to have a markedly increased incidence and/or degree of neonatal hyperbilirubinemia in the first week of life compared to otherwise healthy infants. Depending on other factors that contribute to hyperbilirubinemia in the neonatal period, e.g. ABO blood incompatibility or bruising, in- utero exposure to ATV could potentially increase the incidence of clinically significant neonatal jaundice. Given the small number of study patients, and the fact that the study population is likely not representative of the general population in the United States, data are insufficient to conclude whether in-utero exposure to ATV increases the risk of bilirubin-related complications in exposed neonates. However, given the rare occurrence of acute or chronic bilirubin encephalopathy, if exposed infants are carefully monitored and managed in a facility able to perform phototherapy and exchange transfusions, the risk of developing acute bilirubin encephalopathy is likely to remain low even if ATV exposed infants are at increased risk of hyperbilirubinemia.

2) Is increased monitoring of bilirubin for exposed infants needed who do not have any obvious risk factors for neonatal hyperbilirubinemia (e.g. Coombs positive)?

The available data are inconclusive but appear to suggest that infants exposed in utero to ATV do not have severe hyperbilirubinemia. The AAP recommends universal systematic assessment for the risk of severe hyperbilirubinemia, close follow-up and prompt intervention when indicated.[1] Therefore, routine monitoring for the development of severe hyperbilirubinemia during the first few days of life appears to be reasonable for infants born to mothers taking ATV.

3) Given the small sample size (approx 41 infants total) and the incomplete data collection, do we need more data to further define the risk of neonatal hyperbilirubinemia in ATV exposed neonates?

Given the small sample size, limitations of the data, including incomplete data collection, the lack of infant ATV PK data and the complexity of bilirubin metabolism in utero and in the neonate, the available data are not adequate to fully characterize or define the risk of neonatal hyperbilirubinemia in all ATV exposed neonates. However, review of the data did not identify a safety signal.

Additional information to better characterize ATV's potential to inhibit UGT1A1 in the fetus and neonate and to evaluate the effect of elevated maternal unconjugated bilirubin levels on the fetus and the neonate, may be helpful to determine if ATV exposed neonates, especially those with additional risk factors for the development of severe hyperbilirubinemia, are at risk for the development of complications related to hyperbilirubinemia, including neurologic sequelae.

A prospective cohort study or clinical trial in pregnant HIV positive women exposed to ATV compared to pregnant HIV positive women not exposed to ATV, to assess and compare serum bilirubin levels in pregnant mothers and neonates at pre-specified time points, including birth, and to assess the time of resolution of hyperbilirubinemia in infants, could potentially answer some of the clinical uncertainties. However, per discussions with the clinical reviewers, this type of study may not be feasible due to limited use of ATV in pregnant women. In addition, the paucity of normative data in infants may limit the ability to interpret study results. Although additional information regarding the neurodevelopmental outcome of infants exposed to ATV in utero may be helpful, given the rare occurrence of acute and chronic bilirubin encephalopathy, the unknown effects of low levels of prolonged hyperbilirubinemia in children and the inherent difficulties in collecting long-term neurodevelopmental data, an additional clinical study to assess for adverse neurological outcomes in ATV exposed infants is unlikely to provide additional clinically useful information.

Data obtained from further review of the literature and/or the performance of additional nonclinical studies are unlikely to be able to provide information to better understand the risks associated with in utero exposure of infants born to mothers treated with ATV.

In summary, although the available data are not adequate to fully characterize the risk of in utero ATV exposure in neonates, no documented safety issue exists to justify a postmarketing requirement for an additional clinical study at this time, and additional nonclinical studies and literature review are unlikely to provide additional informative information..

4) Are there other comments or recommendations that PMHS/Pediatrics has for managing the risk(s) of *in utero* exposure to ATV?

None at this time.

SPONSOR'S PROPOSED LABELING CHANGES

1. Dosing recommendations based on S-025 PK Data

Based on PK data in HIV infected pregnant women, the sponsor is proposing adding a statement that says that (b) (4).

Reviewer comment

FDA Pharmacologists' review of the PK data however, are slightly different than the sponsor's interpretation in that they are recommending increasing the atazanavir dose to 400mg + 100 mg ritonavir during the second and third trimester in treatment – experienced patients when given with tenofovir or an H_2-receptor antagonist. There are also insufficient data to recommend a dose for use with tenofovir and H_2-receptor antagonists in treatment-experienced pregnant women. Please see the review of Dr. Jenny Zheng.

2. Addition of New Pregnancy Safety Data

I. Antiretroviral Pregnancy Registry Results

The Antiretroviral Pregnancy Registry interim report published May 2010 covers data from January 1989 to January 31, 2010. The purpose of the Antiretroviral Pregnancy Registry is to detect any major teratogenic effects of antiretroviral drugs to which pregnant women are exposed. Enrollment in the Registry is voluntary. Among first trimester exposure to atazanavir, there are sufficient numbers of first trimester exposures have been monitored to detect at least a two-fold increase in risk of overall birth defects. No such increases have been detected to date.

Reviewer comment
Addition of this information is appropriate.

II. Safety Data from S-025

The sponsor proposes adding safety data from S-025 regarding maternal and neonatal hyperbilirubinemia, maternal lactic acidosis, neonatal jaundice and need for phototherapy.

Reviewer comment
PMHS is working in collaboration with the Division to develop language that accurately reflect the study findings

III. Post-Marketing Data

The sponsor proposes [redacted] (b) (4)

Reviewer comment
The sponsor has been notified that they need to identify which cases are also included in the Antiretroviral Pregnancy Registry data to avoid duplication.

3. Pregnancy Labeling in the format of the Draft Pregnancy and Lactation Labeling Rule

The sponsor's proposed labeling is in the format of the Draft Pregnancy and Lactation Labeling Rule with the following 3 subsections: Fetal Risk Summary, Clinical Considerations, and Data.

Reviewer comment
Although the final rule has not been published, PMHS encourages sponsors to adopt this format, which includes narrative descriptions of the data, while still complying with the current regulations.

Provided below are revisions to the sponsor's proposed labeling that were agreed upon at the labeling meeting with the DAVP on January 5th, 2011.

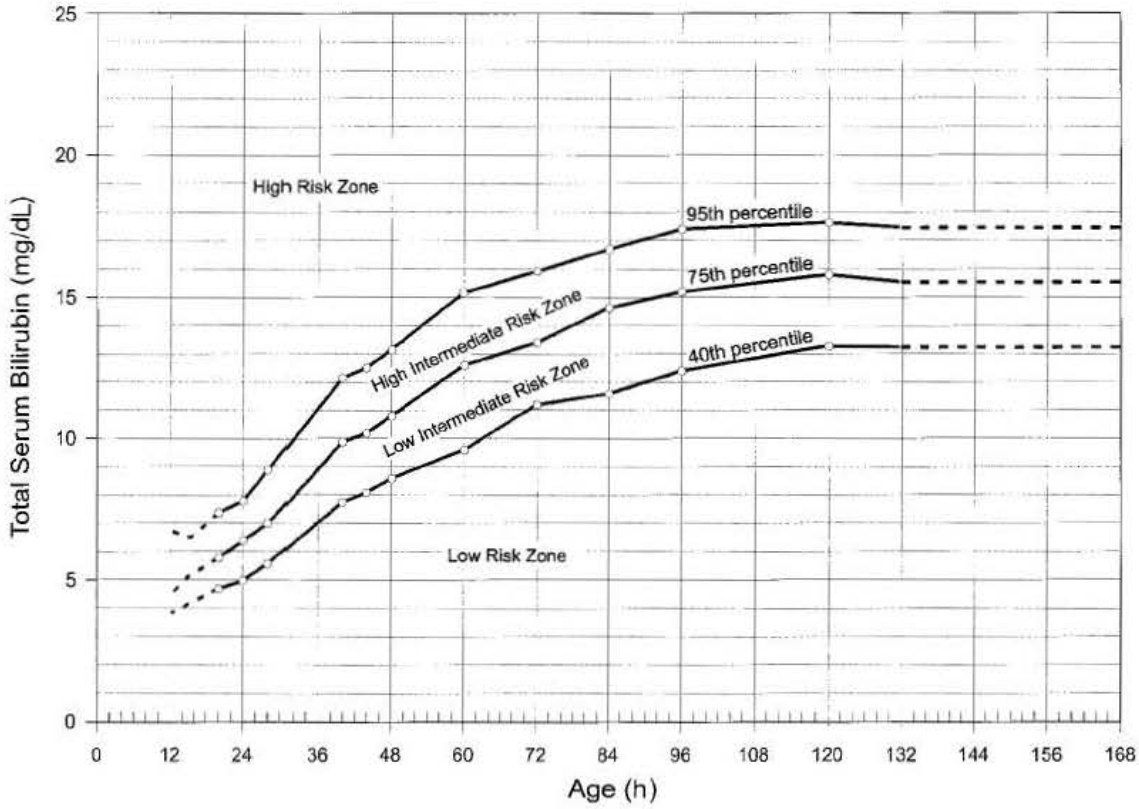
4 Page(s) of Draft Labeling has been Withheld in Full as b4 (CCI/TS) immediately following this page

Appendix I: Risk Factors for Development of Severe Hyperbilirubinemia in Infants of 35 or More Weeks' Gestation (in Approximate Order of Importance) AAP 2004 guidelines

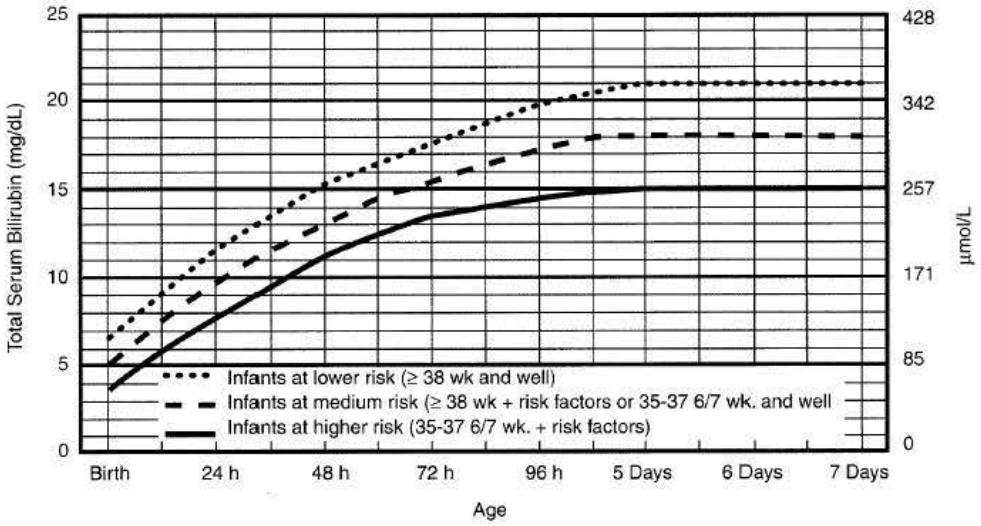
Major risk factors
Predischarge TSB or TcB level in the high-risk zone (Fig 2)[25,31]
Jaundice observed in the first 24 h[30]
Blood group incompatibility with positive direct antiglobulin test, other known hemolytic disease (eg, G6PD deficiency), elevated $ETCO_c$
Gestational age 35–36 wk[39,40]
Previous sibling received phototherapy[40,41]
Cephalohematoma or significant bruising[39]
Exclusive breastfeeding, particularly if nursing is not going well and weight loss is excessive[39,40]
East Asian race[39*]
Minor risk factors
Predischarge TSB or TcB level in the high intermediate-risk zone[25,31]
Gestational age 37–38 wk[39,40]
Jaundice observed before discharge[40]
Previous sibling with jaundice[40,41]
Macrosomic infant of a diabetic mother[42,43]
Maternal age ≥25 y[39]
Male gender[39,40]
Decreased risk (these factors are associated with decreased risk of significant jaundice, listed in order of decreasing importance)
TSB or TcB level in the low-risk zone (Fig 2)[25,31]
Gestational age ≥41 wk[39]
Exclusive bottle feeding[39,40]
Black race[38*]
Discharge from hospital after 72 h[40,44]

* Race as defined by mother's description.

Appendix II: Risk designation of term and near-term well newborns based on their hour-specific serum bilirubin values[4]



Appendix III: Guidelines for phototherapy in hospitalized infants of 35 or more weeks' gestation[1].



- Use total bilirubin. Do not subtract direct reacting or conjugated bilirubin.
- Risk factors = isoimmune hemolytic disease, G6PD deficiency, asphyxia, significant lethargy, temperature instability, sepsis, acidosis, or albumin < 3.0g/dL (if measured)
- For well infants 35-37 6/7 wk can adjust TSB levels for intervention around the medium risk line. It is an option to intervene at lower TSB levels for infants closer to 35 wks and at higher TSB levels for those closer to 37 6/7 wk.
- It is an option to provide conventional phototherapy in hospital or at home at TSB levels 2-3 mg/dL (35-50mmol/L) below those shown but home phototherapy should not be used in any infant with risk factors.

Appendix IV: Grading of Maternal and Infant Adverse Events

WHO Recommendations for Grading Acute and Subacute Toxic Effects:

ITEM	GRADE 1 TOXICITY	GRADE 2 TOXICITY	GRADE 3 TOXICITY	GRADE 4 TOXICITY
BILIRUBIN	1.1 - 1.5 x upper normal	1.6 - 2.5 X upper normal	2.6 - 5 X upper normal	> 5 X upper normal

Division of Aids Toxicity Table for Grading Severity of Pediatric Adverse Experiences:

PARAMETER	GRADE 1 Mild	GRADE 2 Moderate	GRADE 3 Severe	GRADE 4 Potentially Life-Threatening
Bilirubin (Total)				
Pediatric > 14 days	1.1 - 1.5 x ULN	1.6 - 2.5 x ULN	2.6 - 5.0 x ULN	> 5.0 x ULN
Infant ≤ 14 days (non-hemolytic)	NA	20.0 - 25.0 mg/dL *342 - 428 µmol/L*	25.1 - 30.0 mg/dL *429 - 513 µmol/L*	> 30.0 mg/dL *> 513.0 µmol/L*
Infant ≤ 14 days (hemolytic)	NA	NA	20.0 - 25.0 mg/dL *342 - 428 µmol/L*	> 25.0 mg/dL > 428 µmol/L

Appendix V: Demographics and Disease Characteristics of Enrolled Infants

	NUMBER OF SUBJECTS (%)	
	Mothers 3rd Trimester Treatment	
	ATV300/RTV N = 20	ATV400/RTV N = 20
Gest. Age @ Delivery (Weeks)		
MEAN (SE)	38 (0.3)	38 (0.3)
MEDIAN	38	38
MIN, MAX	35, 40	35, 41
MISSING	0	0
Gender: N (%)		
MALE	12 (60)	9 (45)
FEMALE	8 (40)	11 (55)
Race: N (%)		
BLACK/AFRICAN AMERICAN	15 (75)	18 (90)
WHITE	5 (25)	1 (5)
OTHER: MIXED RACE	0	1 (5)
Region: N (%)		
AFRICA	14 (70)	14 (70)
NORTH AMERICA	6 (30)	6 (30)

Percentages are based on subjects with measurements.

Appendix VI: Infants with TSB greater than 4 mg/dL in the first 24 hours of life

Note:
Mother's mean and median maternal bilirubin levels refer to the mean and median of the values during the last 4 weeks of pregnancy.

Infants with an asterisk after the patient identification number also developed a bilirubin level greater than 5 mg/dL within the first 24 hours of life

<u>In Utero Exposure ATV 300 mg/RTV 100 mg</u>:

5-1034* (39.3 weeks gestation)
No intervention.
Mother's bilirubin (mg/dL): Birth 0.5, Mean: 0.8, Median:0.9

Subject ID	Birth Date	Birth Time	Study Day	Age (in hours)	Lab Date	Lab Time	Total Bilirubin (mg/dL)
AI424182-5-1034	(b) (6)		2	9.8	(b) (6)	9:30	5.4
			3	36.8		12:30	10.6
			5	85.3		13:00	12.1
			7	132.7		12:25	10.4
			14	300.3		12:00	3.2
			47	1090.5		10:15	0.4

8-1018* (38.3 weeks gestation)
Met AAP PT Threshold at 1.5 hours. No intervention.
Mother's bilirubin: Birth 5.7, Mean: 4.1, Median:4.3

Subject ID	Birth Date	Birth Time	Study Day	Age (in hours)	Lab Date	Lab Time	Total Bilirubin (mg/dL)
AI424182-8-1018	(b) (6)		1	1.5	(b) (6)	2:30	7.6
			3	59.9		12:56	13.5
			7	152.3		9:20	6.4
			13	298.6		11:38	1.3
			41	971.0		12:00	0.2
			125	2988.0		13:00	0.1

8-1027* (35.6 weeks gestation)
Received phototherapy
Mother's bilirubin (mg/dL): Birth 2.3, Mean 1.9, Median 2.1

Subject ID	Birth Date	Birth Time	Study Day	Age (in hours)	Lab Date	Lab Time	Total Bilirubin (mg/dL)
AI424182-8-1027	(b) (6)		1	0.3	(b) (6)	15:40	5.7
			3	46.6		14:00	13.0
			5	91.3		10:43	9.9
			7	137.5		8:55	9.8
			16	353.6		9:00	8.3
			44	1027.9		11:20	3.3

12-1025 (38.1 weeks gestation)
Received phototherapy
Mother's bilirubin (mg/dL): Birth: 1.2, Mean: 1.4, Median 1.4

Subject ID	Birth Date	Birth Time	Study Day	Age (in hours)	Lab Date	Lab Time	Total Bilirubin (mg/dL)
AI424182-12-1025	(b) (6)		1	5.8	(b) (6)	8:45	4.7
			3	54.9		9:50	12.2
			5	102.5		9:30	13.2
			7	151.5		10:30	15.3
			15	347.0		14:00	4.6
			46	1089.5		12:30	0.8

<u>In Utero Exposure ATV 400 mg/RTV 100 mg</u>:

4-1032 (36 weeks gestation)

No intervention

Mother's bilirubin (mg/dL): Birth 3.8, Mean 2.8, Median 2.9

Subject ID	Birth Date	Birth Time	Study Day	Age (in hours)	Lab Date	Lab Time	Total Bilirubin (mg/dL)
AI424182-4-1032	(b) (6)		1	4.2	(b) (6)	21:19	4.4
			4	64.0		9:10	8.9
			5	92.0		13:05	10.0
			7	136.7		9:50	8.1
			14	305.5		10:40	3.4
			41	953.1		10:15	0.5
			130	3088.7		9:50	0.1

5-1040 (38.4 weeks gestation)

No intervention

Mother's bilirubin (mg/dL): Birth 2.7, Mean 1.2, Median 1.0

Subject ID	Birth Date	Birth Time	Study Day	Age (in hours)	Lab Date	Lab Time	Total Bilirubin (mg/dL)
AI424182-5-1040	(b) (6)		1	0.2	(b) (6)	23:45	4.6
			4	57.4		9:00	7.0
			6	106.4		10:00	2.8
			8	155.9		11:30	1.6
			15	322.9		10:30	0.8
			18	398.4		13:58	0.6
			43	997.9		13:30	0.4

5-1041* (39.1 weeks gestation)

No intervention

Mother's bilirubin (mg/dL): Birth 1.9, Mean 1.4, Median 1.7

Subject ID	Birth Date	Birth Time	Study Day	Age (in hours)	Lab Date	Lab Time	Total Bilirubin (mg/dL)
AI424182-5-1041	(b) (6)		2	17.3	(b) (6)	9:00	8.0
			4	64.8		8:35	5.4
			6	114.6		10:20	2.1
			8	165.9		13:40	1.2
			15	334.0		13:45	0.5
			43	1006.5		14:15	0.2

5-1064* (41.3 weeks gestation)

No intervention

Mother's bilirubin (mg/dL): Birth 5.0, Mean 4.3, Median 5.0

Subject ID	Birth Date	Birth Time	Study Day	Age (in hours)	Lab Date	Lab Time	Total Bilirubin (mg/dL)
AI424182-5-1064	(b) (6)		1	0.7	(b) (6)	13:40	6.2
			3	44.0		9:00	9.3

AI424182-5-1064	(b) (6)	5	92.7	(b) (6)	9:43	3.5
		7	139.6		8:35	2.0
		15	334.5		11:30	0.6
		43	1007.6		12:35	0.4

12-1054 (35 weeks gestation)

Received phototherapy

Mother's bilirubin (mg/dL): Birth 2.7, Mean 2.7, Median 2.8

Subject ID	Birth Date	Birth Time	Study Day	Age (in hours)	Lab Date	Lab Time	Total Bilirubin (mg/dL)
AI424182-12-1054	(b) (6)		1	0.0	(b) (6)	12:42	4.4
			3	49.3		14:00	9.6
			5	93.5		10:10	8.8
			7	140.3		9:00	11.4
			18	410.6		15:15	8.5

14-1049* (37.6 weeks gestation)

No intervention

Mother's bilirubin (mg/dL): Birth 2.3, Mean 1.9, Median 2.3

Subject ID	Birth Date	Birth Time	Study Day	Age (in hours)	Lab Date	Lab Time	Total Bilirubin (mg/dL)
AI424182-14-1049	(b) (6)	7:20	1	3.5	(b) (6)	10:49	4.1
				8.0		15:20	5.1
			3	46.5		5:52	10.4
				59.0		18:17	10.8
			5	98.6		9:55	10.6
			7	147.5		10:50	9.3
			15	339.0		10:17	3.6
			43	1014.2		13:30	0.7

Appendix VII: Bilirubin values in patients with elevated bilirubin levels at greater than 42 days

In Utero Exposure ATV 300 mg/RTV 100 mg:

8-1027 (35.6 weeks gestation)

Received phototherapy

Mother's bilirubin (mg/dL): Birth 2.3, Mean 1.9, Median 2.1

TMP/SMZ started (b) (6)

Subject ID	Birth Date	Birth Time	Study Day	Age (in hours)	Lab Date	Lab Time	Total Bilirubin (mg/dL)
AI424182-8-1027	(b) (6)		1	0.3	(b) (6)	15:40	5.7
			3	46.6		14:00	13.0
			5	91.3		10:43	9.9
			7	137.5		8:55	9.8
			16	353.6		9:00	8.3
			44	1027.9		11:20	3.3

In Utero Exposure ATV 400 mg/RTV 100 mg:

4-1056 (37.6 weeks gestation)

Mother's bilirubin (mg/dL): Birth 0.9, Mean 1.3, Median 1.1

TMP/SMZ started (b) (6)

Subject ID	Birth Date	Birth Time	Study Day	Age (in hours)	Lab Date	Lab Time	Total Bilirubin (mg/dL)
AI424182-4-1056	(b) (6)		1	4.7	(b) (6)	19:00	2.6
			3	50.2		16:25	6.8
			9	189.1		11:20	5.3
			44	1027.3		9:35	2.3
			123	2924.6		10:50	0.6

5-1067 (38.4 weeks)

Mother's bilirubin (mg/dL): Birth 1.9, Mean 1.4, Median 1.6

Subject ID	Birth Date	Birth Time	Study Day	Age (in hours)	Lab Date	Lab Time	Total Bilirubin (mg/dL)
AI424182-5-1067	(b) (6)		1	1.0	(b) (6)	13:30	3.2
			3	44.8		9:15	9.6
			5	96.3		12:45	12.2
			7	144.5		13:00	13.7
			15	336.0		12:30	7.7
			46	1082.0		14:30	2.0

12-1068 (36.3 weeks gestation)

Mother's bilirubin (mg/dL): Birth 0.9, Mean 0.7, Median 0.8

Subject ID	Birth Date	Birth Time	Study Day	Age (in hours)	Lab Date	Lab Time	Total Bilirubin (mg/dL)

AI424182-12-1068	(b) (6)	1	0.4	(b) (6)	7:50	2.3
		3	52.6		12:00	8.3
		5	97.1		8:30	11.7
		7	144.9		8:20	11.6
		14	313.2		8:35	4.2
		42	985.4		8:50	3.0

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

/s/

ELIZABETH L DURMOWICZ

01/14/2011

I have left Hari off the signature box per her request since she is on leave. Thx!

LEYLA SAHIN

01/14/2011

Karen B FEIBUS

01/14/2011

I agree with the information presented, conclusions reached, and recommendations provided in this review.

LISA L MATHIS

01/18/2011

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Office of New Drugs - Immediate Office
Pediatric and Maternal Health Staff
Silver Spring, MD 20993
Telephone 301-796-2200
FAX 301-796-9744

M E M O R A N D U M

DATE: January 12, 2011

FROM: Elizabeth L. Durmowicz, MD, Medical Officer
Leyla Sahin, MD, Medical Officer
Pediatric and Maternal Health Staff

THROUGH: Karen Feibus, MD, Medical Team Leader
Hari Cheryl Sachs, MD, Medical Team Leader
Lisa Mathis, MD, OND Associate Director
Pediatric and Maternal Health Staff

TO: Alan Shapiro, MD, PhD, Medical Reviewer
Mary Singer, MD, PhD, Medical Team Leader
Vanessa M. Perry, MPH, Regulatory Project Manager
Division of Antiviral Products (DAVP)

RE: •In utero exposed neonates with hyperbilirubinemia
•Pregnancy Labeling

Drug: Reyataz® (atazanavir)

Application: NDA 21-567

Supplement: Efficacy: S-025 (Sequence #0069): New Pharmacokinetic (PK) data to support dosing in pregnant women

Dosage form (strength): oral capsule (100 mg, 150 mg, 200 mg, 300 mg)

Sponsor: Bristol-Myers Squibb

Indication (approved): treatment of HIV-1 infection in combination with other antiretroviral agents
(No change in indication sought)

Division Consult Request:
The Division has requested PMHS comment regarding the risks of hyperbilirubinemia in atazanavir (ATV) exposed infants, the appropriate monitoring of these patients and recommendations for risk management. Specific comment is requested on whether in utero ATV exposure results in a higher incidence of hyperbilirubinemia, if ATV exposed neonates are at higher risk of bilirubin related complications, and if additional data are needed to better characterize this risk. The Division also requested input on how to best convey new PK, efficacy and safety data in Pregnancy Labeling.

Materials Reviewed:

- Reyataz® labeling (April 26, 2010)
- Sponsor submission/efficacy supplement S-025: Sequence # 0069 (August 6, 2010)
- Sponsor Submission: Sequence # 0077(November 12, 2010)
- Protocol AI424182 (November 3, 2008)
- Medical Review, atazanavir, NDA 21-567 Kendall Marcus, MD (June 20, 2003)

Background:
Atazanavir, originally approved in June 2003, is a protease inhibitor indicated for use in combination with other antiretroviral agents for the treatment of HIV-1 infection in patients 6 years of age and older. The current approved dosage of atazanavir recommends co-administration with ritonavir (RTV), which provides increased plasma levels of atazanavir.

The sponsor's efficacy supplement, S-025 provides data from a PK and safety study in HIV infected pregnant women evaluating the approved adult dose of 300mg ATV + 100mg RTV (300/100) to an increased dose of 400mg ATV + 100mg RTV (400/100) to determine if an increased dose of ATV is needed in the third trimester. Please see the medical officer review by Dr. Alan Shapiro for a detailed analysis of the safety and efficacy data submitted by the sponsor. The sponsor did not observe significant differences in PK, and is requesting changes in pregnancy labeling to reflect these results; a change in dosing and/or indication is not requested. Please see discussion of PK data (later in this review).

Overview of Study Drugs

Atazanavir
Atazanavir is labeled pregnancy category B, based on negative reproductive and developmental toxicology data. The Antiretroviral Pregnancy Registry report from May 2010 concludes that sufficient numbers of first trimester exposures have been monitored to detect at least a two-fold increase in risk of overall birth defects. No such increases have been detected to date.

Atazanavir is approved in pediatric patients 6 years and older. PREA required studies of atazanavir for use in the treatment of HIV were waived in pediatric patients less than 3

months in 2004 due to the criterion that evidence strongly suggests that the drug product would be unsafe in this pediatric age group. Thus, the Pediatric Use section was revised in 2008 to state that REYATAZ should not be administered to pediatric patients below the age of 3 months due to the risk of kernicterus.

Ritonavir (Norvir®)

Ritonavir is a protease inhibitor initially approved by FDA in 1991 for the treatment of HIV-infection in combination with other antiretroviral agents. It is Pregnancy Category B, based on negative reproductive and developmental toxicology data. The Antiretroviral Pregnancy Registry report from May 2010 concludes that sufficient numbers of first trimester exposures have been monitored to detect at least a two-fold increase in risk of overall birth defects. No such increases have been detected to date. A phase I/II study in pregnancy showed lower levels during pregnancy compared to postpartum[31]. Given low levels in pregnancy when used alone, ritonavir is recommended in low dose for use in combination with another protease inhibitor to increase levels of the other protease inhibitor[7].

Ritonavir is approved in pediatric patients 1 month and older. The adverse event profile seen during clinical trials and through postmarketing experience is similar to that for adult patients.

Management of the HIV Infected Pregnant Woman

The use of antiretroviral agents for HIV-infected women during pregnancy must take into account two separate but related issues:

1. Antiretroviral treatment of maternal HIV infection; and
2. Antiretroviral chemoprophylaxis to reduce the risk of perinatal HIV transmission.

The benefits of antiretroviral therapy for a pregnant woman must be weighed against the risk of adverse events to the woman, fetus, and newborn. According to the Department of Health and Human Services Panel on Treatment of HIV-Infected Pregnant Women and Prevention of Perinatal Transmission Recommendations for Use of Antiretroviral Drugs in Pregnant HIV-Infected Women for Maternal Health and Interventions to Reduce Perinatal HIV Transmission in the United States (May 24, 2010), general principles for treatment of HIV infected women during pregnancy include the following:

- HIV infected pregnant women should receive standard potent combination antiretroviral therapy as recommended for nonpregnant adults, taking into account what is known about use of specific drugs in pregnancy

- For women who require immediate initiation of therapy for their own health, treatment should be initiated as soon as possible, including in the first trimester

- HIV-infected pregnant women who do not require treatment for their own health should also receive three-drug combination antiretroviral regimens for prophylaxis of perinatal transmission

- For women who are receiving antiretroviral drugs solely for prevention of perinatal transmission, delaying initiation of prophylaxis until after the first trimester can be considered

- Use of ZDV as a component of the antiretroviral regimen is recommended when feasible

- Intrapartum intravenous ZDV is recommended for all HIV-infected pregnant women, regardless of their antepartum regimen, to reduce perinatal HIV transmission.

RECOMMENDATIONS FOR USE OF ANTIRETROVIRAL DRUGS DURING PREGNANCY[7]

All women who receive antiretroviral drugs during pregnancy, either for treatment or prophylaxis, should receive a combination regimen including two nucleoside reverse transcriptase inhibitors (NRTIs) and either a non-nucleoside reverse transcriptase inhibitor (NNRTI) or a protease inhibitor (PI) (with or without low-dose ritonavir). The preferred NRTI regimen in pregnancy, based on efficacy studies in preventing perinatal transmission and large experience with use in pregnancy, is zidovudine/lamivudine. Use of zidovudine, both antepartum and intrapartum, is important due to its excellent transplacental passage, unlike many other antiretroviral drugs. Additional mechanisms by which antiretroviral treatment can reduce perinatal transmission include decreasing maternal viral load and post-exposure infant prophylaxis. However, combination antiretroviral drug therapy has been shown to reduce the risk of transmission even among women with low viral load[35].

Lopinavir/ritonavir is the preferred protease inhibitor regimen for pregnant women because of efficacy studies in adults and experience with use in pregnancy. Alternative protease inhibitors include ritonavir-boosted atazanavir, saquinavir, or indinavir, although experience with these regimens in pregnancy is more limited and the latter two may be less well tolerated. Data on use in pregnancy for other PIs are too limited to recommend routine use in pregnancy, although they may be considered if other agents are not tolerated. The DHHS Guidelines list increased unconjugated bilirubin levels exacerbating physiologic hyperbilirubinemia in the neonate as a theoretical concern for atazanavir and indinavir.

Hyperbilirubinemia in Neonates:

Neonatal hyperbilirubinemia, an elevation of unconjugated bilirubin, occurs in essentially all newborn infants secondary to increased bilirubin formation, mainly due to the shorter life of the newborn's red blood cells and a decrease in bilirubin elimination related to a transiently limited ability of the newborn liver to conjugate bilirubin due to the immaturity of UDP-glucuronosyl transferase 1A1(UGT1A1)[3]. The condition is recognized as jaundice in about 60% of healthy term newborns in the United States[3], is usually benign, and has been termed "physiologic jaundice" [1]. Clinical observation of jaundice can be appreciated in the majority of infants with a bilirubin level of greater than

5 mg/dL[6]. Term, healthy, North American, formula-fed infants have mean peak total serum bilirubin (TSB) levels between 5 and 6 mg/dL[19]. Bilirubin levels usually peak at age 72-120 hours, and resolve by age 2-3 weeks[3]. However, per some experts, because more neonates are now breast fed than in previous decades, "normal" bilirubin levels are higher than they were several decades ago and the time to resolution may be more prolonged. Normal values in pediatric patients after infancy and in adults are considered <1.2 mg/dL[27].

Although neonatal jaundice is usually physiologic, unconjugated bilirubin is neurotoxic and at high levels can cause acute and chronic bilirubin encephalopathy[1]. Kernicterus, the chronic form of bilirubin encephalopathy, is associated with significant mortality and morbidity and characterized by choreoathetoid cerebral palsy, paralysis of upward gaze, sensorineural hearing loss, dental enamel dysplasia, and intellectual handicaps[5]. Although investigators have unsuccessfully attempted to correlate the occurrence of kernicterus to a specific or threshold TSB level[3], in general agreement exists that TSB levels greater than 30 mg/dL in healthy term and near-term infants increase the risk of developing kernicterus[5]. Bhutani and Johnson estimate that one in seven patients with a TSB greater than 30 mg/dL develops kernicterus[3]. Bilirubin encephalopathy is rare: in the US, the incidence of acute bilirubin encephalopathy is estimated at 1 in 40,000 live births[3] and the incidence of kernicterus is approximately 1.5 per 100,000 newborns with a higher incidence in preterm infants (4 per 100 000 births) [5].

Defining a normal total serum bilirubin is problematic as the range of normal levels varies widely depending on race, the incidence of breastfeeding, and other genetic and epidemiologic factors[19]. Major risk factors for the development of severe hyperbilirubinemia include jaundice observed in the first 24 hours of life, blood group incompatibility with positive direct antiglobulin test, other known hemolytic disease such as G6PD deficiency, previous sibling received phototherapy, cephalohematoma or significant bruising and exclusive breastfeeding (see Appendix I: Risk Factors for Development of Severe Hyperbilirubinemia in Infants of 35 or More Weeks' Gestation) [1]. Compared with Caucasians, rates of identified hyperbilirubinemia are about twice as high in Asians, half as high in Blacks, and the same in Latinos[23] and "East Asian race" is considered a major risk factor for the development of severe hyperbilirubinemia[1].

Furthermore, the risks of developing bilirubin toxicity may be higher in conditions that affect albumin binding of bilirubin, the blood-brain barrier, and the susceptibility of the brain cells to damage by bilirubin. Hence, premature infants (defined as less than 38 weeks gestation by the American Academy of Pediatrics (AAP) in the Guideline for Management of Hyperbilirubinemia) and patients with asphyxia, significant lethargy, temperature instability, sepsis, acidosis or albumin less than 3.0 g/dL are considered higher risk for bilirubin toxicity[1].

Hyperbilirubinemia in preterm infants is more prevalent, more severe, and the course is more protracted than in term neonates[38]. In a series of studies published from 1958 to 1972, kernicterus was described in premature infants at TSB levels ranging from 10 to 18 mg/dl [38,39]. However, kernicterus is currently a very rare event in premature infants in

neonatal intensive care units. The literature notes that the available data on bilirubin induced neurological injury in preterm infants is complex and additional data are needed to define the risk of elevated bilirubin in premature infants [38,39]. Normative data that are available for term and near-term infants do not appear to be available for preterm infants.

An additional difficulty in determining a normal TSB, is that the TSB is an imprecise indicator of long-term neurodevelopmental outcome unless levels are extremely high and associated with signs and symptoms of bilirubin encephalopathy [1]. Data are inadequate to determine if severe hyperbilirubinemia or prolonged moderate hyperbilirubinemia in the absence of signs and symptoms of acute bilirubin encephalopathy are associated with sequelae [3].

"Significant" hyperbilirubinemia has been defined as greater than the 95th percentile for age in hours [3] based on data obtained from over 17,000 healthy, near term infants born at a Pennsylvania Hospital from 1993 to 1997 [4]. Defined numeric values used commonly are TSB levels greater than 10 mg/dL, greater than 14 mg/dL, and greater than 17 mg/dL on days of life 2, 3 and 4-5, respectively[30]. TSB levels greater than 20 mg/dL are often considered "severe hyperbilirubinemia" and those greater than 25 or 30 mg/dL, "extreme hyperbilirubinemia" [19]. Per Bhutani and Johnson, significant hyperbilirubinemia, i.e. greater than the 95% for age in hours, occurs in 8 to 11% of infants, and approximately 1 in 650-1000 infants greater than 35 weeks gestation can develop serum bilirubin values greater than 25 mg/dL and approximately 1 in 10,000 have levels exceed 30 mg/dL [3].

Management:
Although the development of bilirubin encephalopathy is rare[5], given the seriousness of the condition, newborn infants are monitored to identify those at risk for the development of severe hyperbilirubinemia, and therefore at potential risk for bilirubin encephalopathy. If indicated, infants are treated to avoid potentially toxic levels of serum bilirubin [1]. A nomogram for designation of risk based on the infant's hour-specific serum bilirubin is available and used by practitioners to assess the risk of developing severe hyperbilirubinemia and to establish a monitoring plan based on the assessed level of risk (Appendix II)[1]. In addition, the AAP has established guidelines on when to initiate phototherapy (PT) (Appendix III: Guidelines for phototherapy in hospitalized infants of 35 or more weeks' gestation.) and when to perform an exchange transfusion based on hour-specific serum bilirubin measurements and other risk factors[1]. Phototherapy is used to reduce the risk that the TSB level will reach a level at which exchange transfusion is recommended, and the goal of both procedures is to keep TSB levels below those at which bilirubin encephalopathy has been reported[1].

Atazanavir and Hyperbilirubinemia:
Due to UDP-glucuronosyl transferase 1A1 (UGT1A1) inhibition, most patients treated with atazanavir (ATV) experience asymptomatic elevations in unconjugated bilirubin that are reversible upon discontinuation of the drug. The incidence of hyperbilirubinemia is dose-dependent and a clinical study reported grade 3-4 bilirubin levels (greater than 2.6X upper limit of normal) in 44% of patients exposed to 300 mg ATV. The mean total serum bilirubin (TSB) in patients from study A1424034 (034), one of the two phase 3

pivotal studies, was 6.3 mg/dL (SD 1.4). Per the medical officer review of the original NDA, the occurrence of TSB levels 10 mg/dL or greater occurred in 5 patients without additional associated liver function abnormalities. Based on clinical trials and post-marketing experience, ATV-associated hyperbilirubinemia does not appear to increase the risk for hepatic injury or hepatic enzyme abnormalities.

Reviewer Comment:
Data regarding the time to resolution of the hyperbilirubinemia seen in adults after ATV discontinuation do not appear to be included in the original medical officer review; however, Nettles et al state that hyperbilirubinemia associated with protease inhibitors resolves completely days after the medication is discontinued[22].

The Sponsor notes that data are not available to determine if ATV administration during pregnancy will exacerbate physiological hyperbilirubinemia or increase the risk of kernicterus in neonates and young infants. Per the Sponsor, the placenta allows only unidirectional transport of bilirubin from the fetus to the mother and not from mother to fetus. In contrast, published case reports of Crigler-Najjar syndrome show neonatal hyperbilirubinemia and corresponding high maternal bilirubin levels at the time of delivery (this is discussed later in this review). High maternal bilirubin levels due to ATV administration during pregnancy might theoretically disrupt the normal transplacental transport of fetal bilirubin, and lead to intrauterine hyperbilirubinemia.

Reviewer Comment:
Studies have demonstrated that unconjugated bilirubin in the fetus normally crosses the placenta to reach the maternal circulation as the fetal liver has limited UGT1A1 activity[17]. Per Holstein et al, high levels of maternally derived unconjugated bilirubin may lead to neuronal and astrocytal degeneration in the fetus[12]. Given that the fetus is considered to be at risk from the neurotoxic effects of unconjugated bilirubin[9,12], the risk of intrauterine exposure to elevated levels of unconjugated bilirubin secondary to maternal ATV inhibition should be considered.

The familial unconjugated hyperbilirubinemias, Crigler-Najjar syndromes type I and II and Gilbert syndrome, are caused by genetic lesions encoding for UGT1A1 and result in a spectrum of unconjugated hyperbilirubinemias. The clinical spectrum of these disorders range from the clinically negligible Gilbert syndrome to the severe and often fatal Crigler-Najjar type I syndrome[30], which is characterized by the complete absence of UGT1A1. Information about patients with these syndromes may be useful in understanding the risk of elevated maternal unconjugated bilirubin in the fetus. Gilbert syndrome occurs in 3%–10% of the general population[15] and is considered a benign condition. In most patients, the hyperbilirubinemia of Gilbert syndrome becomes manifest in adolescence or early adulthood[36], and serum bilirubin levels are usually less than 3 mg/dL, although fluctuations may occur especially with illness[11,29]. Review of the literature for reports of pregnancy outcomes in women with Gilbert syndrome did not identify any articles. Although Gilbert syndrome is reported to be more common in males (4:1)[11], given that the occurrence of this condition is common and the literature provides a paucity of information regarding infants born to women with Gilbert

syndrome, the bilirubin levels seen in women with Gilbert syndrome may not be problematic to the fetus.

Crigler-Najjar type I (CN-I) is associated with a progressive and severe neurologic syndrome resembling kernicterus, usually resulting in death within the first two years of life. Total plasma bilirubin levels have been reported in a wide range from 15 to over 50 mg/dL. In Crigler-Najjar type II (CN-II) bilirubin levels are lower than in CN-I and typically range from 10-20 mg/dL. Central nervous system damage is rare, and the majority of patients survive into adulthood without complications[29]. Both CN syndromes are considered rare and pregnancy in CN patients is considered an "exceptional" event[9]; however, of note, patients with CNI have historically been advised to terminate pregnancy due to the risk of bilirubin toxicity. The literature has a few case reports of pregnancy and pregnancy outcome for patients with CNI and CNII[2,9,10,12,13,32]. Pregnancy outcomes were reported in four patients with CNI exposed in utero to TSB levels 12-25 mg/dL[9,10]. Normal neurological outcomes were reported in three patients but quadriplegia was reported at age 18 months in one patient[34]. Of note, one of the three infants with reported normal neurologic outcomes initially had MRI findings consistent with bilirubin deposition and developmental concerns were raised, but by age 4 years the MRI and neurologic and developmental exams were reported to be within normal limits[10]. The other two infants were reported to have normal exams at 18 months and 4 months. For all patients, maternal and infant TSB levels were similar at birth, and all infants were treated aggressively, i.e. two infants were treated with phototherapy and double-volume exchange transfusion and one infant was treated solely with phototherapy. Among the six case reports of pregnancy outcomes in patients with CNII identified by the reviewers[2,12,13,32], all mothers maintained bilirubin levels less than 10 mg/dL, and neonatal bilirubin levels were between 5.1-13.2. Arora and Choudhary observed (based on two case reports in the literature and their own case) that maternal serum bilirubin levels of 9 mg/dl or less before delivery were associated with good neonatal outcomes[2]. Smith and Baker conclude that CN II seems to pose no unique maternal risk during pregnancy and note that the fetus seems to be resistant to elevated maternal unconjugated bilirubin[32].

Per ATV labeling, animal reproduction and pre and post-natal development studies did not identify evidence of adverse fetal effects or teratogenicity with ATV exposure. Per the literature, a paucity of animal data exists.

In summary, although the Sponsor states that the placenta allows only unidirectional transport of bilirubin from the fetus to the mother, the literature suggests that the placenta allows bidirectional passage of bilirubin between mother and fetus, and levels of unconjugated bilirubin in infants with CNI and II were similar to maternal levels. The limited data from patients with familial unconjugated hyperbilirubinemias suggest that bilirubin levels in the range of adult patients treated with ATV in clinical trials may not represent an unacceptable risk to the fetus.

The Sponsor also notes that fetal exposure to ATV that has crossed the placenta has the potential to inhibit infant UGT1A1, hence exaggerating physiologic jaundice and potentially contributing to the development of significant hyperbilirubinemia.

Reviewer Comment:
*Although the Sponsor states the concern that ATV may inhibit **infant** UGT1A1, they do not appear to have discussed the potential impact of ATV on **fetal** UGT1A1. Although inhibition of the UGT1A1 enzyme may occur, studies in rats[16] suggest that elevated unconjugated bilirubin could also potentially stimulate fetal UGT1A1 activity thereby, theoretically, protecting the fetus from exposure to elevated maternal levels of bilirubin. Hence, bilirubin metabolism is complex and a number of unknowns exist regarding the effects of ATV and bilirubin levels on fetal UGT1A1 activity and in utero bilirubin metabolism.*

Labeling lists no contraindications; however the Pediatric Use section states that REYATAZ should not be administered to pediatric patients below the age of 3 months due to the risk of kernicterus.

Reviewer Comment:
Per personal correspondence Alan Shapiro, MD (December 6, 2010), given that other products with well-characterized safety profiles are available to treat HIV infection in infants less than 3 months, studies of ATV were waived in this pediatric subpopulation because the unknown risk of prolonged exposure of young infants to unconjugated bilirubin as well as the risk of PR prolongation outweighed the potential benefits of the drug.

Study AI424182
Protocol Summary:
Study AI424182 was a multi-center, open-label, prospective, single-arm study designed to determine which dosing regimen of ATV/RTV produces adequate drug exposure during pregnancy compared to drug exposure of HIV-infected subjects from historical data. PK and efficacy analyses were based on data from 41 treated mothers and 40 infants. Safety variables included the frequency and duration of hyperbilirubinemia in the neonate at study days 1, 3, 5, and 7 postpartum, the frequency and severity of adverse events (AEs) in the neonates, the frequency and severity of AEs in pregnant women, and the frequency and occurrence of adverse pregnancy or neonatal outcomes. Of note, bilirubin levels were to be evaluated at study days 1, 3, 5, 7, and 14, with additional monitoring as clinically indicated. Cord samples were drawn at delivery for neonatal ATV and RTV exposure testing.

Women with risk factors known to increase the risk of "pathologic jaundice" in neonates were excluded from the study: the exclusion criteria included patients with Rhesus antibody positive, a previous infant who developed hemolytic disease as a newborn and/or had neonatal pathologic jaundice that required phototherapy and a history of glucose-6-phosphate dehydrogenase (G6PD) deficiency. Testing to determine infant

blood type and/or antiglobulin testing to assess for the potential for ABO incompatibility and/or hemolysis was not performed. Breast feeding was not permitted.

Reviewer Comment:
Although the exclusion of women with risk factors known to increase the risk for hyperbilirubinemia in neonates may have been considered an appropriate safety consideration to limit exposure to those infants at lower risk for the development of severe hyperbilirubinemia, the criteria appear to limit the ability to adequately assess the potential for developing hyperbilirubinemia in all infants exposed to ATV as the data are likely to not be applicable to the general population of potentially exposed infants.

Blood samples were to be obtained by venipuncture or from an indwelling catheter (with discard of 0.5 ml of blood). Laboratory tests were to be performed by a central laboratory that is licensed and meets Clinical Laboratory Improvement Amendments (CLIA) regulations or equivalent by country. Blood samples for analysis of ATV and RTV were to be performed at a central analytical laboratory.

Reviewer Comment:
Although blood sampling for bilirubin assessment appears to have been correctly collected, bilirubin analysis appears to have been performed at the local site and the method of analysis does not appear to be specified. Given that inaccuracy of bilirubin determinations has been a long-term concern and that interlaboratory variability of bilirubin measurements is well documented[8,37], the Division should be satisfied that the methods used to assess bilirubin levels were sufficiently similar and carefully evaluated to insure comparability of the reported values.

Maternal adverse events were graded according to the WHO recommendations for Grading Acute and Subacute Toxic Effects and infant adverse events were graded according to criteria adapted from toxicity grading tables for pediatric and infant adverse events from the National Institutes of Health Division of AIDS, DAIDS (see Appendix IV: Grading of Maternal and Infant Adverse Events). For both mother and infants greater than 14 days, Grade 3 and Grade 4 bilirubin toxicity were defined as 2.6-5X and greater than 5 X the upper limit of normal, respectively. For infants 14 days or younger, the definitions for Grade 3 and Grade 4 toxicity were as follows:

PARAMETER	GRADE 1 Mild	GRADE 2 Moderate	GRADE 3 Severe	GRADE 4 Potentially Life-Threatening
Bilirubin (Total)				
Pediatric > 14 days	1.1 - 1.5 x ULN	1.6 - 2.5 x ULN	2.6 - 5.0 x ULN	> 5.0 x ULN
Infant ≤ 14 days (non-hemolytic)	NA	20.0 - 25.0 mg/dL *342 - 428 µmol/L*	25.1 - 30.0 mg/dL *429 - 513 µmol/L*	> 30.0 mg/dL *> 513.0 µmol/L*
Infant ≤ 14 days (hemolytic)	NA	NA	20.0 - 25.0 mg/dL *342 - 428 µmol/L*	> 25.0 mg/dL > 428 µmol/L

Reviewer Comment:
Although the Sponsor does not appear to have provided the upper limit of normal for pediatric patients greater than 14 days or for adult patients and the standard normal ranges of laboratory values may vary between laboratories, total bilirubin levels are generally defined as less than 1.2 mg/dL[27] after the neonatal period. Hence, Grades 2, 3 and 4 toxicities would be considered total bilirubin values of approximately 1.9-3 mg/dL, >3-< 6 mg/dL and ≥ 6 mg/dL respectively.

Per the study protocol, the AAP Clinical Practice Guideline on the management of neonatal hyperbilirubinemia was recommended to guide management of neonates with hyperbilirubinemia in the study and was provided to investigators. However, given that the Guideline has not been validated in populations outside the US or in neonates exposed to antiretroviral drugs in-utero, other than the monitoring mandated by the protocol, the management and monitoring of South African neonates was ultimately at the discretion of the local investigators and clinicians. Although study sites were required to have the ability to perform phototherapy (PT), specific guidance regarding how PT was performed do not appear to be provided, i.e. continuous vs. intermittent, high vs. low intensity.

Reviewer Comment:
South African patients represented the vast majority of study patients, n=28 (40%). However, as discussed below, the variability in management of hyperbilirubinemia is unlikely to have affected the interpretability of the results.

Study Results:
Forty one mothers were treated and 40 in utero exposed infants were followed. Twenty infants were exposed to each dosing cohort, i.e. ATV/RTV 300/100 mg n=20 infants, ATV/RTV 400/100 mg n=20 infants. One mother withdrew consent and her infant was not followed. Race was identified as "Black/African American" in 33 patients, "White" in 6 patients and as "Other: Mixed Race" in 1 patient. Twenty eight patients were treated in sites in South Africa, 10 patients in Puerto Rico and 2 patients in the US (see Appendix V: Demographics and Disease Characteristics of Enrolled Infants).

Reviewer Comment:
As discussed above, the range of normal bilirubin levels varies widely depending on racial composition, and the rate of hyperbilirubinemia in Black patients is reported to be half as high as that in Caucasian patients, and the rate in Asian patients is considered to be twice as high as that in Caucasians[23]. Hence, given that 33/40 (82.5%) patients were identified as Black/African American and no Asian patients were enrolled in this study, the ability of the data to determine the incidence of hyperbilirubinemia in the general population of infants exposed to ATV is limited, especially in Asian patients.

Atazanavir Levels in Maternal vs. Cord Blood**:**
The Sponsor states that relative to the corresponding maternal ATV concentrations at the time of delivery, the ATV concentrations in cord blood were approximately 12% and 19% at ATV/RTV 300/100 mg and ATV/RTV 400/100 mg, respectively. The Sponsor

concluded that the ratio of ATV concentrations in maternal and umbilical cord blood indicates that ATV does not freely cross the placenta; however, the levels observed may be enough to inhibit the infant's UGT1A1 enzyme until the drug is cleared by the infant.

Reviewer Comment:
The sponsor's finding of low transplacental passage of atazanavir at the time of delivery is consistent with the literature regarding other protease inhibitors[20, 21,26]. Per the pediatric reviewer's correspondence with the Clinical Pharmacology Reviewer, Jenny Zheng, PhD (December 10, 2010), the ATV cord blood concentration was about 200 mg/ml, a level that could potentially inhibit the infant's UGT1A1. Thus, given that UGT1A1 is known to be immature at birth, ATV inhibition of UGT1A1 could theoretically further decrease the infant's ability to conjugate bilirubin, possibly increasing the infant's risk for the development of severe and/or prolonged unconjugated hyperbilirubinemia (more below). If the half life of ATV in neonates is similar to that in adults (t½ in healthy adults is 18 hours), the neonate would be expected to clear the ATV within four days. However, as previously noted, from animal data, exposure to high levels of unconjugated bilirubin in utero could potentially stimulate UGT1A1. Thus, the relationship between in-utero drug exposure and bilirubin metabolism is likely to be dependent on a complex interplay of a number of factors, and PK data are not available in infants to determine if enzyme inhibition occurs and/or if enzyme inhibition could be prolonged or delayed

Maternal Bilirubin Levels:
Per the Sponsor, ATV/RTV 400/100 mg dosing was associated with twice as much Grade 3 to Grade 4 hyperbilirubinemia as ATV/RTV 300/100 mg in mothers, i.e. 6 of 20 mothers on ATV/RTV 300/100 mg and 13 of 21 mothers on ATV/RTV 400/100 mg. The maximum maternal bilirubin level reported in mothers exposed to 300 mg ATV and 400 mg ATV was 5.8 mg/dL and 6.4 mg/dL, respectively.

Reviewer Comment:
Although a comparison of bilirubin levels between trials is deferred to the clinical reviewer, the maternal bilirubin level results appear to be consistent with the findings from the adult clinical trials and do not appear to be unexpected. Of importance, the levels do not appear to be higher than those identified in previous trials. If the higher levels of unconjugated bilirubin elevation observed in mothers in this trial and in the adult clinical trials, i.e. 6.3 mg/dL (SD 1.4) are observed in infants within the first 24 hours of life, the levels would likely be considered elevated and may place infants at higher risk for the development of severe hyperbilirubinemia (more below). However, these bilirubin levels are markedly below those at which kernicterus is of concern, specifically 25mg/dL or greater in term infants.

Comparison of Maternal and Infant Bilirubin Levels:
The Sponsor concluded that the correlation between maternal bilirubin, both on the date of delivery and the mean level in the 4 weeks prior to delivery, with that of the infant on the day of delivery was low, and scatterplots of the data were provided:

Scatterplot and Fitted Line of Infant vs. Mother's Total Bilirubin at Delivery Day:
(From the Sponsor)

Reviewer Comment:
At lower maternal bilirubin levels, i.e. less than 2-3 mg/dL, a correlation between maternal and infant bilirubin levels does not appear to exist, and many infants have TSB levels higher than those reported in their mothers. However, per the pediatric reviewers' interpretation of the scatterplot, the data are insufficient to rule out a correlation between higher maternal serum bilirubin measurements at the time of birth and infant bilirubin level measurements, and this correlation may be consistent with the literature reports from patients with CN syndrome discussed above. Specifically, two mothers had bilirubin levels 5 mg/dL or greater at the time of delivery and their infants also had bilirubin levels greater than 5 mg/dL during the first day of life. In addition, one cannot rule out a correlation between mothers with bilirubin levels of 3-4 mg/dL and their infants based on the data. Review by the statistical reviewer could be considered; however, given the limited numbers of mothers with bilirubin levels 5 mg/dL or greater at the time of delivery, definitive conclusions cannot be made from the available data.

Although debate exists, jaundice appearing in neonates within the first 24 hours of life is generally of concern[1,2,25,30] (more below). Given the possibility that elevated maternal bilirubin levels may result in elevated neonatal bilirubin levels at birth or within the first 24 hours of life, a review was performed of infants born to mothers with TSB values 3 mg/dL or greater at any time during pregnancy.

Eight mothers in the study (8/40, 20%) had bilirubin elevations of 3 mg/dL or greater during pregnancy. Three mothers (3/40, 7.5%) had bilirubin levels greater than 5 mg/dL at some point during pregnancy and two mothers (2/40, 5%) had bilirubin levels 5 mg/dL or greater at birth. TSB levels greater than 3 mg/dL during pregnancy were more common in mothers treated with 400 mg ATV.

Table I: Comparison of Maternal and Infant Bilirubin Values in Mothers with Bilirubin Levels 3 mg/dL or greater During Pregnancy:

ATV Dose Cohort	Preterm (P) or Term (T)	Patient #	Maximum maternal TSB value (mg/dL)	Mean/Median maternal TSB values over last 4 weeks (mg/dL)	Maternal TSB at Birth	Infant's first TSB (Time in hours) Percentile Level based on data for term infants and on age in hours*	Infant Course/ Comments
300 mg	P	1022	3.9	3.4/3.6	3.6	4.3 (24.8) <40%	Uneventful
	T	1009	4.1	2.7/2.9	4.1	10.2 (70.8) <40%	TSB 3.0 mg/dL at DOL: 13 (LRV)
		1018	5.8	4.1/4.3	5.7	7.6 (1.5) >>95%	TSB 1.3 mg/dL at DOL: 13, then WNL.
400 mg	P	1032	4.5	2.8/2.9	3.8	4.4 (4.2) >95%	TSB 3.4 mg/dL at DOL: 13, then WNL.
		1050	6.4	3.9/4.4	0.6	3.2 (1.8) >95%	TSB 2.3 mg/dL at DOL: 15 (>1.5-2.5X ULN), then WNL.
		1054	3.8	2.7/2.8	2.7	4.4 (0) >95%	Received PT. TSB 11.4 mg/dL at DOL: 6, 8.5 mg/dL DOL 17 >5X ULN) (LRV).
	T	1043	4.1	1.5/1.2	3.5	2 (5.9) <95%	TSB elevated to within 1 mg/dL of the PT threshold. Patient received PT. Remainder of course uneventful with LRV WNL.
		1064	6.0	4.3/5.0	5.0	6.2 (0.7) >95%	Uneventful

*Percentile Based on Age: Normative data for bilirubin levels in patients less than 24 hours of age are based on data from Bhutani et al[4]. Data are available identifying the 40%, 75% and 95% TSB level for age in hours for term or near term healthy infants 12 hours of age and older. Newman et al, assuming a linear increase in the 95% for TSB levels from birth (2 mg/dL) to 24 hours (8 mg/dL), provide the approximate 95% bilirubin levels for term infants from birth to 24 hours[25].

DOL= Day of Life
LRV = Last Reported Value
WNL = Within Normal Limits

Infants 1018 (300 mg ATV cohort) and 1064 (400 mg ATV cohort), term infants born to mothers with bilirubin levels 5 mg/dL or greater at birth, reported bilirubin levels greater than the 95% for age in hours within the first 24 hours of life. Infant 1018's TSB was greater than the PT threshold and infant 1064's TSB was approximately 1 mg/dL below

the PT threshold. However, these infants did not receive PT and their hyperbilirubinemia resolved without complications.

Three additional infants of mothers with TSB levels greater than 3 mg/dL and less than 5 mg/dL, preterm infants in the 400 mg ATV exposure cohort, had bilirubin levels >95% for age in hours within the first 24 hours of life, i.e., infants 1032, 1050 and 1054. Infant 1032 had TSB of 3.4 mg/dL on DOL 13 and normal TSB levels on study days 41 and 130. Infant 1050 had a TSB 1.5-2.5X ULN for a term infant at DOL 15 and a normal TSB level on study day 43. Infant 1054 received PT and had a last reported bilirubin value of 8.5 mg/dL (>5X ULN) on DOL 17. Given that these patients were premature and normative data do not appear to be available for premature infants, the level of hyperbilirubinemia in the first 24 hours is difficult to interpret. In addition, although infant 1054 had an abnormal bilirubin level on DOL 17, the TSB levels of infants 1032 and 1050 on DOL 13 and DOL 15, respectively, may not be elevated.

Two infants of mothers with TSB levels greater than 3 mg/dL and less than 5 mg/dL (patients 1009 and 1022) did not have bilirubin levels drawn within the first 24 hours of life and although resolution of hyperbilirubinemia was not documented in infant 1009, the course of hyperbilirubinemia for both infants appears unremarkable.

The remaining infant (patient 1043), a term infant in the 400 mg exposure cohort did not have a bilirubin level greater than the 95% at birth. The infant's TSB reached within 1 mg/dL of the PT threshold, the infant received PT and the bilirubinemia resolved. This infant's mother's bilirubin was 3.5 mg/dL at birth, maximum bilirubin during pregnancy was 4.1 mg/dL and the mother's mean and median bilirubin levels during the last 4 weeks of pregnancy were 1.5 mg/dL and 1.2 mg/dL, respectively, which may suggest that the infant did not have prolonged exposure to maternal TSB values greater than 3 mg/dL.

In summary, bilirubin data from the first 24 hours of life are available for six of eight infants of mothers with TSB levels greater than 3 mg/dL at some point during pregnancy. Of these six patients, five had a bilirubin greater than the 95% for age in hours for term infants in the first day of life based on the interpretation of normative data from term infants used by Newman et al (of note, using this method, 31 infants, 77.5% of study infants, were identified as having a TSB level greater than the 95% for age in the first 24 hours of life[25], more below). Four of five infants were in the 400 mg exposure cohort and three of five were premature. None of the patients had complicated courses. Of particular interest, the infants born to mothers with TSB levels 5 mg/dL or greater at birth who also had TSB levels 5 mg/dL or greater within the first 24 hours of life had uneventful resolution of the bilirubinemia without intervention. While there is a theoretical concern that maternal ATV in the infant circulation could inhibit UGT1A1 enzyme activity, it is also possible that chronic elevated unconjugated bilirubin may somehow protect the fetus/neonate through stimulation of fetal UGT1A1 activity or through another placental or fetal mechanism. Based on the relatively small sample size, incomplete data collection, incomplete information about potential confounding factors such as ABO blood group incompatibility and the paucity of normative data on bilirubin levels in the first 24 hours of life in term and preterm infants, determining whether a

correlation exists between maternal and infant serum total bilirubin levels at birth does not appear possible.

Infant Bilirubin Levels:
The Sponsor concluded that the bilirubin elevations were most likely physiologic and reported that jaundice occurred in 20/40 patients (50%). Per the Sponsor, increased total bilirubin was the only Grade 3 to Grade 4 liver function abnormality and observed in 7 of 40 infants (3 infants whose mothers were on ATV/RTV 300/100 mg and 4 infants whose mothers were on ATV/RTV 400/100 mg). Six of 40 infants had phototherapy (PT) performed and two patients, 8-1027 and 4-1043, had an SAE of hyperbilirubinemia or jaundice reported.

1. Incidence of Hyperbilirubinemia in Neonates:
To evaluate the incidence of hyperbilirubinemia in the study patients, the pediatric reviewer plotted the highest bilirubin level obtained at 12 hours of age or older for each patient on the Nomogram to Assess the Risk of Developing Severe Hyperbilirubinemia which provides the normative serum bilirubin values for healthy term and near term infants as determined by Bhutani et al (see Appendix II)[4].

Table 2: Number of Infants per Risk Zone per the Bhutani Nomogram to Assess Risk of Developing Severe Hyperbilirubinemia

Risk Zone	**Number of patients** (% total n=40)	**300 mg** (% total n=20)	**400 mg** (% total n=20)
Low Risk bilirubin level (0-<40%)*	21 (52.5)	12 (60)	9 (45)
Low Intermediate Risk (40-<75%)*	11 (27.5)	2 (10)	9 (45)
High Intermediate Risk (75-<95%)*	5 (12.5)	5 (25)	0
High Risk (≥ 95%)*	3 (7.5)	1 (5)	2 (10)

Note: The percentile ranking is based on age in hours

Reviewer Comment:
The distribution of the data appear to indicate that study infants did not have a markedly increased incidence and severity of hyperbilirubinemia than would be expected based on normative data from Bhutani et al[4]. Of note, of the three patients categorized as High Risk for developing severe hyperbilirubinemia, only one patient met the criteria established by the AAP for the initiation of PT based on gestational age and hour-specific bilirubin measurement (patient 8-1027) and two of the patients received phototherapy (patients 8-1027 and 4-1043). The patients who received phototherapy were those for which hyperbilirubinemia was reported as an SAE.

2. Incidence of Hyperbilirubinemia in the First 24 Hours of Life:
As noted earlier, jaundice appearing in the first 24 hours of life is generally of concern[1,2,25,30], and is considered a risk factor for the development of severe hyperbilirubinemia[1]. Newman et al concluded from a retrospective review of over 700 newborns that jaundice at less than 24 hours was uncommon, occurring in only 6.7% of newborns[25]. Normative data from Bhutani et al are available to identify the 40%, 75% and 95% TSB level for age in hours for term or near term healthy infants 12 hours of age and older[4]; however, normative data do not appear to be available for preterm infants or patients less than 12 hours of age. Hence, Newman et al assumed a linear increase in the 95% for TSB levels from birth (2 mg/dL) to 24 hours (8 mg/dL) to provide the approximate 95% TSB levels for term infants from birth to 24 hours[25].

To estimate the incidence of severe bilirubinemia in the first 24 hours of life, the line used by Newman et al to identify infants with bilirubin levels greater than the 95% was used:

Table 3: Incidence of Hyperbilirubinemia within the first 24 hours based on normative data from term or near term healthy infants:

	Dosing Exposure Cohort	Preterm	Term
No bilirubin level in the first 24 hours	300 mg	1	1
	400 mg	0	2
Bilirubin level <95% for age in hours	300 mg	2	1
	400 mg	1	1
Bilirubin level >95% for age in hours	300 mg	6	9
	400 mg	9	7

Reviewer Comment:
Using the line developed by Newman et al to identify infants with bilirubin levels greater than the 95% for age in hours identified 31 infants (77.5% of study patients) as having a TSB level greater than the 95% for age in the first 24 hours of life. However, this method of determining the 95% TSB for age in hours relies on the assumption that the rise in bilirubin is linear, and plotting the data on the graph provided by Newman et al may be prone to some degree of inaccuracy due to the small scale of the graph. In addition, the line developed by Newman et al is based on normative data from term infants, and therefore may not be relevant to preterm infants.

Ten infants (25% of study patients) 4 in the 300 mg exposure cohort and 6 in the 400 mg exposure cohort (4 premature and 6 term), were identified with bilirubin levels 4 mg/dL or greater within the first day of life. Six infants (15% of study patients), 3 in each study exposure cohort (2 premature and 1 term), were identified with bilirubin levels of 5 mg/dL in the first 24 hours of life (see Appendix VI: Infants with TSB greater than 4 mg/dL in the first 24 hours of life). When plotted on the line used by Newman et al to identify infants with bilirubin levels greater than the 95%, all 6 infants with bilirubin

levels greater than 5mg/dL within the first 24 hours of life had TSB levels greater than the 95%.

Reviewer Comment:
Although the data may suggest that the presence of hyperbilirubinemia may be increased in the first 24 hours, none of the patients had bilirubin related complications and few qualified for phototherapy (see below). Hence, the implications of these findings are unclear. Given that the interpretation of TSB levels is based upon age in hours and other clinical and epidemiologic factors[19], the reviewers defer to the Division to determine if including the number of patients with TSB levels greater than 4 mg/dL or 5 mg/dL in the first 24 hours of life would be helpful information for providers and therefore should be included in labeling.

3. Incidence of Hyperbilirubinemia Potentially Requiring Treatment in Neonates:
As discussed above, the threshold for the initiation of PT as recommended by the AAP is based on gestational age and additional risk factors that may put an infant at higher risk for bilirubin toxicity, such as isoimmune hemolytic disease and systemic illness. Although information was not provided regarding maternal or infant blood type, or direct antiglobulin testing, i.e. Coombs testing, no concerns or signs/symptoms of isoimmune hemolytic disease appear to be documented for any patient. Review of the final clinical study report data did not identify additional risk factors for the development of severe hyperbilirubinemia, such as cephalohematoma or significant bruising, or identify that patients were considered at higher risk for bilirubin toxicity secondary to conditions such as low albumin or sepsis.

Reviewer comment:
Data on maternal and infant blood type, and Coombs testing would have provided important information on the contribution of hemolysis to any elevated bilirubin levels in the infants.

To evaluate the severity of the hyperbilirubinemia in exposed infants, the pediatric reviewer plotted the bilirubin levels for each patient on the nomogram developed by the AAP as a guideline for the initiation of phototherapy (Appendix III). In the cohort exposed to 300 mg ATV and 400 mg ATV, the bilirubin levels remained 2 mg/dL or more below the phototherapy (PT) threshold in 17/20 (85%) and 9/20 (45%) patients, respectively. Two patients in the 300 mg ATV exposed cohort exceeded the PT threshold compared to no patients in the 400 mg ATV exposure cohort; however, 4 patients in the 400 mg ATV exposed cohort came within 1 mg/dL of the PT threshold compared to no patients in the 300 mg ATV exposed cohort:

Table 4: Location of the Infants on the Nomogram for the Guideline for the Initiation of Phototherapy

Dosing Exposure Cohort	Number of patients that surpassed the PT threshold	Number of patients that were within 1 mg/dL of the PT threshold	Number of patients within 1-2 mg/dL of the PT threshold	Number of patients 2 mg/dL or more below the PT threshold.
300 mg ATV	2	0	1	17
400 mg ATV	0	4	7	9

Reviewer Comment:
The patients in the 400 mg ATV exposure group appear to have had TSB levels that were closer to the threshold identified for the initiation of PT. Hence, patients in the 400 mg ATV dosing exposure cohort may have a slightly increased incidence and severity of hyperbilirubinemia compared to the 300 mg exposure cohort.

4. Phototherapy (PT):
As noted by the Sponsor, six patients received phototherapy, three patients from each dosing exposure cohort. All patients were identified as Black/African American. Five patients were treated at a South African site and one patient was treated at the Puerto Rico site.

Reviewer Comment:
The courses of the patients that received PT do not appear to be remarkable, and no patient developed severe hyperbilirubinemia. Although two patients, 8-1027 (35.6 week gestation, 300 mg ATV exposure cohort) and 12-1054 (35 week, 400 mg ATV exposure cohort), met the PT threshold established by the AAP, the other 4 patients do not appear to have met the "strict" threshold level based on the available data. However, the Guideline notes that PT may be initiated at TSB levels 2-3 mg/dL below the recommended threshold level, and these 4 patients met the less stringent criteria. Three of the four patients had an uneventful course, though complete resolution of hyperbilirubinemia was not documented in a 37.7 week, 400 mg ATV exposure cohort patient (12-1044), i.e. last TSB level was 8 mg/dL at day of life 7. Patient 12-1025, a term infant in the 300 mg ATV exposure cohort, may have had a more prolonged course than expected. Despite PT, the patient's serum bilirubin level peaked on day of life 6 (15.3 mg/dL), and on day of life 14, the level remained 4.6 mg/dL or 2.6-5X the upper limit of normal. TSB level was normal on study day 46 (more below). Although some patients may have been managed more conservatively than the AAP Guideline recommends, the variability in management of hyperbilirubinemia is unlikely to have affected the interpretability of the results.

Prolonged Jaundice:
Per the Sponsor, in the third week of life (15-18 days), three of 20 infants (15%) born to women treated with REYATAZ/ritonavir 300/100 mg and four of 20 infants (20%) born to women treated with REYATAZ/ritonavir 400/100 mg experienced Grade 3–4 bilirubin toxicity (>3 mg/dL). As discussed above, physiologic jaundice generally resolves in the first 2- 3 weeks of life to normal values of less than 1.2 mg/dL[27]. Causes of prolonged

jaundice include hemolytic disease, breast milk jaundice, prematurity, Gilbert syndrome. Crigler-Najjar syndrome, bowel obstruction, congenital hypothyroidism and galactosemia[11,14].

Reviewer Comment:
ATV drug concentrations in cord blood were approximately 12-19% of maternal concentrations, and ATV clearance is expected in the first few days of life based on the half life of ATV in adult patients. Therefore, prolonged UGT1A1 suppression or prolonged hyperbilirubinemia secondary to ATV would not be anticipated (per Dr. Zheng, the clinical pharmacology reviewer); however, initial scan of the infant bilirubin data at time points 14 days and greater appeared to identify elevated levels. Consequently, the number of infants with elevated bilirubin levels at age 14 days was examined:

Table 5: Infants with elevated bilirubin measurements at age 14 days or older (Normal bilirubin considered 1.2 mg/dL)

Patient Age (Day of Life)	Dosing Exposure Cohort	TSB level >1.5- 2.5 x ULN (>1.92-3.12 mg/dL)		TSB level > 2.5 - 5 x ULN (>3.12-6 mg/dL)		TSB level >5 x ULN (>6.0 mg/dL)		Total number of patients with TSB > 1.5 x ULN per cohort	Total number of patients with TSB > 1.5 x ULN
		Preterm	Term	Preterm	Term	Preterm	Term		
≥14-21 days	300 mg	-	-	-	1008, 1025	1027	-	3	9
	400 mg	1050, 1055,	-	1049	1065	1054*	1067	6	
> 21 days	300 mg	-	-	1027	-	-	-	1	1
	400 mg	-	-	-	-	-	-	0	
> 42 days	300 mg	-	-	1027	-	-	-	1	4
	400 mg	1056, 1068	1067	-	-	-	-	3	

Note: Patient 12-1054 had a bilirubin level of 8.5 mg/dL at day of life 17 and did not have further TSB levels reported.

Reviewer Comment:
Given that hyperbilirubinemia usually resolves within the first 2-3 weeks of life, the patients with elevated TSB levels after 21 days are of interest. Four patients had an elevated TSB 1.5 X ULN at a time point greater than 42 days of age (See Appendix VII: Bilirubin values in patients with elevated bilirubin levels at greater than 42 days).

Three patients were premature, three patients were in the 400 mg exposure cohort and only one had a documented return of TSB to normal. Although two patients were treated with trimethoprim sulfamethoxazole (SMX/TMP), the medication was started on the day the bilirubin level was performed (for patient 1027, November 27, 2007) or after the bilirubin level was evaluated (for patient 1056, bilirubin was assessed on October 27, 2008 and SMX/TMP treatment started on November 3, 2008). Maternal bilirubin levels

were unremarkable in all 4 patients, i.e. maximum maternal TSB value of the four patients was 2.5 mg/dL and the range of mean and median maternal bilirubin values were 0.7-1.9 mg/dL and 0.8-2.1 mg/dL.

Although premature infants may have a more protracted course of hyperbilirubinemia and normative data are not available, elevated bilirubin levels at 6-7 weeks of age appears unusual, and the reason for elevated bilirubin levels at this time point is unclear to the PMHS reviewers. Although low levels of unconjugated bilirubin levels are unlikely to have clinical significance, data are not available to assess the safety of a prolonged course of hyperbilirubinemia and hence a longer period of exposure to low levels of unconjugated bilirubin in infants.

Consult Questions:

1) Do neonates with in utero exposure to ATV have a higher incidence of neonatal hyperbilirubinemia as compared to healthy neonates? If yes, does the increased incidence and/or degree of neonatal hyperbilirubinemia place the ATV exposed neonates at higher risk of bilirubin related complications?

In the small group of study patients exposed to ATV when compared to the normative data of the incidence of hyperbilirubinemia in term infants from Bhutani et al[4] and analyzed based on the Guideline from the AAP on TSB levels for which phototherapy is recommended[1], the data suggest that study infants do not experience an increased incidence or degree of neonatal hyperbilirubinemia compared to healthy infants. The cumulative data from the 400 mg exposure dosing cohort (n=20) may suggest that these patients may have a slightly increased incidence and severity of hyperbilirubinemia compared to the 300 mg exposure cohort, but the data are inconclusive.

Study infants did not develop severe hyperbilirubinemia and were managed without complication; however, the study population excluded mothers more likely to have an infant at risk for the development of severe hyperbilirubinemia. In addition, the vast majority of patients (greater than 80%) were identified as Black/African American, a race with half the incidence of hyperbilirubinemia compared to Caucasians and a quarter of the incidence compared to Asians[23]. Therefore, the study data are not likely to be applicable to the general population of infants that may be exposed to ATV.

The study data and the literature raise the question whether infants of mothers treated with ATV could be at risk for the development of more severe hyperbilirubinemia secondary to two factors: the risk of an increased bilirubin load and/or the risk of decreased bilirubin clearance. As noted in the literature, passive placental transfer of unconjugated bilirubin to the fetus appears to occur at higher maternal bilirubin levels although a threshold level has not been identified. Hence, if an infant born to a mother treated with ATV develops hemolysis and/or has a condition that results in an increased red blood cell load, such as significant bruising or cephalohematoma, the combination of both increased unconjugated bilirubin from transplacental acquisition and from increased production as well as decreased bilirubin clearance secondary to UGT1A1

inhibition could hypothetically result in more severe and/or prolonged hyperbilirubinemia. Data are insufficient to determine whether prolonged low levels of hyperbilirubinemia either in-utero or during the neonatal period result in adverse effects.

In summary, ATV exposed infants in the study did not appear to have a markedly increased incidence and/or degree of neonatal hyperbilirubinemia in the first week of life compared to otherwise healthy infants. Depending on other factors that contribute to hyperbilirubinemia in the neonatal period, e.g. ABO blood incompatibility or bruising, in- utero exposure to ATV could potentially increase the incidence of clinically significant neonatal jaundice. Given the small number of study patients, and the fact that the study population is likely not representative of the general population in the United States, data are insufficient to conclude whether in-utero exposure to ATV increases the risk of bilirubin-related complications in exposed neonates. However, given the rare occurrence of acute or chronic bilirubin encephalopathy, if exposed infants are carefully monitored and managed in a facility able to perform phototherapy and exchange transfusions, the risk of developing acute bilirubin encephalopathy is likely to remain low even if ATV exposed infants are at increased risk of hyperbilirubinemia.

2) Is increased monitoring of bilirubin for exposed infants needed who do not have any obvious risk factors for neonatal hyperbilirubinemia (e.g. Coombs positive)?

The available data are inconclusive but appear to suggest that infants exposed in utero to ATV do not have severe hyperbilirubinemia. The AAP recommends universal systematic assessment for the risk of severe hyperbilirubinemia, close follow-up and prompt intervention when indicated.[1] Therefore, routine monitoring for the development of severe hyperbilirubinemia during the first few days of life appears to be reasonable for infants born to mothers taking ATV.

3) Given the small sample size (approx 41 infants total) and the incomplete data collection, do we need more data to further define the risk of neonatal hyperbilirubinemia in ATV exposed neonates?

Given the small sample size, limitations of the data, including incomplete data collection, the lack of infant ATV PK data and the complexity of bilirubin metabolism in utero and in the neonate, the available data are not adequate to fully characterize or define the risk of neonatal hyperbilirubinemia in all ATV exposed neonates. However, review of the data did not identify a safety signal.

Additional information to better characterize ATV's potential to inhibit UGT1A1 in the fetus and neonate and to evaluate the effect of elevated maternal unconjugated bilirubin levels on the fetus and the neonate, may be helpful to determine if ATV exposed neonates, especially those with additional risk factors for the development of severe hyperbilirubinemia, are at risk for the development of complications related to hyperbilirubinemia, including neurologic sequelae.

A prospective cohort study or clinical trial in pregnant HIV positive women exposed to ATV compared to pregnant HIV positive women not exposed to ATV, to assess and compare serum bilirubin levels in pregnant mothers and neonates at pre-specified time points, including birth, and to assess the time of resolution of hyperbilirubinemia in infants, could potentially answer some of the clinical uncertainties. However, per discussions with the clinical reviewers, this type of study may not be feasible due to limited use of ATV in pregnant women. In addition, the paucity of normative data in infants may limit the ability to interpret study results. Although additional information regarding the neurodevelopmental outcome of infants exposed to ATV in utero may be helpful, given the rare occurrence of acute and chronic bilirubin encephalopathy, the unknown effects of low levels of prolonged hyperbilirubinemia in children and the inherent difficulties in collecting long-term neurodevelopmental data, an additional clinical study to assess for adverse neurological outcomes in ATV exposed infants is unlikely to provide additional clinically useful information.

Data obtained from further review of the literature and/or the performance of additional nonclinical studies are unlikely to be able to provide information to better understand the risks associated with in utero exposure of infants born to mothers treated with ATV.

In summary, although the available data are not adequate to fully characterize the risk of in utero ATV exposure in neonates, no documented safety issue exists to justify a postmarketing requirement for an additional clinical study at this time, and additional nonclinical studies and literature review are unlikely to provide additional informative information..

4) Are there other comments or recommendations that PMHS/Pediatrics has for managing the risk(s) of *in utero* exposure to ATV?

None at this time.

SPONSOR'S PROPOSED LABELING CHANGES

1. Dosing recommendations based on S-025 PK Data

Based on PK data in HIV infected pregnant women, the sponsor is proposing adding a statement that says that (b) (4)

Reviewer comment

FDA Pharmacologists' review of the PK data however, are slightly different than the sponsor's interpretation in that they are recommending increasing the atazanavir dose to 400mg + 100 mg ritonavir during the second and third trimester in treatment – experienced patients when given with tenofovir or an H_2-receptor antagonist. There are also insufficient data to recommend a dose for use with tenofovir and H_2-receptor antagonists in treatment-experienced pregnant women. Please see the review of Dr. Jenny Zheng.

2. Addition of New Pregnancy Safety Data

I. Antiretroviral Pregnancy Registry Results

The Antiretroviral Pregnancy Registry interim report published May 2010 covers data from January 1989 to January 31, 2010. The purpose of the Antiretroviral Pregnancy Registry is to detect any major teratogenic effects of antiretroviral drugs to which pregnant women are exposed. Enrollment in the Registry is voluntary. Among first trimester exposure to atazanavir, there are sufficient numbers of first trimester exposures have been monitored to detect at least a two-fold increase in risk of overall birth defects. No such increases have been detected to date.

Reviewer comment
Addition of this information is appropriate.

II. Safety Data from S-025

The sponsor proposes adding safety data from S-025 regarding maternal and neonatal hyperbilirubinemia, maternal lactic acidosis, neonatal jaundice and need for phototherapy.

Reviewer comment
PMHS is working in collaboration with the Division to develop language that accurately reflect the study findings

III. Post-Marketing Data

The sponsor proposes [redacted] (b) (4)

Reviewer comment
The sponsor has been notified that they need to identify which cases are also included in the Antiretroviral Pregnancy Registry data to avoid duplication.

3. Pregnancy Labeling in the format of the Draft Pregnancy and Lactation Labeling Rule

The sponsor's proposed labeling is in the format of the Draft Pregnancy and Lactation Labeling Rule with the following 3 subsections: Fetal Risk Summary, Clinical Considerations, and Data.

Reviewer comment
Although the final rule has not been published, PMHS encourages sponsors to adopt this format, which includes narrative descriptions of the data, while still complying with the current regulations.

Provided below are revisions to the sponsor's proposed labeling that were agreed upon at the labeling meeting with the DAVP on January 5th, 2011.

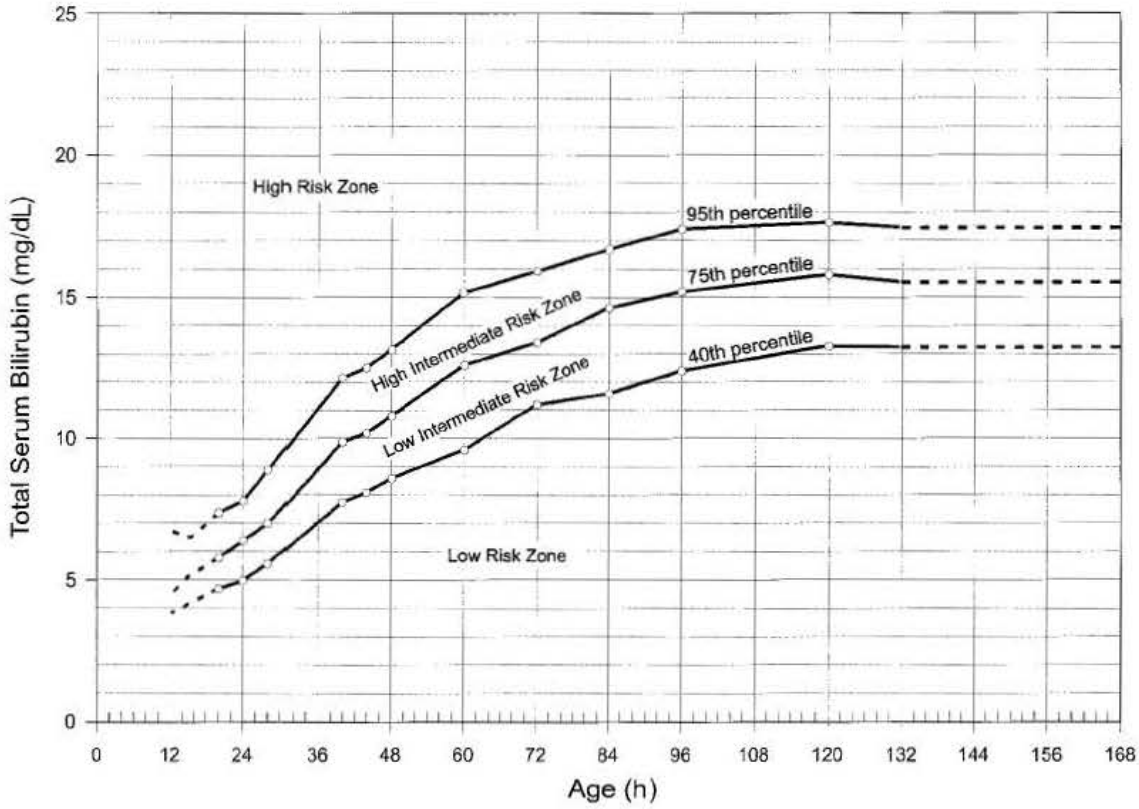
4 Page(s) of Draft Labeling has been Withheld in Full as b4 (CCI/TS) immediately following this page

Appendix I: Risk Factors for Development of Severe Hyperbilirubinemia in Infants of 35 or More Weeks' Gestation (in Approximate Order of Importance) AAP 2004 guidelines

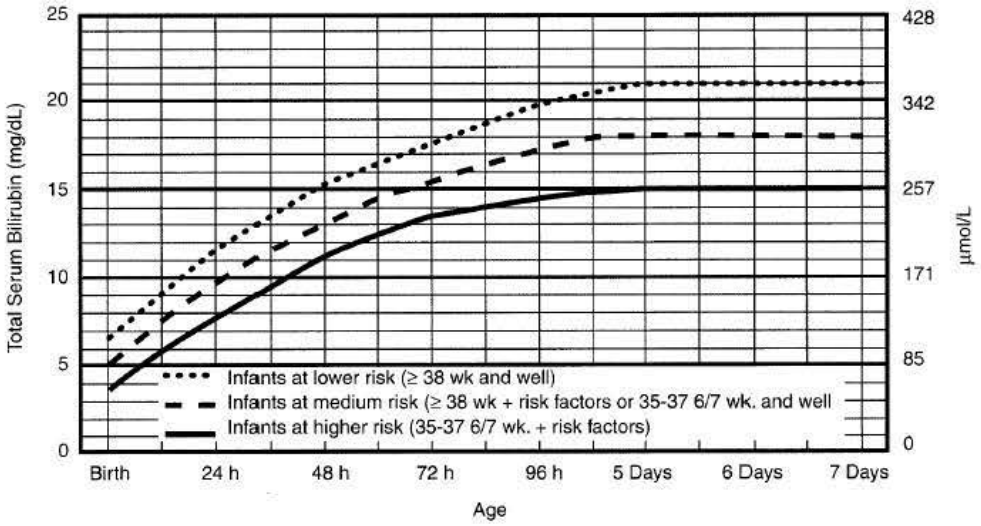
Major risk factors
Predischarge TSB or TcB level in the high-risk zone (Fig 2)[25,31]
Jaundice observed in the first 24 h[30]
Blood group incompatibility with positive direct antiglobulin test, other known hemolytic disease (eg, G6PD deficiency), elevated $ETCO_c$
Gestational age 35–36 wk[39,40]
Previous sibling received phototherapy[40,41]
Cephalohematoma or significant bruising[39]
Exclusive breastfeeding, particularly if nursing is not going well and weight loss is excessive[39,40]
East Asian race[39*]
Minor risk factors
Predischarge TSB or TcB level in the high intermediate-risk zone[25,31]
Gestational age 37–38 wk[39,40]
Jaundice observed before discharge[40]
Previous sibling with jaundice[40,41]
Macrosomic infant of a diabetic mother[42,43]
Maternal age ≥25 y[39]
Male gender[39,40]
Decreased risk (these factors are associated with decreased risk of significant jaundice, listed in order of decreasing importance)
TSB or TcB level in the low-risk zone (Fig 2)[25,31]
Gestational age ≥41 wk[39]
Exclusive bottle feeding[39,40]
Black race[38*]
Discharge from hospital after 72 h[40,44]

* Race as defined by mother's description.

Appendix II: Risk designation of term and near-term well newborns based on their hour-specific serum bilirubin values[4]



Appendix III: Guidelines for phototherapy in hospitalized infants of 35 or more weeks' gestation[1].



- Use total bilirubin. Do not subtract direct reacting or conjugated bilirubin.
- Risk factors = isoimmune hemolytic disease, G6PD deficiency, asphyxia, significant lethargy, temperature instability, sepsis, acidosis, or albumin < 3.0g/dL (if measured)
- For well infants 35-37 6/7 wk can adjust TSB levels for intervention around the medium risk line. It is an option to intervene at lower TSB levels for infants closer to 35 wks and at higher TSB levels for those closer to 37 6/7 wk.
- It is an option to provide conventional phototherapy in hospital or at home at TSB levels 2-3 mg/dL (35-50mmol/L) below those shown but home phototherapy should not be used in any infant with risk factors.

Appendix IV: Grading of Maternal and Infant Adverse Events

WHO Recommendations for Grading Acute and Subacute Toxic Effects:

ITEM	GRADE 1 TOXICITY	GRADE 2 TOXICITY	GRADE 3 TOXICITY	GRADE 4 TOXICITY
BILIRUBIN	1.1 - 1.5 x upper normal	1.6 - 2.5 X upper normal	2.6 - 5 X upper normal	> 5 X upper normal

Division of Aids Toxicity Table for Grading Severity of Pediatric Adverse Experiences:

PARAMETER	GRADE 1 Mild	GRADE 2 Moderate	GRADE 3 Severe	GRADE 4 Potentially Life-Threatening
Bilirubin (Total)				
Pediatric > 14 days	1.1 - 1.5 x ULN	1.6 - 2.5 x ULN	2.6 - 5.0 x ULN	> 5.0 x ULN
Infant ≤ 14 days (non-hemolytic)	NA	20.0 - 25.0 mg/dL *342 - 428 µmol/L*	25.1 - 30.0 mg/dL *429 - 513 µmol/L*	> 30.0 mg/dL *> 513.0 µmol/L*
Infant ≤ 14 days (hemolytic)	NA	NA	20.0 - 25.0 mg/dL *342 - 428 µmol/L*	> 25.0 mg/dL > 428 µmol/L

Appendix V: Demographics and Disease Characteristics of Enrolled Infants

	NUMBER OF SUBJECTS (%)	
	Mothers 3rd Trimester Treatment	
	ATV300/RTV N = 20	ATV400/RTV N = 20
Gest. Age @ Delivery (Weeks)		
MEAN (SE)	38 (0.3)	38 (0.3)
MEDIAN	38	38
MIN, MAX	35, 40	35, 41
MISSING	0	0
Gender: N (%)		
MALE	12 (60)	9 (45)
FEMALE	8 (40)	11 (55)
Race: N (%)		
BLACK/AFRICAN AMERICAN	15 (75)	18 (90)
WHITE	5 (25)	1 (5)
OTHER: MIXED RACE	0	1 (5)
Region: N (%)		
AFRICA	14 (70)	14 (70)
NORTH AMERICA	6 (30)	6 (30)

Percentages are based on subjects with measurements.

Appendix VI: Infants with TSB greater than 4 mg/dL in the first 24 hours of life

Note:
Mother's mean and median maternal bilirubin levels refer to the mean and median of the values during the last 4 weeks of pregnancy.

Infants with an asterisk after the patient identification number also developed a bilirubin level greater than 5 mg/dL within the first 24 hours of life

<u>In Utero Exposure ATV 300 mg/RTV 100 mg</u>:

5-1034* (39.3 weeks gestation)
No intervention.
Mother's bilirubin (mg/dL): Birth 0.5, Mean: 0.8, Median:0.9

Subject ID	Birth Date	Birth Time	Study Day	Age (in hours)	Lab Date	Lab Time	Total Bilirubin (mg/dL)
AI424182-5-1034	(b) (6)		2	9.8	(b) (6)	9:30	5.4
			3	36.8		12:30	10.6
			5	85.3		13:00	12.1
			7	132.7		12:25	10.4
			14	300.3		12:00	3.2
			47	1090.5		10:15	0.4

8-1018* (38.3 weeks gestation)
Met AAP PT Threshold at 1.5 hours. No intervention.
Mother's bilirubin: Birth 5.7, Mean: 4.1, Median:4.3

Subject ID	Birth Date	Birth Time	Study Day	Age (in hours)	Lab Date	Lab Time	Total Bilirubin (mg/dL)
AI424182-8-1018	(b) (6)		1	1.5	(b) (6)	2:30	7.6
			3	59.9		12:56	13.5
			7	152.3		9:20	6.4
			13	298.6		11:38	1.3
			41	971.0		12:00	0.2
			125	2988.0		13:00	0.1

8-1027* (35.6 weeks gestation)
Received phototherapy
Mother's bilirubin (mg/dL): Birth 2.3, Mean 1.9, Median 2.1

Subject ID	Birth Date	Birth Time	Study Day	Age (in hours)	Lab Date	Lab Time	Total Bilirubin (mg/dL)
AI424182-8-1027	(b) (6)		1	0.3	(b) (6)	15:40	5.7
			3	46.6		14:00	13.0
			5	91.3		10:43	9.9
			7	137.5		8:55	9.8
			16	353.6		9:00	8.3
			44	1027.9		11:20	3.3

12-1025 (38.1 weeks gestation)
Received phototherapy
Mother's bilirubin (mg/dL): Birth: 1.2, Mean: 1.4, Median 1.4

Subject ID	Birth Date	Birth Time	Study Day	Age (in hours)	Lab Date	Lab Time	Total Bilirubin (mg/dL)
AI424182-12-1025	(b) (6)		1	5.8	(b) (6)	8:45	4.7
			3	54.9		9:50	12.2
			5	102.5		9:30	13.2
			7	151.5		10:30	15.3
			15	347.0		14:00	4.6
			46	1089.5		12:30	0.8

<u>In Utero Exposure ATV 400 mg/RTV 100 mg</u>:

4-1032 (36 weeks gestation)

No intervention

Mother's bilirubin (mg/dL): Birth 3.8, Mean 2.8, Median 2.9

Subject ID	Birth Date	Birth Time	Study Day	Age (in hours)	Lab Date	Lab Time	Total Bilirubin (mg/dL)
AI424182-4-1032	(b) (6)		1	4.2	(b) (6)	21:19	4.4
			4	64.0		9:10	8.9
			5	92.0		13:05	10.0
			7	136.7		9:50	8.1
			14	305.5		10:40	3.4
			41	953.1		10:15	0.5
			130	3088.7		9:50	0.1

5-1040 (38.4 weeks gestation)

No intervention

Mother's bilirubin (mg/dL): Birth 2.7, Mean 1.2, Median 1.0

Subject ID	Birth Date	Birth Time	Study Day	Age (in hours)	Lab Date	Lab Time	Total Bilirubin (mg/dL)
AI424182-5-1040	(b) (6)		1	0.2	(b) (6)	23:45	4.6
			4	57.4		9:00	7.0
			6	106.4		10:00	2.8
			8	155.9		11:30	1.6
			15	322.9		10:30	0.8
			18	398.4		13:58	0.6
			43	997.9		13:30	0.4

5-1041* (39.1 weeks gestation)

No intervention

Mother's bilirubin (mg/dL): Birth 1.9, Mean 1.4, Median 1.7

Subject ID	Birth Date	Birth Time	Study Day	Age (in hours)	Lab Date	Lab Time	Total Bilirubin (mg/dL)
AI424182-5-1041	(b) (6)		2	17.3	(b) (6)	9:00	8.0
			4	64.8		8:35	5.4
			6	114.6		10:20	2.1
			8	165.9		13:40	1.2
			15	334.0		13:45	0.5
			43	1006.5		14:15	0.2

5-1064* (41.3 weeks gestation)

No intervention

Mother's bilirubin (mg/dL): Birth 5.0, Mean 4.3, Median 5.0

Subject ID	Birth Date	Birth Time	Study Day	Age (in hours)	Lab Date	Lab Time	Total Bilirubin (mg/dL)
AI424182-5-1064	(b) (6)		1	0.7	(b) (6)	13:40	6.2
			3	44.0		9:00	9.3

AI424182-5-1064	(b) (6)	5	92.7	(b) (6)	9:43	3.5
		7	139.6		8:35	2.0
		15	334.5		11:30	0.6
		43	1007.6		12:35	0.4

12-1054 (35 weeks gestation)

Received phototherapy

Mother's bilirubin (mg/dL): Birth 2.7, Mean 2.7, Median 2.8

Subject ID	Birth Date	Birth Time	Study Day	Age (in hours)	Lab Date	Lab Time	Total Bilirubin (mg/dL)
AI424182-12-1054	(b) (6)		1	0.0	(b) (6)	12:42	4.4
			3	49.3		14:00	9.6
			5	93.5		10:10	8.8
			7	140.3		9:00	11.4
			18	410.6		15:15	8.5

14-1049* (37.6 weeks gestation)

No intervention

Mother's bilirubin (mg/dL): Birth 2.3, Mean 1.9, Median 2.3

Subject ID	Birth Date	Birth Time	Study Day	Age (in hours)	Lab Date	Lab Time	Total Bilirubin (mg/dL)
AI424182-14-1049	(b) (6)	7:20	1	3.5	(b) (6)	10:49	4.1
				8.0		15:20	5.1
			3	46.5		5:52	10.4
				59.0		18:17	10.8
			5	98.6		9:55	10.6
			7	147.5		10:50	9.3
			15	339.0		10:17	3.6
			43	1014.2		13:30	0.7

Appendix VII: Bilirubin values in patients with elevated bilirubin levels at greater than 42 days

In Utero Exposure ATV 300 mg/RTV 100 mg:

8-1027 (35.6 weeks gestation)

Received phototherapy

Mother's bilirubin (mg/dL): Birth 2.3, Mean 1.9, Median 2.1

TMP/SMZ started (b) (6)

Subject ID	Birth Date	Birth Time	Study Day	Age (in hours)	Lab Date	Lab Time	Total Bilirubin (mg/dL)
AI424182-8-1027	(b) (6)		1	0.3	(b) (6)	15:40	5.7
			3	46.6		14:00	13.0
			5	91.3		10:43	9.9
			7	137.5		8:55	9.8
			16	353.6		9:00	8.3
			44	1027.9		11:20	3.3

In Utero Exposure ATV 400 mg/RTV 100 mg:

4-1056 (37.6 weeks gestation)

Mother's bilirubin (mg/dL): Birth 0.9, Mean 1.3, Median 1.1

TMP/SMZ started (b) (6)

Subject ID	Birth Date	Birth Time	Study Day	Age (in hours)	Lab Date	Lab Time	Total Bilirubin (mg/dL)
AI424182-4-1056	(b) (6)		1	4.7	(b) (6)	19:00	2.6
			3	50.2		16:25	6.8
			9	189.1		11:20	5.3
			44	1027.3		9:35	2.3
			123	2924.6		10:50	0.6

5-1067 (38.4 weeks)

Mother's bilirubin (mg/dL): Birth 1.9, Mean 1.4, Median 1.6

Subject ID	Birth Date	Birth Time	Study Day	Age (in hours)	Lab Date	Lab Time	Total Bilirubin (mg/dL)
AI424182-5-1067	(b) (6)		1	1.0	(b) (6)	13:30	3.2
			3	44.8		9:15	9.6
			5	96.3		12:45	12.2
			7	144.5		13:00	13.7
			15	336.0		12:30	7.7
			46	1082.0		14:30	2.0

12-1068 (36.3 weeks gestation)

Mother's bilirubin (mg/dL): Birth 0.9, Mean 0.7, Median 0.8

Subject ID	Birth Date	Birth Time	Study Day	Age (in hours)	Lab Date	Lab Time	Total Bilirubin (mg/dL)

AI424182-12-1068	(b) (6)	1	0.4	(b) (6) 7:50	2.3
		3	52.6	12:00	8.3
		5	97.1	8:30	11.7
		7	144.9	8:20	11.6
		14	313.2	8:35	4.2
		42	985.4	8:50	3.0

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/s/

ELIZABETH L DURMOWICZ

01/14/2011

Hari has been left off the signature block per her request since she is on leave. This is the entry to attach to the MH consult request. Entry earlier this AM was attached to the pediatric consult request.

LEYLA SAHIN

01/14/2011

Karen B FEIBUS

01/14/2011

I agree with the information presented, conclusions reached, and recommendations provided in this review.

LISA L MATHIS

01/18/2011

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology

Date:	January 6, 2011
To:	Debra Birnkrant, MD, Director Division of Anti-Viral Products (DAVP)
Through:	Robert Boucher, MD, MPH, Director Division of Pharmacovigilance II Office of Surveillance and Epidemiology
From:	Kelly Cao, PharmD, Safety Evaluator Team Leader Division of Pharmacovigilance II, OSE
Subject:	Hyperbilirubinemia and hypoglycemia in neonates exposed in-utero
Drug Name(s):	atazanavir sulfate (Reyataz®)
Application Type/Number:	NDA 21567
Submission Number:	Supplement 25
Applicant/sponsor:	Bristol Myers Squibb Co
OSE RCM #:	2010-2492

1 INTRODUCTION

This document reviews AERS for reports of hyperbilirubinemia, kernicterus, and hypoglycemia in neonates exposed to atazanavir in-utero. DAVP received a new efficacy supplement (S-25) for NDA 21567 (Reyataz®) with a study on atazanavir boosted with ritonavir (ATV/RTV) as part of highly active anti-retroviral therapy (HAART) therapy in HIV-1 infected pregnant women. The medical officer reviewing the Supplement noted neonatal hyperbilirubinemia and hypoglycemia as potential safety concerns and requested an OSE review of AERS database.

2 METHODS AND MATERIALS

AERS SELECTION OF CASES

The AERS database was searched on November 16, 2010 for neonatal reports of atazanavir and the following preferred terms (PT): *blood bilirubin increased, blood bilirubin unconjugated increased, jaundice neonatal, hyperbilirubinaemia, hyperbilirubinaemia neonatal, hypoglycaemia, hypoglycaemia neonatal,* and *kernicterus.* Age was limited from 0 to 1 year.

3 RESULTS

ADVERSE EVENT CASES

The AERS search retrieved eleven reports (crude count). After removal of duplicates and reports of non-interest (i.e. no in-utero exposure), there were a total of 6 unique cases. The 6 cases reported the following events of interest: hyperbilirubinemia (n=6), jaundice (n=1), and hypoglycemia (n=3). There were no reports of neonatal kernicterus. Details are provided below.

Hyperbilirubinemia (n=6): The gestational age ranged from 31 to 42 weeks, median 36 weeks. Two cases reported bilirubin levels, the highest total bilirubin levels were 10.6 mg/dL (day 2) and 160 umol/L [equivalent to 9.4 mg/dL] (day 3). The neonate with a total bilirubin level equivalent to 9.4 mg/dL was also reported to have jaundice. These two neonates received phototherapy, and hyperbilirubinemia resolved after 1-2 days in one neonate and was unknown in the other. None of the other four cases reported treatment for hyperbilirubinemia. Hyperbilirubinemia was reported to have occurred at $\leq$ 3 days of life in five cases (unknown-1). No deaths were reported. One "case" was actually a report of two infants with hyperbilirubinemia but had very limited information.

Five of six neonates reported risk factors for hyperbilirubinemia (5 were premature or borderline premature, 2 were septic with metabolic acidosis, 2 had a diabetic mother, and one reported the use of oxytocin and also had thalassemia alpha and anemia).

The remaining case reported a neonate born at 42 weeks gestation with raised bilirubin on the day of birth requiring an ICU stay. No specific treatment for hyperbilirubinemia was reported and no levels were provided. No maternal medical problems or complications during delivery or postpartum period were reported. No other pertinent information was provided.

Hypoglycemia (n=3): All three neonates were born premature (33, 36 and 36 weeks gestation) and had other risk factors for hypoglycemia.

Two of the neonates were twins of each other whose mother was diabetic. They were also suspected of having sepsis. Blood glucose levels were not reported. Hypoglycemia was reported to have occurred on the day of birth and was treated with intravenous fluids and feedings. The hypoglycemia resolved the following day.

The 3rd neonate was delivered by an emergency c-section due to acute severe maternal pancreatitis and fetal cardiac arrhythmia. The blood glucose values were as low as 20 mg/dL at 10 and 32 hours after birth. The hypoglycemic episodes recurred despite infusions of dextrose 10 and 30% solutions, and intravenous treatment with glucagon. Hypoglycemia was reported to have resolved within a few days.

4 DISCUSSION

Because the incidence of physiologic hyperbilirubinemia is high in infants, particularly in preterm infants, and various factors including disease state can affect bilirubin levels, the contributory role of atazanavir exposure and its association with hyperbilirubinemia in these cases is unknown. Approximately 60-70% of term infants and ~80% of preterm infants develop jaundice in the first week of life.[1] The incidence is higher in populations living at higher altitudes and also varies with ethnicity. Some risk factors for neonatal hyperbilirubinemia include sepsis, acidosis, asphyxia, temperature instability, G6PD deficiency, hemolytic disease (ABO or G6PD deficiency), borderline prematurity (35-38 weeks), exclusive breast-feeding, East Asian or American Indian ethnicity, cephalohematoma or significant bruising, maternal diabetes, family history of neonatal jaundice, and use of oxytocin in labor. [1]

The three cases of hypoglycemia are all confounded by two or more risk factors for neonatal hypoglycemia, including perinatal stress, sepsis, maternal diabetes, and prematurity. Approximately 40% of infants of diabetic mothers have hypoglycemia.[1]

5 CONCLUSIONS

Based on the paucity of AERS data and confounding risk factors noted in the cases, no conclusions can be made concerning the association between in-utero exposure to ritonavir-boosted atazanavir and neonatal hyperbilirubinemia, jaundice, kernicterus, and hypoglycemia.

[1] Stat!Ref online electronic medical library. Neonatology: Management, Procedures, On-Call Problems, Diseases, and Drugs - 6th Ed. (2009). Part IV - Diseases and Disorders. Accessed 11/17/10.

APPENDIX

Line listing of AERS cases of neonatal hyperbilirubinemia and hypoglycemia associated with in-utero atazanavir exposure, as of November 16, 2010 (n=6)

ISR#	Country	Event Year or Received Year	Gestational Age (weeks) Birth Weight	Event of interest	Comments	Treatment/ Outcome
7038004	Great Britain	2009	42 3035 gm	Blood bilirubin increased	Raised bili on day of birth requiring ICU treatment. APGAR 9 at one min, 10 at five min. No maternal medical problems or complications during delivery or postpartum period were reported.	HO
6705847	US	2008	37 3000 gm	Hyperbilirubinemia neonatal	The neonate had poor respiratory effort with intermittent spontaneous breathing with ventilator support required, systolic murmur 3/6, 2+ femoral pulses bilaterally, hepatosplenomegaly, poor tone and few spontaneous movements of extremities. Also reported ECHO confirmed congenital VSD, PDA and dilated coronary arteries, pulmonary hypertension, thalassemia alpha, congenital hepatomegaly and anemia. APGAR 1 at one min, 5 at five min. On day 3 of life patient developed direct hyperbilirubinemia. On day of life 5 developed thrombocytopenia and left portal vein thrombosis. Maternal HIV infection and hypertension. Mother given oxytocin during delivery.	HO,LT
5239885	US	2006	36 2093 gm	Hypoglycemia, hyperbilirubinemia	On day of birth (day 0) she experienced hypoglycemia (diabetic mother and premature) and suspected sepsis (started ampicillin and gentamicin). APGAR 8 at 1 min and 9 at 5 min.	Photo-therapy HO

					On day 1 hypoglycemia resolved and patient experienced metabolic acidosis, abdominal distension, and jitteriness. Experienced hyperbili on day 2 of life (birth is day 0). Total bili 10.6 (day 2), 6 (day 6). Treated with phototherapy. Resolved in 1-2 days. On day 4 metabolic acidosis resolved.	
5239925	US	2006	36 2280 gm	Hyperbilirubinemia, hypoglycemia, hyperbilirubinemia neonatal	On an unreported date, he experienced hyperbilirubinemia, hypoglycemia (diabetic mother and premature), suspected sepsis (48 hrs of ampicillin and gentamicin), metabolic acidosis, abdominal distension, bradycardia, and jitteriness. APGAR 8 at 5 min and 9 at 10 min. Experienced hyperbili on day 2 of life (birth is day 0). Treated with phototherapy. Discharged from the hospital on day of life 6.	HO
4747508	France	2005	33 2500 gm	Hypoglycemia, jaundice neonatal	Baby delivered via emergency c-section due to mother's acute severe pancreatitis and fetal cardiac arrhythmia. ART discontinued 4 days prior to c-section. APGAR 10-10. Within a few hours after delivery the neonate experienced recurrent severe hypoglycemia despite iv glucose and Glucagon. On day 3 of life patient experienced jaundice of moderate intensity, diagnosed with pre-term jaundice. Total bili160 umol/L at day 3 of life, conjugated 8 umol/L. On day 7 diagnosed with hemorrhagic colitis.	Photo-therapy HO
4778532	US	2005	31	Hyperbilirubinemia	Report on two infants. Limited information.	Not reported

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/s/

KELLY Y CAO
01/06/2011

ROBERT M BOUCHER
01/06/2011

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 # 21-567 BLA#	NDA Supplement #:S- 025 BLA STN #	Efficacy Supplement Type SE- 5
Proprietary Name: Reyataz Established/Proper Name: atazanavir sulfate Dosage Form: capsule Strengths: 100, 150, 200, 300 mg		
Applicant: Bristol Meyers Squibb Company Agent for Applicant (if applicable):		
Date of Application: 8.6.10 Date of Receipt: 8.6.10 Date clock started after UN:		
PDUFA Goal Date: 2.6.11	Action Goal Date (if different): 2.4.11	
Filing Date: 10.5.10	Date of Filing Meeting: 9.20.10	
Chemical Classification: (1,2,3 etc.) (original NDAs only)		
Proposed indication(s)/Proposed change(s): To update the label with the results of study AI424182 that was conducted in HIV-infected pregnant women using atazanavir with ritonavir		

Type of Original NDA: AND (if applicable) Type of NDA Supplement: ***If 505(b)(2): Draft the "505(b)(2) Assessment" form found at:*** ***http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/ucm027499.html*** ***and refer to Appendix A for further information.***	☐ 505(b)(1) ☐ 505(b)(2) ☒ 505(b)(1) ☐ 505(b)(2)
Review Classification: ***If the application includes a complete response to pediatric WR, review classification is Priority.*** ***If a tropical disease priority review voucher was submitted, review classification is Priority.***	☐ Standard ☒ Priority ☐ Tropical Disease Priority Review Voucher submitted
Resubmission after withdrawal? ☐	Resubmission after refuse to file? ☐
Part 3 Combination Product? ☐ ***If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults***	☐ Convenience kit/Co-package ☐ Pre-filled drug delivery device/system ☐ Pre-filled biologic delivery device/system ☐ Device coated/impregnated/combined with drug ☐ Device coated/impregnated/combined with biologic ☐ Drug/Biologic ☐ Separate products requiring cross-labeling ☐ Possible combination based on cross-labeling of separate products ☐ Other (drug/device/biological product)

☐ Fast Track ☐ Rolling Review ☐ Orphan Designation ☐ Rx-to-OTC switch, Full ☐ Rx-to-OTC switch, Partial ☐ Direct-to-OTC Other:	☐ PMC response ☐ PMR response: ☐ FDAAA [505(o)] ☐ PREA deferred pediatric studies [21 CFR 314.55(b)/21 CFR 601.27(b)] ☐ Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) ☐ Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)

Collaborative Review Division (*if OTC product*):

List referenced IND Number(s): 56,897

Goal Dates/Product Names/Classification Properties	**YES**	**NO**	**NA**	**Comment**
PDUFA and Action Goal dates correct in tracking system? ***If no, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.***	X			
Are the proprietary, established/proper, and applicant names correct in tracking system? ***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.***	X			
Are all classification properties [e.g., orphan drug, OTC, 505(b)(2)] entered into tracking system? ***If no, ask the document room staff to make the appropriate entries.***	X			
Application Integrity Policy	**YES**	**NO**	**NA**	**Comment**
Is the application affected by the Application Integrity Policy (AIP)? ***Check the AIP list at: http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm***		X		
If yes, explain in comment column.				
If affected by AIP, has OC/DMPQ been notified of the submission? **If yes,** date notified:				
User Fees	**YES**	**NO**	**NA**	**Comment**
Is Form 3397 (User Fee Cover Sheet) included with authorized signature?	X			

User Fee Status	Payment for this application:
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.	☒ Paid ☐ Exempt (orphan, government) ☐ Waived (e.g., small business, public health) ☐ Not required

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.	Payment of other user fees: ☒ Not in arrears ☐ In arrears

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?			X	
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)].**			X	
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)]?** ***Note:*** *If you answered yes to any of the above questions, the application may be refused for filing under 21 CFR 314.101(d)(9).*			X	
Is there unexpired exclusivity on the active moiety (e.g., 5-year, 3-year, orphan or pediatric exclusivity)? ***Check the Electronic Orange Book at:*** ***http://www.fda.gov/cder/ob/default.htm*** **If yes**, please list below:			X	

Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration

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 108(b)(2).Unexpired, 3-year exclusivity will only block the approval, not the submission of a 505(b)(2) application.

Exclusivity	**YES**	**NO**	**NA**	**Comment**
Does another product have orphan exclusivity for the same indication? ***Check the Electronic Orange Book at:*** ***http://www.fda.gov/cder/ob/default.htm***		X		
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)]**? ***If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007)***		X		

Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? ***(NDAs/NDA efficacy supplements only)*** **If yes**, # years requested: 3 years ***Note:*** *An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.*	X			
Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use (***NDAs only***)?		X		
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)? ***If yes, contact Mary Ann Holovac, Director of Drug Information, OGD/DLPS/LRB.***			X	

Format and Content				
Do not check mixed submission if the only electronic component is the content of labeling (COL).	☐ All paper (except for COL) ☒ All electronic ☐ Mixed (paper/electronic) ☒ CTD ☐ Non-CTD ☐ 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).	**X**			
Index: Does the submission contain an accurate comprehensive index?	**X**			
Is the submission complete as required under 21 CFR 314.50 (*NDAs/NDA efficacy supplements*) or under 21 CFR 601.2 (*BLAs/BLA efficacy supplements*) including: ☐ legible ☐ English (or translated into English) ☐ pagination ☐ navigable hyperlinks (electronic submissions only) **If no**, explain.	**X**			

[1] http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072349.pdf

BLAs only: Companion application received if a shared or divided manufacturing arrangement? **If yes**, BLA #			**X**	
Forms and Certifications				
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.*				
Application Form	**YES**	**NO**	**NA**	**Comment**
Is form FDA 356h included with authorized signature per 21 CFR 314.50(a)? ***If foreign applicant, <u>both</u> the applicant and the U.S. agent must sign the form [see 21 CFR 314.50(a)(5)].***	X			
Are all establishments and their registration numbers listed on the form/attached to the form?		X		
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)?	X			
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)? ***Forms must be signed by the APPLICANT, not an Agent [see 21 CFR 54.2(g)].*** ***Note:*** *Financial disclosure is required for bioequivalence studies that are the basis for approval.*	X			
Clinical Trials Database	**YES**	**NO**	**NA**	**Comment**
Is form FDA 3674 included with authorized signature? ***If yes, ensure that the application is also coded with the supporting document category, "Form 3674."*** ***If no, ensure that language requesting submission of the form is included in the acknowledgement letter sent to the applicant***	X			
Debarment Certification	**YES**	**NO**	**NA**	**Comment**
Is a correctly worded Debarment Certification included with authorized signature? ***Certification is not required for supplements if submitted in the original application; If foreign applicant, <u>both</u> the applicant and the U.S. Agent must sign the certification [per Guidance for Industry: Submitting Debarment Certifications].*** ***Note:*** *Debarment Certification should use wording in FD&C Act*	X			

section 306(k)(l) 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…"				
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? ***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)*** ***If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.***			X	

Controlled Substance/Product with Abuse Potential	**YES**	**NO**	**NA**	**Comment**
For NMEs: Is an Abuse Liability Assessment, including a proposal for scheduling, submitted per 21 CFR 314.50(d)(5)(vii)? ***If yes,*** *date consult sent to the Controlled Substance Staff:* For non-NMEs: *Date of consult sent to Controlled Substance Staff*:			**X**	

Pediatrics	**YES**	**NO**	**NA**	**Comment**
PREA Does the application trigger PREA? ***If yes, notify PeRC RPM (PeRC meeting is required)***[2] ***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 reviewed by PeRC prior to approval of the application/supplement.*		X		
If the application triggers PREA, are the required pediatric assessment studies or a full waiver of pediatric studies included?			X	
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? ***If no, request in 74-day letter***	X			partial deferral for ≥ 3 months to < 6 years

[2] http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027829.htm

If a request for full waiver/partial waiver/deferral is included, does the application contain the certification(s) required under 21 CFR 314.55(b)(1), (c)(2), (c)(3)/21 CFR 601.27(b)(1), (c)(2), (c)(3) ***If no, request in 74-day letter***	X			
BPCA (NDAs/NDA efficacy supplements only): Is this submission a complete response to a pediatric Written Request? ***If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required)***[3]		X		
Proprietary Name	**YES**	**NO**	**NA**	**Comment**
Is a proposed proprietary name submitted? ***If yes, ensure that the application is also coded with the supporting document category, "Proprietary Name/Request for Review."***			X	
REMS	**YES**	**NO**	**NA**	**Comment**
Is a REMS submitted? ***If yes, send consult to OSE/DRISK and notify OC/ DCRMS via the DCRMSRMP mailbox***			X	
Prescription Labeling	☐ **Not applicable**			
Check all types of labeling submitted.	☒ Package Insert (PI) ☒ Patient Package Insert (PPI) ☐ Instructions for Use (IFU) ☐ Medication Guide (MedGuide) ☒ Carton labels ☐ Immediate container labels ☐ Diluent ☐ Other (specify)			
	YES	**NO**	**NA**	**Comment**
Is Electronic Content of Labeling (COL) submitted in SPL format? ***If no, request in 74-day letter.***	X			
Is the PI submitted in PLR format?[4]	X			
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?			X	

[3] http://inside fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027837.htm

[4] http://inside fda.gov:9003/CDER/OfficeofNewDrugs/StudyEndpointsandLabelingDevelopmentTeam/ucm025576.htm

If no waiver or deferral, request PLR format in 74-day letter.				
All labeling (PI, PPI, MedGuide, IFU, carton and immediate container labels) consulted to DDMAC?	X			
MedGuide, PPI, IFU (plus PI) consulted to OSE/DRISK? (*send WORD version if available*)	X			
Carton and immediate container labels, PI, PPI sent to OSE/DMEPA and appropriate CMC review office (OBP or ONDQA)?	X			
OTC Labeling	☒ **Not Applicable**			
Check all types of labeling submitted.	☐ Outer carton label ☐ Immediate container label ☐ Blister card ☐ Blister backing label ☐ Consumer Information Leaflet (CIL) ☐ Physician sample ☐ Consumer sample ☐ Other (specify)			
	YES	**NO**	**NA**	**Comment**
Is electronic content of labeling (COL) submitted? ***If no, request in 74-day letter.***				
Are annotated specifications submitted for all stock keeping units (SKUs)? ***If no, request in 74-day letter.***				
If representative labeling is submitted, are all represented SKUs defined? ***If no, request in 74-day letter.***				
All labeling/packaging, and current approved Rx PI (if switch) sent to OSE/DMEPA?				
Other Consults	**YES**	**NO**	**NA**	**Comment**
Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team) ***If yes, specify consult(s) and date(s) sent:***			X	
Meeting Minutes/SPAs	**YES**	**NO**	**NA**	**Comment**
End-of Phase 2 meeting(s)? **Date(s):** ***If yes, distribute minutes before filing meeting***		X		
Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? **Date(s):** ***If yes, distribute minutes before filing meeting***		X		

Any Special Protocol Assessments (SPAs)? **Date(s):** ***If yes, distribute letter and/or relevant minutes before filing meeting***		X		

ATTACHMENT

MEMO OF FILING MEETING

DATE: 9.20.10

BLA/NDA/Supp #: 21-567/S-025

PROPRIETARY NAME: Reyataz

ESTABLISHED/PROPER NAME: atazanavir sulfate

DOSAGE FORM/STRENGTH: 100, 150, 200, 300 mg

APPLICANT: Bristol Meyers Squibb Company

PROPOSED INDICATION(S)/PROPOSED CHANGE(S): To update the current label with the results of study AI424182 that was conducted in HIV-infected pregnant women using atazanavir with ritonavir.

BACKGROUND: NDA 21-567/S-025- Reyataz/Atazanavir is a protease inhibitor for the treatment of HIV infection. This application was submitted to provide data from study AI424182, a study of atazanavir and ritonavir in HIV-infected pregnant women with corresponding labeling revisions. The application was submitted to expand the population to include HIV-infected pregnant women; however there are no new dosing regimens. The application was submitted on August 6, 2010 and is a priority review. The filing date is October 5, 2010 and the PDUFA goal date is February 6, 2011. The midcycle meeting is November 8, 2010 and the wrap up meeting is January 10, 2011.

REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Venessa M Perry	Y
	CPMS/TL:	Vicky Tyson	Y
Cross-Discipline Team Leader (CDTL)	Sarah Robertson		Y
Clinical	Reviewer:	Alan Shapiro	Y
	TL:	Mary Singer	Y
Social Scientist Review (*for OTC products*)	Reviewer:		
	TL:		

OTC Labeling Review (*for OTC products*)	Reviewer:		
	TL:		
Clinical Microbiology (*for antimicrobial products*)	Reviewer:	Lisa Naeger	Y
	TL:	Jules O'Rear	Y

Clinical Pharmacology	Reviewer:	Jenny Zheng	Y
	TL:	Sarah Robertston	Y
Biostatistics No biostats in the NDA	Reviewer:	Thomas Hammerstrom	Y
	TL:	Greg Soon	N
Nonclinical (Pharmacology/Toxicology) No PT in the NDA	Reviewer:	KM Wu	Y
	TL:	Hanan Ghantous	Y
Statistics (carcinogenicity)	Reviewer:		
	TL:		
Immunogenicity (assay/assay validation) *(for BLAs/BLA efficacy supplements)*	Reviewer:		
	TL:		
Product Quality (CMC)	Reviewer:	Brian Rogers	N
	TL:	Dorota Mateka	Y
Quality Microbiology *(for sterile products)*	Reviewer:		
	TL:		
CMC Labeling Review	Reviewer:		
	TL:		
Facility Review/Inspection	Reviewer:		
	TL:		
OSE/DMEPA (proprietary name)	Reviewer:	Lori Cantin	N(PM present)
	TL:	Kristina Toliver	N
OSE/DRISK (REMS)	Reviewer:	Debra Boxwell	N(PM present)
	TL:	Kelly Cao	N
OC/DCRMS (REMS)	Reviewer:		
	TL:		

Bioresearch Monitoring (DSI)	Reviewer:	Tony El Hage Martin Yau	Y Y
	TL:	Tejashri Purohit-Sheth	N
Controlled Substance Staff (CSS)	Reviewer:		
	TL:		
Other reviewers	Leyla Sahin, MHT, Karen Feibus, TL Lynn Panholzer, DDMAC, Michelle Safarik, TL		Y(L. Sahin)
Other attendees	Brantley Dorch, OSE PM		Y

FILING MEETING DISCUSSION:

GENERAL • 505(b)(2) filing issues? **If yes,** list issues:	☒ Not Applicable ☐ YES ☐ NO
• Per reviewers, are all parts in English or English translation? **If no**, explain:	☒ YES ☐ NO
• Electronic Submission comments **List comments**:	☒ Not Applicable
CLINICAL **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
• Clinical study site(s) inspections(s) needed? **If no,** explain:	☒ YES ☐ NO
• Advisory Committee Meeting needed? **Comments**: ***If no, for an original NME or BLA application, include the reason. For example:***	☐ YES Date if known: ☒ NO ☐ To be determined Reason:

○ ***this drug/biologic is not the first in its class*** ○ ***the clinical study design was acceptable*** ○ ***the application did not raise significant safety or efficacy issues*** ○ ***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***	
• Abuse Liability/Potential **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
• 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? **Comments**:	☒ Not Applicable ☐ YES ☐ NO
CLINICAL MICROBIOLOGY **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
CLINICAL PHARMACOLOGY **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
• Clinical pharmacology study site(s) inspections(s) needed?	☒ YES ☐ NO
BIOSTATISTICS **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
NONCLINICAL (PHARMACOLOGY/TOXICOLOGY)	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter

Comments:	

IMMUNOGENICITY (BLAs/BLA efficacy supplements only) **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
PRODUCT QUALITY (CMC) **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
Environmental Assessment • Categorical exclusion for environmental assessment (EA) requested? **If no**, was a complete EA submitted? **If EA submitted**, consulted to EA officer (OPS)? **Comments**:	☐ Not Applicable ☒ YES ☐ NO ☐ YES ☐ NO ☒ YES ☐ NO
Quality Microbiology (for sterile products) • Was the Microbiology Team consulted for validation of sterilization? (**NDAs/NDA supplements only**) **Comments**:	☒ Not Applicable ☐ YES ☐ NO
Facility Inspection • Establishment(s) ready for inspection? ▪ Establishment Evaluation Request (EER/TBP-EER) submitted to DMPQ? **Comments**:	☒ Not Applicable ☐ YES ☐ NO ☐ YES ☐ NO

Facility/Microbiology Review (BLAs only) **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
CMC Labeling Review **Comments**:	 ☐ Review issues for 74-day letter

REGULATORY PROJECT MANAGEMENT

Signatory Authority:

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

Comments:

REGULATORY CONCLUSIONS/DEFICIENCIES

☐	The application is unsuitable for filing. Explain why:
☒	The application, on its face, appears to be suitable for filing. Review Issues: ☐ No review issues have been identified for the 74-day letter. ☒ Review issues have been identified for the 74-day letter. List (optional): Review Classification: ☐ Standard Review ☒ Priority Review

ACTIONS ITEMS

☐	Ensure that any updates to the review and chemical classifications and other properties [e.g., orphan drug, OTC, 505(b)(2)], are entered into tracking system.
☐	If RTF, notify everybody who already received a consult request, OSE PM, and Product Quality PM (to cancel EER/TBP-EER).
☐	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.

☐	BLA/BLA supplements: If filed, send 60-day filing letter
☐	If priority review: • 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 DMPQ (so facility inspections can be scheduled earlier)
☐	Send review issues/no review issues by day 74
☐	Conduct labeling review and include labeling issues in the 74-day letter
☐	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 (BLAs/BLA supplements only) [These sheets may be found at: http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027822]
☐	Other

Appendix A (NDA and NDA Supplements only)

NOTE: The term "original application" or "original NDA" as used in this appendix denotes the NDA submitted. It does not refer to the reference drug product or "reference listed drug."

An original application is likely to be a 505(b)(2) application if:

(1) it relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application,
(2) it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval, or
(3) it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)

Types of products for which 505(b)(2) applications are likely to be submitted include: fixed-dose combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations); OTC monograph deviations (see 21 CFR 330.11); new dosage forms; new indications; and, new salts.

An efficacy supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2).

An efficacy supplement is a 505(b)(1) supplement if the supplement contains all of the information needed to support the approval of the change proposed in the supplement. For example, if the supplemental application is for a new indication, the supplement is a 505(b)(1) if:

(1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies),

(2) No additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application, and.

(3) All other “criteria” are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely

for approval on published literature based on data to which the applicant does not have a right of reference).

An efficacy supplement is a 505(b)(2) supplement if:

(1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2),

(2) The applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement, or

(3) The applicant is relying upon any data they do not own or to which they do not have right of reference.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your OND ADRA or OND IO.

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

/s/

VENESSA M PERRY
10/04/2010

VICTORIA L TYSON
10/04/2010

DSI CONSULT
Request for Biopharmaceutical Inspections

DATE: 9.20.10

TO: Associate Director for Bioequivalence
Division of Scientific Investigations, HFD-48

THROUGH: Debra Birnkrant, MD
Director, Division of Antiviral Products, HFD-530

FROM: Venessa M Perry, MPH, Regulatory Project Manager, Division of Antiviral Products

SUBJECT: **Request for Biopharmaceutical Inspections**
NDA 21567/S-025
Reyataz, 100, 150, 200, 300 mg capsules
Bristol Myers Squibb Company
Attn: Lisa Percival, Director, Global Regulatory Strategy
5 Research Parkway, Room 252A
Mailstop 2CW-506
Wallingford, CT 06492
203.677.6803

Study/Site Identification:

As discussed with you, the following studies/sites pivotal to approval (OR, raise question regarding the quality or integrity of the data submitted and) have been identified for inspection:

Study #	Clinical Site (name, address, phone, fax, contact person, if available)	Analytical Site (name, address, phone, fax, contact person, if available)
AI424182	See below	(b) (4)

International Inspections:

(Please note: International inspections require sign-off by the ORM Division Director or DPE Division Director.)

We have requested an international inspection because:

x There is a lack of domestic data that solely supports approval;

X Other (please explain): The site with the majority of the patients for the study is located in South Africa.

Goal Date for Completion:

We request that the inspections be conducted and the Inspection Summary Results be provided by **As soon as possible**. We intend to issue an action letter on this application by **February 4, 2011**.

Should you require any additional information, please contact Venessa M Perry, MPH, Regulatory Project Manager, 301.796.4891.

Concurrence:
Mary Singer, MD/Sarah Robertson, Pharm D
Alan Shapiro, MD/Jenny Zheng, Pharm D

Clinical Sites

Site 4

Zorrilla, Carmen M.D. University Of Puerto Rico (Office)
Dept Of Obgyn,Maternal Infant
Studies Ctr P.O.Box 365067
San Juan 00936-5067
Puerto Rico
Medical Sciences Campus-Dept Of
Obgyn (Previous Office)

Maternal Infant Studies Ctr Cemi
P.O. Box 365067
San Juan 00936-5067
Puerto Rico

University Of Puerto Rico (Previous
Office)
Upr School Of Medicine Maternal
Infant Studies Ctr Biomedical Bldg Ii,
1st Floor
Rio Piedras 00935
Puerto Rico

University Of Puerto Rico (Patient
Treatment)
Maternal Infant Studies Center
(Cemi) Biomedical Building Ii, 1st
Floor
Rio Piedras 00935
Puerto Rico

Subinvestigator and responsible medical personnel

(b) (6)

Phone numbers:
787-753-5913
787-771-4740
787-766-0025

Site 5

Conradie, F MBChB.
Helen Joseph Hospital (Office)
Hiv Clinical Trial Unit Perth Road
Westdene, Gauteng 2092
South Africa

Helen Joseph Hospital (Patient Treatment)
Hiv Clinical Trial Unit Perth Road
Westdene, Gauteng 2092
South Africa

Johannesburg Hospital (Patient Treatment)
Room 29, Area 454 Green Block,
Jubilee Rd
Parktown, Gauteng 2193
South Africa

Coronation Hospital (Patient Treatment)
Cnr Oudshoorn & Fuel Rds Nhls Lab,
2nd Floor
Newclare, Gauteng 2093
South Africa

Sub investigators and responsible medical personnel

Phone:

27 11 276 8800

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

/s/

VENESSA M PERRY
09/23/2010

DEBRA B BIRNKRANT
09/23/2010

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-567/S025

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

EXCLUSIVITY SUMMARY

NDA # 21-567 SUPPL # 025 HFD # 530

Trade Name Reyataz

Generic Name atazanavir sulfate

Applicant Name Bristol Myers Squibb Company

Approval Date, If Known February 4, 2011

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, and all efficacy supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?

YES ☒ NO ☐

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3,SE4, SE5, SE6, SE7, SE8

SE5

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES ☒ NO ☐

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

d) Did the applicant request exclusivity?

YES ☒ NO ☐

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

3 years

e) Has pediatric exclusivity been granted for this Active Moiety?

YES ☐ NO ☒

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

2. Is this drug product or indication a DESI upgrade?

YES ☐ NO ☒

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES
(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES ☒ NO ☐

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# 21-567 Reyataz atazanavir sulfate

NDA#

NDA#

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES ☐ NO ☒

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered “NO” for original approvals of new molecular entities.)
IF “YES,” GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of

summary for that investigation.

YES ☒ NO ☐

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES ☒ NO ☐

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES ☒ NO ☐

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES ☐ NO ☒

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES ☐ NO ☒

If yes, explain:

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

AI424182, a study of ATV/RTV in HIV infected pregnant women

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES ☐ NO ☒

Investigation #2 YES ☐ NO ☐

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES ☐ NO ☒

Investigation #2 YES ☐ NO ☐

If you have answered "yes" for one or more investigation, identify the NDA in which a

similar investigation was relied on:

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

AI424182, a study of ATV/RTV in HIV infected pregnant women

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1		!
		!
IND # 56, 897	YES ☒	! NO ☐
		! Explain:

Investigation #2		!
		!
IND #	YES ☐	! NO ☐
		! Explain:

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1	!
	!
YES ☐	! NO ☐

Explain:	! Explain:
Investigation #2	!
	!
YES ☐	! NO ☐
Explain:	! Explain:

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES ☐ NO ☒

If yes, explain:

==========

Name of person completing form: Venessa M Perry, MPH
Title: Regulatory Project Manager
Date: 2.11.2011

Name of Office/Division Director signing form: Jeffrey Murray, MD
Title: Deputy Director

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05

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

/s/

VENESSA M PERRY
02/01/2011

JEFFREY S MURRAY
02/01/2011

NDA NO. 21-567

AI424182 (PREGNANCY) SNDA

CERTIFICATION: DEBARRED PERSONS

As required by Section 306(k)(1) of the Federal Food, Drug and Cosmetics Act, Bristol-Myers Squibb Company certifies that it has not used and will not use in any capacity the services of any person listed as debarred under Section 306 (a) or (b) of the Federal Food, Drug and Cosmetics Act in connection with this Application.

Lisa Percival

28 June 2010
Certification Date

Lisa Percival
Director, Global Regulatory Strategy
Bristol-Myers Squibb Company
5 Research Parkway
Wallingford, CT 06492
(203) 677-6803

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION[1]

NDA # 21-567 BLA #	NDA Supplement # S-025 BLA STN #	If NDA, Efficacy Supplement Type: SE-5
Proprietary Name: Reyataz Established/Proper Name: atazanavir sulfate Dosage Form: 100, 150, 200 and 300 mgcapsule		Applicant: Bristol Myers Squibb Company Agent for Applicant (if applicable):
RPM: Venessa M Perry. MPH		Division: Division of Antiviral Products

NDAs:
NDA Application Type: ☐ 505(b)(1) ☐ 505(b)(2)
Efficacy Supplement: ☒ 505(b)(1) ☐ 505(b)(2)

(A supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2). Consult page 1 of the 505(b)(2) Assessment or the Appendix to this Action Package Checklist.)

505(b)(2) Original NDAs and 505(b)(2) NDA supplements:
Listed drug(s) relied upon for approval (include NDA #(s) and drug name(s)):

Provide a brief explanation of how this product is different from the listed drug.

If no listed drug, explain.
- ☐ This application relies on literature.
- ☐ This application relies on a final OTC monograph.
- ☐ Other (explain)

Two months prior to each action, review the information in the 505(b)(2) Assessment and submit the draft to CDER OND IO for clearance. Finalize the 505(b)(2) Assessment at the time of the approval action.

On the day of approval, check the Orange Book again for any new patents or pediatric exclusivity.

☐ No changes ☐ Updated Date of check:

If pediatric exclusivity has been granted or the pediatric information in the labeling of the listed drug changed, determine whether pediatric information needs to be added to or deleted from the labeling of this drug.

❖ Actions	
• Proposed action • User Fee Goal Date is 2.4.11	☒ AP ☐ TA ☐ CR
• Previous actions *(specify type and date for each action taken)*	☒ None
❖ If accelerated approval or approval based on efficacy studies in animals, were promotional materials received? Note: Promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see http://www fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf). If not submitted, explain _____	☐ Received

[1] The **Application Information** section is (only) a checklist. The **Contents of Action Package** section (beginning on page 5) lists the documents to be included in the Action Package.

❖ Application Characteristics [2]

Review priority: ☐ Standard ☒ Priority
Chemical classification (new NDAs only):

☐ Fast Track
☐ Rolling Review
☐ Orphan drug designation
☐ Rx-to-OTC full switch
☐ Rx-to-OTC partial switch
☐ Direct-to-OTC

NDAs: Subpart H
☐ Accelerated approval (21 CFR 314.510)
☐ Restricted distribution (21 CFR 314.520)
Subpart I
☐ Approval based on animal studies

BLAs: Subpart E
☐ Accelerated approval (21 CFR 601.41)
☐ Restricted distribution (21 CFR 601.42)
Subpart H
☐ Approval based on animal studies

☐ Submitted in response to a PMR
☐ Submitted in response to a PMC
☐ Submitted in response to a Pediatric Written Request

REMS: ☐ MedGuide
☐ Communication Plan
☐ ETASU
☐ REMS not required

Comments:

❖ BLAs only: Ensure *RMS-BLA Product Information Sheet for TBP* and *RMS-BLA Facility Information Sheet for TBP* have been completed and forwarded to OPI/OBI/DRM (Vicky Carter)	☐ Yes, dates
❖ BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2 *(approvals only)*	☐ Yes ☐ No
❖ Public communications *(approvals only)*	
• Office of Executive Programs (OEP) liaison has been notified of action	☐ Yes ☒ No
• Press Office notified of action (by OEP)	☐ Yes ☒ No
• Indicate what types (if any) of information dissemination are anticipated	☐ None ☐ HHS Press Release ☐ FDA Talk Paper ☐ CDER Q&As ☒ Other BMS Press Release

[2] Answer all questions in all sections in relation to the pending application, i.e., if the pending application is an NDA or BLA supplement, then the questions should be answered in relation to that supplement, not in relation to the original NDA or BLA. For example, if the application is a pending BLA supplement, then a new *RMS-BLA Product Information Sheet for TBP* must be completed.

❖ Exclusivity	
• Is approval of this application blocked by any type of exclusivity?	☒ No ☐ Yes
• NDAs and BLAs: Is there existing orphan drug exclusivity for the "same" drug or biologic for the proposed indication(s)? *Refer to 21 CFR 316.3(b)(13) for the definition of "same drug" for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification.*	☒ No ☐ Yes If, yes, NDA/BLA # and date exclusivity expires:
• (b)(2) NDAs only: Is there remaining 5-year exclusivity that would bar effective approval of a 505(b)(2) application)? *(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)*	☐ No ☐ Yes If yes, NDA # and date exclusivity expires:
• (b)(2) NDAs only: Is there remaining 3-year exclusivity that would bar effective approval of a 505(b)(2) application? *(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)*	☐ No ☐ Yes If yes, NDA # and date exclusivity expires:
• (b)(2) NDAs only: Is there remaining 6-month pediatric exclusivity that would bar effective approval of a 505(b)(2) application? *(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)*	☐ No ☐ Yes If yes, NDA # and date exclusivity expires:
• NDAs only: Is this a single enantiomer that falls under the 10-year approval limitation of 505(u)? *(Note that, even if the 10-year approval limitation period has not expired, the application may be tentatively approved if it is otherwise ready for approval.)*	☐ No ☐ Yes If yes, NDA # and date 10-year limitation expires:
❖ Patent Information (NDAs only)	
• Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought. If the drug is an old antibiotic, skip the Patent Certification questions.	☒ Verified ☐ Not applicable because drug is an old antibiotic.
• Patent Certification [505(b)(2) applications]: Verify that a certification was submitted for each patent for the listed drug(s) in the Orange Book and identify the type of certification submitted for each patent.	21 CFR 314.50(i)(1)(*i*)(A) ☐ Verified 21 CFR 314.50(i)(1) ☐ (ii) ☐ (iii)
• [505(b)(2) applications] If the application includes a **paragraph III** certification, it cannot be approved until the date that the patent to which the certification pertains expires (but may be tentatively approved if it is otherwise ready for approval).	☐ No paragraph III certification Date patent will expire
• [505(b)(2) applications] For **each paragraph IV** certification, verify that the applicant notified the NDA holder and patent owner(s) of its certification that the patent(s) is invalid, unenforceable, or will not be infringed (review documentation of notification by applicant and documentation of receipt of notice by patent owner and NDA holder). *(If the application does not include any paragraph IV certifications, mark "N/A" and skip to the next section below (*Summary Reviews*)).*	☐ N/A (no paragraph IV certification) ☐ Verified

- [505(b)(2) applications] For **each paragraph IV** certification, based on the questions below, determine whether a 30-month stay of approval is in effect due to patent infringement litigation.

  Answer the following questions for **each** paragraph IV certification:

  (1) Have 45 days passed since the patent owner's receipt of the applicant's notice of certification? ☐ Yes ☐ No

  (Note: The date that the patent owner received the applicant's notice of certification can be determined by checking the application. The applicant is required to amend its 505(b)(2) application to include documentation of this date (e.g., copy of return receipt or letter from recipient acknowledging its receipt of the notice) (see 21 CFR 314.52(e))).

  *If "**Yes**," skip to question (4) below. If "**No**," continue with question (2).*

  (2) Has the patent owner (or NDA holder, if it is an exclusive patent licensee) submitted a written waiver of its right to file a legal action for patent infringement after receiving the applicant's notice of certification, as provided for by 21 CFR 314.107(f)(3)? ☐ Yes ☐ No

  *If "**Yes,**" there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip the rest of the patent questions.*

  *If "**No**," continue with question (3).*

  (3) Has the patent owner, its representative, or the exclusive patent licensee filed a lawsuit for patent infringement against the applicant? ☐ Yes ☐ No

  (Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2))).

  *If "**No**," the patent owner (or NDA holder, if it is an exclusive patent licensee) has until the expiration of the 45-day period described in question (1) to waive its right to bring a patent infringement action or to bring such an action. After the 45-day period expires, continue with question (4) below.*

  (4) Did the patent owner (or NDA holder, if it is an exclusive patent licensee) submit a written waiver of its right to file a legal action for patent infringement within the 45-day period described in question (1), as provided for by 21 CFR 314.107(f)(3)? ☐ Yes ☐ No

  *If "**Yes,**" there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (*Summary Reviews*).*

  *If "**No**," continue with question (5).*

(5) Did the patent owner, its representative, or the exclusive patent licensee bring suit against the (b)(2) applicant for patent infringement within 45 days of the patent owner's receipt of the applicant's notice of certification? (Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)). If no written notice appears in the NDA file, confirm with the applicant whether a lawsuit was commenced within the 45-day period). *If "**No**," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (*Summary Reviews*).* *If "**Yes**," a stay of approval may be in effect. To determine if a 30-month stay is in effect, consult with the OND ADRA and attach a summary of the response.*	☐ Yes ☐ No
CONTENTS OF ACTION PACKAGE	
❖ Copy of this Action Package Checklist[3]	yes
Officer/Employee List	
❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list *(approvals only)*	☒ Included
Documentation of consent/non-consent by officers/employees	☒ Included
Action Letters	
❖ Copies of all action letters *(including approval letter with final labeling)*	Action(s) and date(s) 2.4.2011
Labeling	
❖ Package Insert *(write submission/communication date at upper right of first page of PI)*	
• Most recent draft labeling. If it is division-proposed labeling, it should be in track-changes format.	2.3.2011
• Original applicant-proposed labeling	8.6.2010
• Example of class labeling, if applicable	

[3] Fill in blanks with dates of reviews, letters, etc.

❖ Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling *(write submission/communication date at upper right of first page of each piece)*	☐ Medication Guide ☒ Patient Package Insert ☐ Instructions for Use ☐ Device Labeling ☐ None
• Most-recent draft labeling. If it is division-proposed labeling, it should be in track-changes format.	2.1.2011
• Original applicant-proposed labeling	8.6.2010
• Example of class labeling, if applicable	
❖ Labels (**full color** carton and immediate-container labels) *(write submission/communication date on upper right of first page of each submission)*	
• Most-recent draft labeling	na
❖ Proprietary Name • Acceptability/non-acceptability letter(s) *(indicate date(s))* • Review(s) *(indicate date(s))*	na na
❖ Labeling reviews *(indicate dates of reviews and meetings)*	☒ RPM ☒ DMEPA 1.31.11 ☐ DRISK ☒ DDMAC 1.18.11 ☐ CSS ☐ Other reviews
Administrative / Regulatory Documents	
❖ Administrative Reviews *(e.g., RPM Filing Review[4]/Memo of Filing Meeting) (indicate date of each review)* ❖ All NDA (b)(2) Actions: Date each action cleared by (b)(2) Clearance Cmte ❖ NDA (b)(2) Approvals Only: 505(b)(2) Assessment *(indicate date)*	10.4.2010, 10.4.2010 ☒ Not a (b)(2) ☒ Not a (b)(2)
❖ NDAs only: Exclusivity Summary *(signed by Division Director)*	☒ Included
❖ Application Integrity Policy (AIP) Status and Related Documents http://www fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm	
• Applicant is on the AIP	☐ Yes ☒ No
• This application is on the AIP o If yes, Center Director's Exception for Review memo *(indicate date)* o If yes, OC clearance for approval *(indicate date of clearance communication)*	☐ Yes ☒ No ☐ Not an AP action
❖ Pediatrics *(approvals only)* • Date reviewed by PeRC _____ If PeRC review not necessary, explain: _____ • Pediatric Page/Record *(approvals only, must be reviewed by PERC before finalized)*	☐ Included
❖ Debarment certification (original applications only): verified that qualifying language was not used in certification and that certifications from foreign applicants are cosigned by U.S. agent *(include certification)*	☒ Verified, statement is acceptable
❖ Outgoing communications *(letters (except action letters), emails, faxes, telecons)*	8/17/2010, 9/8, 9/16, 9/21, 9/23, 10/4, 10/13, 10/22, 10/24,11/8,

[4] Filing reviews for scientific disciplines should be filed behind the respective discipline tab.

	12/7, 12/14, 12/16/2010, 1/5/2011, 1/13, 1/14, 1/18, 1/19, 1/21, 1/24, 1/27, 1/28, 1/31, 2/1/2011
❖ Internal memoranda, telecons, etc.	NA
❖ Minutes of Meetings	
• Regulatory Briefing *(indicate date of mtg)*	☒ No mtg
• If not the first review cycle, any end-of-review meeting *(indicate date of mtg)*	☒ N/A or no mtg
• Pre-NDA/BLA meeting *(indicate date of mtg)*	☒ No mtg
• EOP2 meeting *(indicate date of mtg)*	☒ No mtg
• Other milestone meetings (e.g., EOP2a, CMC pilots) *(indicate dates of mtgs)*	
❖ Advisory Committee Meeting(s)	☒ No AC meeting
• Date(s) of Meeting(s)	
• 48-hour alert or minutes, if available *(do not include transcript)*	
Decisional and Summary Memos	
❖ Office Director Decisional Memo *(indicate date for each review)*	☒ None
Division Director Summary Review *(indicate date for each review)*	☒ None
Cross-Discipline Team Leader Review *(indicate date for each review)*	☐ None 2.2.2011
PMR/PMC Development Templates *(indicate total number)*	☒ None
Clinical Information[5]	
❖ Clinical Reviews	
• Clinical Team Leader Review(s) *(indicate date for each review)*	NA
• Clinical review(s) *(indicate date for each review)*	2.1.2011
• Social scientist review(s) (if OTC drug) *(indicate date for each review)*	☒ None
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, check here ☐ and include a review/memo explaining why not *(indicate date of review/memo)*	
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers *(indicate date of each review)*	☒ None
❖ Controlled Substance Staff review(s) and Scheduling Recommendation *(indicate date of each review)*	☒ Not applicable
❖ Risk Management • REMS Documents and Supporting Statement *(indicate date(s) of submission(s))* • REMS Memo(s) and letter(s) *(indicate date(s))* • Risk management review(s) and recommendations (including those by OSE and CSS) *(indicate date of each review and indicate location/date if incorporated into another review)*	☒ None
❖ DSI Clinical Inspection Review Summary(ies) *(include copies of DSI letters to investigators)*	☐ None requested 1.19.2011

[5] Filing reviews should be filed with the discipline reviews.

Clinical Microbiology ☐ None	
❖ Clinical Microbiology Team Leader Review(s) *(indicate date for each review)*	☒ None
Clinical Microbiology Review(s) *(indicate date for each review)*	☐ None 9.20.10
Biostatistics ☐ None	
❖ Statistical Division Director Review(s) *(indicate date for each review)*	☒ None
Statistical Team Leader Review(s) *(indicate date for each review)*	☒ None
Statistical Review(s) *(indicate date for each review)*	☐ None 10.6.2010
Clinical Pharmacology ☐ None	
❖ Clinical Pharmacology Division Director Review(s) *(indicate date for each review)*	☒ None
Clinical Pharmacology Team Leader Review(s) *(indicate date for each review)*	☐ None
Clinical Pharmacology review(s) *(indicate date for each review)*	☐ None 2.1.2011
❖ DSI Clinical Pharmacology Inspection Review Summary *(include copies of DSI letters)*	☐ None
Nonclinical ☐ None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) *(indicate date for each review)*	☒ None
• Supervisory Review(s) *(indicate date for each review)*	☒ None
• Pharm/tox review(s), including referenced IND reviews *(indicate date for each review)*	☐ None 1.26.2011
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer *(indicate date for each review)*	☒ None
❖ Statistical review(s) of carcinogenicity studies *(indicate date for each review)*	☒ No carc
❖ ECAC/CAC report/memo of meeting	☒ None Included in P/T review, page
❖ DSI Nonclinical Inspection Review Summary *(include copies of DSI letters)*	☒ None requested
Product Quality ☐ None	
❖ Product Quality Discipline Reviews	
• ONDQA/OBP Division Director Review(s) *(indicate date for each review)*	☒ None
• Branch Chief/Team Leader Review(s) *(indicate date for each review)*	☒ None
• Product quality review(s) including ONDQA biopharmaceutics reviews *(indicate date for each review)*	☐ None 9.14.10
❖ Microbiology Reviews ☐ NDAs: Microbiology reviews (sterility & pyrogenicity) (OPS/NDMS) *(indicate date of each review)* ☐ BLAs: Sterility assurance, microbiology, facilities reviews (DMPQ/MAPCB/BMT) *(indicate date of each review)*	☒ Not needed
❖ Reviews by other disciplines/divisions/Centers requested by CMC/quality reviewer *(indicate date of each review)*	☒ None

❖ Environmental Assessment (check one) (original and supplemental applications)	
☒ Categorical Exclusion *(indicate review date)(all original applications and all efficacy supplements that could increase the patient population)*	9.14.2010
☐ Review & FONSI *(indicate date of review)*	
☐ Review & Environmental Impact Statement *(indicate date of each review)*	
❖ Facilities Review/Inspection	
☐ NDAs: Facilities inspections (include EER printout) *(date completed must be within **2 years** of action date) (only original NDAs and supplements that include a new facility or a change that affects the manufacturing sites[6])*	Date completed: ☐ Acceptable ☐ Withhold recommendation ☒ Not applicable
☐ BLAs: TB-EER *(date of most recent TB-EER must be within **30 days** of action date) (original and supplemental BLAs)*	Date completed: ☐ Acceptable ☐ Withhold recommendation
❖ NDAs: Methods Validation *(check box only, do not include documents)*	☐ Completed ☐ Requested ☐ Not yet requested ☒ Not needed (per review)

[6] I.e., a new facility or a change in the facility, or a change in the manufacturing process in a way that impacts the Quality Management Systems of the facility.

Appendix to Action Package Checklist

An NDA or NDA supplemental application is likely to be a 505(b)(2) application if:

(1) It relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application.
(2) **Or** it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval.
(3) **Or** it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)

Types of products for which 505(b)(2) applications are likely to be submitted include: fixed-dose combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations); OTC monograph deviations(see 21 CFR 330.11); new dosage forms; new indications; and, new salts.

An efficacy supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2).

An efficacy supplement is a 505(b)(1) supplement if the supplement contains all of the information needed to support the approval of the change proposed in the supplement. For example, if the supplemental application is for a new indication, the supplement is a 505(b)(1) if:

(1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies).
(2) **And** no additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application.
(3) **And** all other “criteria” are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely for approval on published literature based on data to which the applicant does not have a right of reference).

An efficacy supplement is a 505(b)(2) supplement if:

(1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2).
(2) **Or** the applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement.
(3) **Or** the applicant is relying upon any data they do not own or to which they do not have right of reference.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your ODE’s ADRA.

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

/s/

VENESSA M PERRY
02/04/2011

Perry, Venessa

From: Percival, Lisa [Lisa.Percival@bms.com]
Sent: Wednesday, September 08, 2010 10:33 AM
To: Perry, Venessa
Subject: RE: Clinical sites
Attachments: Appendix 1.5.pdf; study-ai424182-csr-addend02.pdf; Jose Tiran FD.pdf; FD-1.pdf; HHunter Hammill FD.pdf

Hi Venessa,
Attached is Appendix 1.5 of the study report, which provides the addresses for all the sites. The phone contact information was not included in that appendix, so the information is provided below:

Site Number	Phone	Fax
002	713-799-8994	713-799-9931
004	787-753-5913 or 787-771-4740 or 787-766-0025	787-771-4739
005	27 11 276 8800	27 11 482 2130
008	27 11 989 9703 or 27 11 989 9704	27 11 989 9762
012	27 12 341 1646	27 12 341 1655
014	561-832-6770	561-832-3292

Regarding the Financial Disclosures for Site 002. Those disclosures were not included in the dossier because the site did not contribute significantly to the treatment/evaluation of patients in the trial. I am also attaching Addendum 02 to the study report (included in the dossier as well), which shows that the site enrolled two patients, but neither were eligible, and therefore were not treated. Nonetheless, I'm sending you the disclosures here as requested. If we interpret the requirements correctly that these disclosures are not required, is it ok to not send a separate official submission?

Please let me know if you need any other information or if you have any difficulty contacting the sites.
Thank you and best regards,
Lisa

From: Perry, Venessa [mailto:Venessa.Perry@fda.hhs.gov]
Sent: Tuesday, September 07, 2010 3:22 PM
To: Percival, Lisa
Subject: Clinical sites

Hi Lisa,

Per our discussion, please forward the complete contact information for the primary investigators and sites (0002,0004, 0005, 0008, 0012, 0014). Also there is no financial disclosure information for site 0002. Thank you for your assistance.

Venessa

Venessa M Perry, MPH
Regulatory Project Manager
FDA/CDER/OND/Division of Antiviral Products
10903 New Hampshire Avenue, Building 22, Room 6377
Silver Spring, MD 20903
301.796.4891 voice
301.796.9883 fax
Venessa.Perry@fda.hhs.gov

Perry, Venessa

From: Percival, Lisa [Lisa.Percival@bms.com]
Sent: Tuesday, September 21, 2010 12:59 PM
To: Perry, Venessa
Subject: RE: Fax regarding NDA 21567
Attachments: REFERENCE 6_study (b)(4)05-119a-report-addend01[1].pdf; REFERENCE 4_Study (b)(4)05-119A Report Amend01[1].pdf; REFERENCE 3_Study (b)(4)05-119A Report[1].pdf; REFERENCE 5_study-ai424182-validation-report-(b)(4)06-014[1].pdf

Hi Venessa,
I'm so sorry for the delay in responding. In the reference section of Module 2.7.1, the analytical and validation reports were referenced (references 3-6). The first two were hyperlinked. References 5 and 6 were cross referenced to the previous eCTD IND submissions. I am attaching all of the requested reports here for your convenience, but am hoping you agree we do not need to submit these officially since they've been hyperlinked or cross-referenced accordingly??
Thanks so much for your collaboration and patience!
Kind regards,
Lisa

From: Perry, Venessa [mailto:Venessa.Perry@fda.hhs.gov]
Sent: Monday, September 20, 2010 12:14 PM
To: Percival, Lisa
Subject: RE: Fax regarding NDA 21567

Hi Lisa,

The datasets are fine and they are able to open them. However, Clin Pharm is having difficulty locating the analytical report and the validation report. Please provide that as well in the submission and electronically. Thank you.

Venessa

Venessa M Perry, MPH
Regulatory Project Manager
FDA/CDER/OND/Division of Antiviral Products
10903 New Hampshire Avenue, Building 22, Room 6377
Silver Spring, MD 20903
301.796.4891 voice
301.796.9883 fax
Venessa.Perry@fda.hhs.gov

From: Percival, Lisa [mailto:Lisa.Percival@bms.com]
Sent: Friday, September 17, 2010 1:15 PM
To: Perry, Venessa

Subject: RE: Fax regarding NDA 21567

No problem. When you do get a chance to go through everything, please confirm if you agree we will only submit the response document to the NDA. We'll probably do that by early-mid next week.
Thanks again and have a great weekend.
Lisa

From: Perry, Venessa [mailto:Venessa.Perry@fda.hhs.gov]
Sent: Friday, September 17, 2010 12:47 PM
To: Percival, Lisa
Subject: RE: Fax regarding NDA 21567

Thanks for proving this information so promptly Lisa!

Venessa

Venessa M Perry, MPH
Regulatory Project Manager
FDA/CDER/OND/Division of Antiviral Products
10903 New Hampshire Avenue, Building 22, Room 6377
Silver Spring, MD 20903
301.796.4891 voice
301.796.9883 fax
Venessa.Perry@fda.hhs.gov

From: Percival, Lisa [mailto:Lisa.Percival@bms.com]
Sent: Friday, September 17, 2010 12:41 PM
To: Perry, Venessa
Subject: RE: Fax regarding NDA 21567

Hi Venessa,
Please find attached the following:

1. response document to specific FDA questions
2. requested datasets: please note these are already in the eCTD backbone (described in the response but included via email for your convenience)
3. two dataset description files (one for tabulations and one for analysis)

Please let me know if you have any questions at all.
Thanks and regards,
Lisa

From: Perry, Venessa [mailto:Venessa.Perry@fda.hhs.gov]
Sent: Thursday, September 16, 2010 1:00 PM
To: Percival, Lisa
Subject: RE: Fax regarding NDA 21567

Great. thanks!

Venessa M Perry, MPH
Regulatory Project Manager
FDA/CDER/OND/Division of Antiviral Products
10903 New Hampshire Avenue, Building 22, Room 6377
Silver Spring, MD 20903
301.796.4891 voice
301.796.9883 fax
Venessa.Perry@fda.hhs.gov

From: Percival, Lisa [mailto:Lisa.Percival@bms.com]
Sent: Thursday, September 16, 2010 12:33 PM
To: Perry, Venessa
Subject: RE: Fax regarding NDA 21567

Hi Venessa,
We will definitely reply by tomorrow.
Thanks and regards,
Lisa

From: Perry, Venessa [mailto:Venessa.Perry@fda.hhs.gov]
Sent: Thursday, September 16, 2010 8:23 AM
To: Percival, Lisa
Subject: Fax regarding NDA 21567
Importance: High

Lisa,

Please find attached a fax regarding NDA 21567. Please let me know if you will be able to respond to the request by Friday. Thanks

Venessa

Venessa M Perry, MPH
Regulatory Project Manager
FDA/CDER/OND/Division of Antiviral Products
10903 New Hampshire Avenue, Building 22, Room 6377
Silver Spring, MD 20903
301.796.4891 voice
301.796.9883 fax
Venessa.Perry@fda.hhs.gov

Perry, Venessa

From: Percival, Lisa [Lisa.Percival@bms.com]
Sent: Friday, October 22, 2010 10:37 AM
To: Perry, Venessa
Subject: RE: Fax regarding bilirubin

Thank you so much! We will submit no later than the 14th of November.
Have a great weekend.
Lisa

From: Perry, Venessa [mailto:Venessa.Perry@fda.hhs.gov]
Sent: Friday, October 22, 2010 10:17 AM
To: Percival, Lisa
Subject: RE: Fax regarding bilirubin

Hi Lisa,

Thank you for your response. I spoke with the review team and they indicated that an additional two weeks is fine, however not past November 14, 20010. Thanks

Venessa

Venessa M Perry, MPH
Regulatory Project Manager
FDA/CDER/OND/Division of Antiviral Products
10903 New Hampshire Avenue, Building 22, Room 6377
Silver Spring, MD 20903
301.796.4891 voice
301.796.9883 fax
Venessa.Perry@fda.hhs.gov

From: Percival, Lisa [mailto:Lisa.Percival@bms.com]
Sent: Friday, October 22, 2010 9:26 AM
To: Perry, Venessa
Subject: RE: Fax regarding bilirubin

Hi Venessa,
I received the email/fax below, and have been working with the team to respond as soon as possible. We had to first determine all of the information requested that we do not already have in the database, and was only just able to send the request to the sites for the additional information. We expect them to turn it around quickly, but then still need time to get the data entered and analyzed as requested. This is definitely our priority, but we don't think it will be possible to submit by 1-Nov. Is it possible to get an extra week two weeks?
Thank you for your consideration.
Kind regards,
Lisa

From: Perry, Venessa [mailto:Venessa.Perry@fda.hhs.gov]
Sent: Wednesday, October 13, 2010 3:43 PM
To: Percival, Lisa
Subject: Fax regarding bilirubin
Importance: High

Lisa:

Thanks for your response to the previous advice letter. Please find another fax regarding bilirubin data. For the bilirubin data we are requesting (time in hours from birth that each sample was obtained). Please go back to the patient chart if needed even though the data may not have been collected that way on the Case Report Form. The hours from birth for each sample is critical for our analysis. A response is requested by COB November 1, 2010.

Thanks

Venessa

Venessa M Perry, MPH
Regulatory Project Manager
FDA/CDER/OND/Division of Antiviral Products
10903 New Hampshire Avenue, Building 22, Room 6377
Silver Spring, MD 20903
301.796.4891 voice
301.796.9883 fax
Venessa.Perry@fda.hhs.gov

From: Percival, Lisa [mailto:Lisa.Percival@bms.com]
Sent: Tuesday, October 12, 2010 8:18 PM
To: Perry, Venessa
Subject: RE: NDA 21567 filing letter

Hi Venessa,
I am confirming receipt of the filing letter. Please find attached our response to the last FDA fax, dated 22-Sep-2010, as an unofficial submission. We will submit officially to the NDA separately. Please let me know if there are any additional questions regarding those responses.
I know that there were additional requests in the filing letter and will work on responding to those as soon as possible.
Thank you!
Regards,
Lisa

From: Perry, Venessa [mailto:Venessa.Perry@fda.hhs.gov]
Sent: Tuesday, October 12, 2010 9:46 AM
To: Percival, Lisa
Subject: NDA 21567 filing letter

Dear Lisa:

Please find attached a copy of the filing letter for NDA 21567. The letter went out in the mail last week in the event you have not received it as of yet. Please let me know if you have any questions. Thank you.

Venessa

Venessa M Perry, MPH
Regulatory Project Manager
FDA/CDER/OND/Division of Antiviral Products
10903 New Hampshire Avenue, Building 22, Room 6377
Silver Spring, MD 20903
301.796.4891 voice
301.796.9883 fax
Venessa.Perry@fda.hhs.gov

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Perry, Venessa

From: Percival, Lisa [Lisa.Percival@bms.com]
Sent: Sunday, October 24, 2010 9:14 PM
To: Perry, Venessa
Subject: RE: NDA 21567

Hi Venessa,
One of our programmers has found the problem and is working on fixing it. So far, we've only found it in the BMS proprietary datasets (not the SDTM datasets) but they are still double checking. I will update you tomorrow when I have more information. Thank you!
Kind regards,
Lisa

From: Perry, Venessa [mailto:Venessa.Perry@fda.hhs.gov]
Sent: Friday, October 22, 2010 4:40 PM
To: Percival, Lisa
Subject: RE: NDA 21567

It appears that they are gone for the day, therefore I will have them contact you directly on Monday.

Venessa

Venessa M Perry, MPH
Regulatory Project Manager
FDA/CDER/OND/Division of Antiviral Products
10903 New Hampshire Avenue, Building 22, Room 6377
Silver Spring, MD 20903
301.796.4891 voice
301.796.9883 fax
Venessa.Perry@fda.hhs.gov

From: Percival, Lisa [mailto:Lisa.Percival@bms.com]
Sent: Friday, October 22, 2010 4:40 PM
To: Perry, Venessa
Subject: Re: NDA 21567

Ok, thanks.

From: Perry, Venessa <Venessa.Perry@fda.hhs.gov>
To: Percival, Lisa
Sent: Fri Oct 22 16:36:10 2010
Subject: RE: NDA 21567

In the variable label. We are trying to reach the stat review team to see if they can explain further. However, they may be gone for the day. If so we will get back to you on Monday. They may have to call you directly.

Venessa M Perry, MPH
Regulatory Project Manager
FDA/CDER/OND/Division of Antiviral Products
10903 New Hampshire Avenue, Building 22, Room 6377
Silver Spring, MD 20903
301.796.4891 voice
301.796.9883 fax
Venessa.Perry@fda.hhs.gov

From: Percival, Lisa [mailto:Lisa.Percival@bms.com]
Sent: Friday, October 22, 2010 4:29 PM
To: Perry, Venessa
Subject: RE: NDA 21567

A few more questions:
Would it be possible to send me a screen shot that shows the problem?
Are the carriage returns in the dataset label or the variable label?
Thanks,
Lisa

From: Perry, Venessa [mailto:Venessa.Perry@fda.hhs.gov]
Sent: Friday, October 22, 2010 4:26 PM
To: Percival, Lisa
Subject: RE: NDA 21567

The original datasets.....for example: AESAESTR

Venessa M Perry, MPH
Regulatory Project Manager
FDA/CDER/OND/Division of Antiviral Products
10903 New Hampshire Avenue, Building 22, Room 6377
Silver Spring, MD 20903
301.796.4891 voice
301.796.9883 fax
Venessa.Perry@fda.hhs.gov

From: Percival, Lisa [mailto:Lisa.Percival@bms.com]
Sent: Friday, October 22, 2010 4:08 PM
To: Perry, Venessa
Subject: RE: NDA 21567

Hi Venessa,
Are you referring to the datasets when opened in your viewer or the ones I sent via email on 9/17? Our stats

team has checked the datasets and they do not see carriage returns. We are still looking into it with some of our experts to see if our team missed something, but if you can let me know if you're working with the ones from email or the ones in the viewer, that may help.
Thanks,
Lisa

From: Perry, Venessa [mailto:Venessa.Perry@fda.hhs.gov]
Sent: Friday, October 22, 2010 1:51 PM
To: Percival, Lisa
Subject: NDA 21567
Importance: High

Hi Lisa:

In your NDA 21-567 submission, every datasets SAS LABEL has a carriage return in it. This carriage return interferes with our analysis program jReview.
Please edit your datasets to remove all carriage returns from the SAS LABEL and re-submit it as soon as possible.

Thanks

Venessa

Venessa M Perry, MPH
Regulatory Project Manager
FDA/CDER/OND/Division of Antiviral Products
10903 New Hampshire Avenue, Building 22, Room 6377
Silver Spring, MD 20903
301.796.4891 voice
301.796.9883 fax
Venessa.Perry@fda.hhs.gov

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Perry, Venessa

From: Percival, Lisa [Lisa.Percival@bms.com]
Sent: Tuesday, December 14, 2010 2:02 PM
To: Perry, Venessa
Subject: RE: Reference in reyataz label
Attachments: psur-20jun09-to-19dec09[1].pdf

Hi Venessa,
The document is in Module 5 of submission 0071, dated 16-Aug-2010.
I hope this helps.
Thanks and regards,
Lisa

From: Perry, Venessa [mailto:Venessa.Perry@fda.hhs.gov]
Sent: Tuesday, December 14, 2010 10:55 AM
To: Percival, Lisa
Subject: Reference in reyataz label

Hi Lisa,

The medical officer is trying to locate a copy of the following reference:

azanavir Sulfate; Capsules and Powder, 6-month Periodic Safety Update Report, Period Covered: 20 June 2009 to 19 December 2009. Bristol-Myers Squibb Document Control Number 930041852.

Can you provide me with it or let me know where it can be found? Thanks

Venessa

Venessa M Perry, MPH
Regulatory Project Manager
FDA/CDER/OND/Division of Antiviral Products
10903 New Hampshire Avenue, Building 22, Room 6377
Silver Spring, MD 20903
301.796.4891 voice
301.796.9883 fax
Venessa.Perry@fda.hhs.gov

Perry, Venessa

From: Wang, Hwei-Gene [HweiGene.Wang@bms.com]
Sent: Friday, January 14, 2011 11:38 AM
To: Perry, Venessa
Subject: RE: NDA 21567 label

Dear Venessa:

Regarding Reyataz (NDA #21-567 (S-025)), we are still working on the requested revisions. Can you please clarify the following in order for us to respond as quickly as possible:

1. Nonclinical Toxicology labeling revisions in Sections 8 and 13, can you please share with us the source of human data and animal data used to re-calculate the multiples to be based upon ATV 300/RTV 100?
2. Is it possible to provide a reference for what the 95th percentile by age is in the statement: '(b) (4) [redacted]?

I know it is a lot of ask but because we have to confirm the re-calculations, is there any possibility of receiving an answer to the nonclinical question today?

Many thanks,

Heidi

From: Perry, Venessa [mailto:Venessa.Perry@fda.hhs.gov]
Sent: Thursday, January 13, 2011 3:15 PM
To: Wang, Hwei-Gene
Cc: Percival, Lisa
Subject: RE: NDA 21567 label

Heidi,

Thanks for the question. You are correct in that the numbering should be according to the CFR with 10 as the Overdosage and end with 17. However there is no 17 in the original label you sent. Also, you can delete indications and usage, under recent major changes, since its been over a year and no changes were made to that section. I left a message for you as well. Please let me know if you have additional questions.

Thanks

Venessa

Venessa M Perry, MPH
Regulatory Project Manager
FDA/CDER/OND/Division of Antiviral Products
10903 New Hampshire Avenue, Building 22, Room 6377
Silver Spring, MD 20903
301.796.4891 voice

301.796.9883 fax
Venessa.Perry@fda.hhs.gov

From: Wang, Hwei-Gene [mailto:HweiGene.Wang@bms.com]
Sent: Thursday, January 13, 2011 1:33 PM
To: Perry, Venessa
Cc: Percival, Lisa
Subject: RE: NDA 21567 label

Dear Venessa:

Before we send our response to the Reyataz labeling comments (NDA #21-567 (S-025)), can you please clarify your email message below regarding re-numbering for the sections? Are you asking us to change the numbers of those sections or are you explaining that the numbering changes in your version are not applicable because you didn't have access to fix them?

In case of the former, we are concerned with making this change because it seems to be against the current requirements? Pursuant to CRF 201.56 d(1) (Requirements on content and format of labeling for human prescription drug and biological products), Overdosage is Section 10 and Patient Counseling Information is **Section 17. When a section or subsection is omitted from the Full Prescribing Information, the section must also** be omitted from the Contents (§ 201.56(d)(4)). The heading "Full Prescribing Information: Contents" must be followed by an asterisk and the following statement must appear at the end of the Contents: "*Sections or subsections omitted from the Full Prescribing Information are not listed" (§ 201.56(d)(4)).

Any clarification you can provide us is much appreciated as we prepare the revised USPI.

Regards,

Heidi

Heidi Wang, PhD
Bristol-Myers Squibb
Global Regulatory Sciences, US Liaison

203-677-7618 (Office)
(b) (6)

From: Percival, Lisa
Sent: Thursday, January 13, 2011 12:50 PM
To: Wang, Hwei-Gene
Subject: FW: NDA 21567 label

From: Perry, Venessa [mailto:Venessa.Perry@fda.hhs.gov]
Sent: Tuesday, January 11, 2011 11:48 AM
To: Percival, Lisa

Subject: RE: NDA 21567 label

Lisa,

Please find attached a fax and the label attached with recommended changes. I have attached the label as a PDF and word document for your use. Because of the macros we were unable to change the numbering for the sections. Section 9 should be over dosage, with the last section 15 as the PI.
Please let me know if you have any questions. Thanks

Venessa

Venessa M Perry, MPH
Regulatory Project Manager
FDA/CDER/OND/Division of Antiviral Products
10903 New Hampshire Avenue, Building 22, Room 6377
Silver Spring, MD 20903
301.796.4891 voice
301.796.9883 fax
Venessa.Perry@fda.hhs.gov

From: Percival, Lisa [mailto:Lisa.Percival@bms.com]
Sent: Tuesday, January 11, 2011 10:02 AM
To: Perry, Venessa
Subject: RE: NDA 21567 label

perfect...thanks!

From: Perry, Venessa [mailto:Venessa.Perry@fda.hhs.gov]
Sent: Tuesday, January 11, 2011 9:56 AM
To: Percival, Lisa
Subject: RE: NDA 21567 label

The comments will be send via email thru a fax. Thanks

Venessa

Venessa M Perry, MPH
Regulatory Project Manager
FDA/CDER/OND/Division of Antiviral Products
10903 New Hampshire Avenue, Building 22, Room 6377
Silver Spring, MD 20903
301.796.4891 voice
301.796.9883 fax
Venessa.Perry@fda.hhs.gov

From: Percival, Lisa [mailto:Lisa.Percival@bms.com]

Sent: Tuesday, January 11, 2011 9:52 AM
To: Perry, Venessa
Subject: RE: NDA 21567 label

Hi Venessa,
I hope you are also doing well. Thank you for letting me know. Will you be sending the comments via fax then or still by email?
Thanks again,
Lisa

From: Perry, Venessa [mailto:Venessa.Perry@fda.hhs.gov]
Sent: Tuesday, January 11, 2011 9:51 AM
To: Percival, Lisa
Subject: NDA 21567 label

Good Morning Lisa,

I hope you are doing well.

We have finished our review of the label and have a number of suggested changes. I can not change the numbering of the sections in the document. For some reason the macros will not allow it. Therefore I am sending you the label under separate cover for your review. Thanks.

Venessa

Venessa M Perry, MPH
Regulatory Project Manager
FDA/CDER/OND/Division of Antiviral Products
10903 New Hampshire Avenue, Building 22, Room 6377
Silver Spring, MD 20903
301.796.4891 voice
301.796.9883 fax
Venessa.Perry@fda.hhs.gov

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Perry, Venessa

From: Wang, Hwei-Gene [HweiGene.Wang@bms.com]
Sent: Tuesday, January 18, 2011 7:43 AM
To: Perry, Venessa
Subject: RE: NDA 21567 label

Venessa:

Many thanks and I look forward to hearing regarding Question 1.

Best,

Heidi

From: Perry, Venessa [mailto:Venessa.Perry@fda.hhs.gov]
Sent: Tuesday, January 18, 2011 7:41 AM
To: Wang, Hwei-Gene
Subject: RE: NDA 21567 label

For question 2.

Please look at the following references:

1 Bhutani VK, Johnson L. Kernicterus in the 21st century: frequently asked questions. *Journal of Perinatology*. 2009;29:S20–S24.

2 Bhutani VK, Johnson L, Sivieri EM. Predictive ability of a predischarge hour-specific serum bilirubin for subsequent significant hyperbilirubinemia in healthy term and near-term newborns. *Pediatrics*. 1999;103:6–14.

3 Sarici SU, Yurdakok M, Muhittin SA, et al. An Early (Sixth-Hour) Serum Bilirubin Measurement is Useful in Predicting the Development of Significant Hyperbilirubinemia and Severe ABO Hemolytic Disease in a Selective High-Risk Population of Newborns with ABO Incompatibility. *Pediatrics* 2002;109;e53

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301.796.9883 fax
Venessa.Perry@fda.hhs.gov

From: Wang, Hwei-Gene [mailto:HweiGene.Wang@bms.com]

Sent: Tuesday, January 18, 2011 7:33 AM
To: Perry, Venessa
Subject: RE: NDA 21567 label

Venessa:

It is no problem and thanks for forwarding our questions.

Also as an fyi that I am working from home again today because CT is having an ice/snow storm now. There is a thick sheet of ice/snow mixture on the road. If you want to reach me, you can do it through e-mail or call my cell at (b) (6).

Many thanks.

Heidi

From: Perry, Venessa [mailto:Venessa.Perry@fda.hhs.gov]
Sent: Monday, January 17, 2011 11:16 PM
To: Wang, Hwei-Gene
Subject: RE: NDA 21567 label

Heidi,

I left the office early on Friday so I am just getting your message. I will forward your questions to the reveiwers and will get back to you Tuesday, hopefully. Thanks

Venessa

From: Wang, Hwei-Gene [HweiGene.Wang@bms.com]
Sent: Friday, January 14, 2011 11:38 AM
To: Perry, Venessa
Subject: RE: NDA 21567 label

Dear Venessa:

Regarding Reyataz (NDA #21-567 (S-025)), we are still working on the requested revisions. Can you please clarify the following in order for us to respond as quickly as possible:

1. Nonclinical Toxicology labeling revisions in Sections 8 and 13, can you please share with us the source of human data and animal data used to re-calculate the multiples to be based upon ATV 300/RTV 100?
2. Is it possible to provide a reference for what the 95th percentile by age is in the statement: "(b) (4) ?

I know it is a lot of ask but because we have to confirm the re-calculations, is there any possibility of receiving an answer to the nonclinical question today?

Many thanks,

Heidi

From: Perry, Venessa [mailto:Venessa.Perry@fda.hhs.gov]
Sent: Thursday, January 13, 2011 3:15 PM
To: Wang, Hwei-Gene
Cc: Percival, Lisa
Subject: RE: NDA 21567 label

Heidi,

Thanks for the question. You are correct in that the numbering should be according to the CFR with 10 as the Overdosage and end with 17. However there is no 17 in the original label you sent. Also, you can delete indications and usage, under recent major changes, since its been over a year and no changes were made to that section. I left a message for you as well. Please let me know if you have additional questions.

Thanks

Venessa

Venessa M Perry, MPH
Regulatory Project Manager
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Silver Spring, MD 20903
301.796.4891 voice
301.796.9883 fax
Venessa.Perry@fda.hhs.gov

From: Wang, Hwei-Gene [mailto:HweiGene.Wang@bms.com]
Sent: Thursday, January 13, 2011 1:33 PM
To: Perry, Venessa
Cc: Percival, Lisa
Subject: RE: NDA 21567 label

Dear Venessa:

Before we send our response to the Reyataz labeling comments (NDA #21-567 (S-025)), can you please clarify your email message below regarding re-numbering for the sections? Are you asking us to change the numbers of those sections or are you explaining that the numbering changes in your version are not applicable because you didn't have access to fix them?

In case of the former, we are concerned with making this change because it seems to be against the current requirements? Pursuant to CRF 201.56 d(1) (Requirements on content and format of labeling for human prescription drug and biological products), Overdosage is Section 10 and Patient Counseling Information is Section 17. When a section or subsection is omitted from the Full Prescribing Information, the section must also be omitted from the Contents (§ 201.56(d)(4)). The heading "Full Prescribing Information: Contents" must be followed by an asterisk and the following statement must appear at the end of the Contents: "*Sections or subsections omitted from the Full Prescribing Information are not listed" (§ 201.56(d)(4)).

Any clarification you can provide us is much appreciated as we prepare the revised USPI.

Regards,

Heidi

Heidi Wang, PhD
Bristol-Myers Squibb
Global Regulatory Sciences, US Liaison

203-677-7618 (Office)
(b) (6)

From: Percival, Lisa
Sent: Thursday, January 13, 2011 12:50 PM
To: Wang, Hwei-Gene
Subject: FW: NDA 21567 label

From: Perry, Venessa [mailto:Venessa.Perry@fda.hhs.gov]
Sent: Tuesday, January 11, 2011 11:48 AM
To: Percival, Lisa
Subject: RE: NDA 21567 label

Lisa,

Please find attached a fax and the label attached with recommended changes. I have attached the label as a PDF and word document for your use. Because of the macros we were unable to change the numbering for the sections. Section 9 should be over dosage, with the last section 15 as the PI.
Please let me know if you have any questions. Thanks

Venessa
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Silver Spring, MD 20903
301.796.4891 voice
301.796.9883 fax
Venessa.Perry@fda.hhs.gov

From: Percival, Lisa [mailto:Lisa.Percival@bms.com]
Sent: Tuesday, January 11, 2011 10:02 AM
To: Perry, Venessa
Subject: RE: NDA 21567 label

perfect...thanks!

From: Perry, Venessa [mailto:Venessa.Perry@fda.hhs.gov]
Sent: Tuesday, January 11, 2011 9:56 AM
To: Percival, Lisa

Perry, Venessa

From: Wang, Hwei-Gene [HweiGene.Wang@bms.com]
Sent: Wednesday, January 19, 2011 10:32 AM
To: Perry, Venessa
Subject: RE: NDA 21567 label

Venessa:

Thanks for the answer to question 1. We are very close to responding to the revised Reyataz label (NDA 21567).

However, based on the 3 references on question 2, ie, the 95th percentile by age, we are a bit confused. Can you please clarify as to the specific criteria used for the following sentence, (b) (4)

[redacted]

'? In particular:

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

Many thanks,

Heidi

From: Perry, Venessa [mailto:Venessa.Perry@fda.hhs.gov]
Sent: Tuesday, January 18, 2011 9:21 AM
To: Wang, Hwei-Gene
Subject: RE: NDA 21567 label

Regarding question 1

Please fill in the blanks of table provided below:

Dosing Regimen	Study no.	Animal NOAEL (mg/kg)	Animal NOAEL AUC_{24h} (ng·h/mL)	Human AUC_{24h} (ng·h/mL)*	AUC_{24h} Ratio (Animal/Hum
Mouse Carcinogenicity Study					
Rat Carcinogenicity Study					
Rat Teratogenicity Study					
Rabbit Teratogenicity Study					
Rat Maternal Toxicity					

*: Please refer to and provide AUC_{24h} values in recent human pk data using ATV/RTV 300/1000 mg (e.g., 43388 ng.h/ml or others with study number).

Venessa M Perry, MPH
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Venessa.Perry@fda.hhs.gov

From: Wang, Hwei-Gene [mailto:HweiGene.Wang@bms.com]
Sent: Tuesday, January 18, 2011 7:43 AM
To: Perry, Venessa
Subject: RE: NDA 21567 label

Venessa:

Many thanks and I look forward to hearing regarding Question 1.

Best,

Heidi

From: Perry, Venessa [mailto:Venessa.Perry@fda.hhs.gov]
Sent: Tuesday, January 18, 2011 7:41 AM
To: Wang, Hwei-Gene
Subject: RE: NDA 21567 label

For question 2.

Please look at the following references:

1 Bhutani VK, Johnson L. Kernicterus in the 21st century: frequently asked questions. *Journal of Perinatology*. 2009;29:S20–S24.

2 Bhutani VK, Johnson L, Sivieri EM. Predictive ability of a predischarge hour-specific serum bilirubin for subsequent significant hyperbilirubinemia in healthy term and near-term newborns. *Pediatrics*. 1999;103:6–14.

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Many thanks.

Heidi

From: Perry, Venessa [mailto:Venessa.Perry@fda.hhs.gov]
Sent: Monday, January 17, 2011 11:16 PM
To: Wang, Hwei-Gene
Subject: RE: NDA 21567 label

Heidi,

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Venessa

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To: Perry, Venessa
Subject: RE: NDA 21567 label

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Regarding Reyataz (NDA #21-567 (S-025)), we are still working on the requested revisions. Can you please clarify the following in order for us to respond as quickly as possible:

1. Nonclinical Toxicology labeling revisions in Sections (b) (4)
2. Is it possible to provide a reference for (b) (4)

(b) (4)

I know it is a lot of ask but because we have to confirm the re-calculations, is there any possibility of receiving an answer to the nonclinical question today?

Many thanks,

Heidi

From: Perry, Venessa [mailto:Venessa.Perry@fda.hhs.gov]
Sent: Thursday, January 13, 2011 3:15 PM
To: Wang, Hwei-Gene
Cc: Percival, Lisa
Subject: RE: NDA 21567 label

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Silver Spring, MD 20903
301.796.4891 voice
301.796.9883 fax
Venessa.Perry@fda.hhs.gov

From: Wang, Hwei-Gene [mailto:HweiGene.Wang@bms.com]
Sent: Thursday, January 13, 2011 1:33 PM
To: Perry, Venessa
Cc: Percival, Lisa
Subject: RE: NDA 21567 label

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Regards,

Heidi

Heidi Wang, PhD
Bristol-Myers Squibb
Global Regulatory Sciences, US Liaison

203-677-7618 (Office)
(b) (6)

From: Percival, Lisa
Sent: Thursday, January 13, 2011 12:50 PM
To: Wang, Hwei-Gene
Subject: FW: NDA 21567 label

From: Perry, Venessa [mailto:Venessa.Perry@fda.hhs.gov]
Sent: Tuesday, January 11, 2011 11:48 AM
To: Percival, Lisa
Subject: RE: NDA 21567 label

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Please let me know if you have any questions. Thanks

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301.796.4891 voice
301.796.9883 fax
Venessa.Perry@fda.hhs.gov

From: Percival, Lisa [mailto:Lisa.Percival@bms.com]

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/s/

VENESSA M PERRY
02/01/2011

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation IV

FACSIMILE TRANSMITTAL SHEET

DATE: February 1, 2011

To: Heidi Wang, PhD, Associate Director, US Liaison	Venessa M Perry, MPH Regulatory Project Manager
Company: Bristol-Myers Squibb	Division of Antiviral Products
Fax number: 203.677.7435	**Fax number:** 301.796.9883
Phone number: 203.677.7618	**Phone number:** 301.796.4891

Subject: NDA 21-567/S-025

Total no. of pages including cover: 2

Document to be mailed: ☐ YES ☑ NO

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Division of Antiviral Drug Products
Food and Drug Administration
Rockville MD 20857

MEMORANDUM OF FACSIMILE CORRESPONDENCE

Date: February 1, 2011

Sponsor: Bristol-Myers Squibb

NDA: 21-567/S-025

Drug: Reyataz ® (atazanavir sulfate) capsules

To: Heidi Wang, PhD, US, Liason

From: Venessa M Perry, MPH, Regulatory Project Manager

Through: Alan Shapiro, MD, Medical Reviewer
Mary Singer, MD, Medical Team Leader

Subject: NDA 21-567 Reyataz ® (atazanavir sulfate)

The following comments are being conveyed to you on behalf of the clinical review team in reference to your submission dated August 6, 2010 to provide data from AI424182, a study of ATV/RTV in HIV infected pregnant women. Please see the following comment regarding your proposed labeling revisions submitted on January 31, 2011:

Several minor editorial changes have been made; but in addition, we do not concur with your proposed change in the Highlights/Dosage and Administration section:

[redacted] (b) (4)

[redacted]

[redacted]

We also do not concur with adding the caveat [redacted] (b) (4)
[redacted] **(see excerpt below).** [redacted] (b) (4)
[redacted]
[redacted]

(b) (4) [redacted]

[redacted]

Infants With Glucose < 40 mg/dL (< 2.2 mmol/L) Unexplained by Maternal Glucose Intolerance, Difficult Delivery, or Sepsis

ATV/RTV	PID DOB Time of Birth	Date and Time of Draw	Hours from Birth	Glucose	Method of glucose collection	Time to Lab Processing	Fasting for Glucose Test	Clinical Diagnosis of Hypoglycemia	Treatment Given for Hypoglycemia	Comments
300/100	5-1011 (b) (6) 3:10 pm	(b) (6) 4:00 pm	0.83	3.1 mmol/L	Accutrend heelstick	N/A	Y	No	No	3.1 mmol = 56 mg/dL
		(b) (6) UNK	<8.83*	36 mg/dL	Venous, SST, placed on ice	Within 1 hr	Y			
300/100	5-1026 (b) (6) 7:45 am	(b) (6) 9:40 am	1.92	2.8 mmol/L	Accutrend heelstick	N/A	Y	Yes	No	2.8 mmol = 50 mg/dL Infant was fed at 10:00 am
		(b) (6) UNK	<16.25*	32 mg/dL	Venous, SST, placed on ice	Within 1 hr	Y			
400/100	5-1059 (b) (6) 11:40 pm	(b) (6) 12:12 am	0.53	4.6 mmol/L	Accutrend heelstick	N/A	Y	No	No	4.6 mmol = 83 mg/dL
		(b) (6) UNK	<24.33*	27 mg/dL	Venous, SST, placed on ice	Within 1 hr	N			

* For unknown collection times, the upperbound, i.e. hours from birth for the sample is shown

Please provide a response by 12 pm February 2, 2011.

MATERIAL SHOULD BE VIEWED AS UNOFFICIAL CORRESPONDENCE. Please feel free to contact me if you have any questions regarding the contents of this transmission at 301-796-4891.

_____

Venessa M Perry, MPH
Regulatory Project Manager
Division of Antiviral Products

87 Page(s) of Draft Labeling has been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/

VENESSA M PERRY
02/01/2011

Perry, Venessa

From: Perry, Venessa
Sent: Monday, January 31, 2011 10:17 AM
To: 'Wang, Hwei-Gene'
Cc: Percival, Lisa
Subject: RE: Fax with label attached

Heidi,

I received your message this morning. The reviewers would like the data included. In addition, you may follow the AMA style guide for the use of abbreviations such as "eg". Thanks.

Venessa

Venessa M Perry, MPH
Regulatory Project Manager
FDA/CDER/OND/Division of Antiviral Products
10903 New Hampshire Avenue, Building 22, Room 6377
Silver Spring, MD 20903
301.796.4891 voice
301.796.9883 fax
Venessa.Perry@fda.hhs.gov

From: Wang, Hwei-Gene [mailto:HweiGene.Wang@bms.com]
Sent: Friday, January 28, 2011 3:33 PM
To: Perry, Venessa
Cc: Percival, Lisa
Subject: RE: Fax with label attached

Dear Venessa:

Thanks for your clarification and it is very helpful.

BMS would like to ask FDA to consider a proposal to [redacted] (b) (4) of the revised draft Reyataz USPI (pregnancy submission). Therefore, the revised [redacted] (b) (4) [redacted]. The rationale is that the re-analysis of the [redacted] (b) (4) [redacted]

Can you please let us know if FDA agrees with this proposal at your earliest convenience?

Many thanks,

Heidi

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

/s/

VENESSA M PERRY
01/31/2011

A

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation IV

FACSIMILE TRANSMITTAL SHEET

DATE: January 28, 2011

To: Heidi Wang, PhD, Associate Director, US Liaison	Venessa M Perry, MPH Regulatory Project Manager
Company: Bristol-Myers Squibb	Division of Antiviral Products
Fax number: 203.677.7435	**Fax number:** 301.796.9883
Phone number: 203.677.7618	**Phone number:** 301.796.4891

Subject: NDA 21-567/S-025

Total no. of pages including cover: 2

Document to be mailed: ☐ YES ☑ NO

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Division of Antiviral Drug Products
Food and Drug Administration
Rockville MD 20857

MEMORANDUM OF FACSIMILE CORRESPONDENCE

Date: January 28, 2011

Sponsor: Bristol-Myers Squibb

NDA: 21-567/S-025

Drug: Reyataz ® (atazanavir sulfate) capsules

To: Heidi Wang, PhD, US, Liason

From: Venessa M Perry, MPH, Regulatory Project Manager

Through: Alan Shapiro, MD, Medical Reviewer
Mary Singer, MD, Medical Team Leader

Subject: NDA 21-567 Reyataz ® (atazanavir sulfate)

The following comments are being conveyed to you on behalf of the clinical review team in reference to your submission dated August 6, 2010 to provide data from AI424182, a study of ATV/RTV in HIV infected pregnant women and in response to your email correspondence on January 27, 2011 regarding the most recent label of January 27, 2011.

- Physicians should make decisions about the dosing of REYATAZ in children rather than the parents. (b) (4)

- Our recent proposed labeling omitted an intended modification to the "**What is REYATAZ**" section of patient information which explains the current age range for REYATAZ. Please see highlighted bolded text below.

  What is REYATAZ?

  REYATAZ is a prescription medicine used with other anti-HIV medicines to treat people who are infected with the human immunodeficiency virus (HIV) **greater than six years of age**. HIV is the virus that causes acquired immune deficiency syndrome (AIDS). REYATAZ is a type of anti-HIV medicine called a protease inhibitor. HIV infection destroys CD4+ (T) cells, which are important to the immune system. The immune system helps fight infection. After a large number of (T) cells are destroyed, AIDS develops. REYATAZ helps to block HIV protease, an enzyme that is needed for the HIV virus to multiply. REYATAZ may lower the amount of HIV in your blood, help your body keep its supply of CD4+ (T) cells, and reduce the risk of death and illness associated with HIV.

MATERIAL SHOULD BE VIEWED AS UNOFFICIAL CORRESPONDENCE. Please feel free to contact me if you have any questions regarding the contents of this transmission at 301-796-4891.

_____

Venessa M Perry, MPH
Regulatory Project Manager
Division of Antiviral Products

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/s/

VENESSA M PERRY
01/28/2011

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation IV

FACSIMILE TRANSMITTAL SHEET

DATE: January 27, 2011

To: Heidi Wang, PhD, Associate Director, US Liaison	Venessa M Perry, MPH Regulatory Project Manager
Company: Bristol-Myers Squibb	Division of Antiviral Products
Fax number: 203.677.7435	**Fax number:** 301.796.9883
Phone number: 203.677.7618	**Phone number:** 301.796.4891

Subject: NDA 21-567/S-025

Total no. of pages including cover: 2

Document to be mailed: ☐ YES ☑ NO

~~DEPARTMENT OF HEALTH & HUMAN SERVICES~~ ~~Public Health Service~~

Division of Antiviral Drug Products
Food and Drug Administration
Rockville MD 20857

MEMORANDUM OF FACSIMILE CORRESPONDENCE

Date: January 27, 2011

Sponsor: Bristol-Myers Squibb

NDA: 21-567/S-025

Drug: Reyataz ® (atazanavir sulfate) capsules

To: Heidi Wang, PhD, US, Liason

From: Venessa M Perry, MPH, Regulatory Project Manager

Through: Sarah Robertson, PharmD, Clinical Pharmacology Team Leader

Subject: NDA 21-567 Reyataz ® (atazanavir sulfate)

The following comments are being conveyed to you on behalf of the clinical review team in reference to your submission dated August 6, 2010 to provide data from AI424182, a study of ATV/RTV in HIV infected pregnant women.

- **Please find the updated label with our recommendations attached.**
- **In addition, please update the values in Table 17 (Sect. 12.3) to reflect the revised PK parameters excluding the data from Run 20.**

Please provide a response by close of business January 31, 2011.

MATERIAL SHOULD BE VIEWED AS UNOFFICIAL CORRESPONDENCE. Please feel free to contact me if you have any questions regarding the contents of this transmission at 301-796-4891.

_____
Venessa M Perry, MPH
Regulatory Project Manager
Division of Antiviral Products

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/s/

VENESSA M PERRY
01/27/2011

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation IV

FACSIMILE TRANSMITTAL SHEET

DATE: January 24, 2011

To: Heidi Wang, PhD, Associate Director, US Liaison	Venessa M Perry, MPH Regulatory Project Manager
Company: Bristol-Myers Squibb	Division of Antiviral Products
Fax number: 203.677.7435	**Fax number:** 301.796.9883
Phone number: 203.677.7618	**Phone number:** 301.796.4891

Subject: NDA 21-567/S-025

Total no. of pages including cover: 2

Document to be mailed: YES ☑ NO

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Division of Antiviral Drug Products
Food and Drug Administration
Rockville MD 20857

MEMORANDUM OF FACSIMILE CORRESPONDENCE

Date: January 24, 2011

Sponsor: Bristol-Myers Squibb

NDA: 21-567/S-025

Drug: Reyataz ® (atazanavir sulfate) capsules

To: Heidi Wang, PhD, US, Liason

From: Venessa M Perry, MPH, Regulatory Project Manager

Through: Kuei- Meng Wu, PhD, Pharmacology toxicology Reviewer
Hanan Ghantous, PhD Pharmacology Toxicology Team Leader

Subject: NDA 21-567 Reyataz ® (atazanavir sulfate)

The following comments are being conveyed to you on behalf of the clinical review team in reference to your submission dated August 6, 2010 to provide data from AI424182, a study of ATV/RTV in HIV infected pregnant women. Please see the following questions regarding your proposed labeling revisions submitted on January 21, 2011:

1. Please clarify how AUC_{24h} values were derived from the mouse and rat carcinogenicity studies in view of the fact that there were only two time point of measurements available for each study and that original reports seemed to indicate that AUC could not be reliably obtained.

2. Additionally, were any extrapolations made or are there existing equivalent studies in the same species that are supportive of the values provided?

Please provide a response by close of business January 25, 2011.

MATERIAL SHOULD BE VIEWED AS UNOFFICIAL CORRESPONDENCE. Please feel free to contact me if you have any questions regarding the contents of this transmission at 301-796-4891.

_____
Venessa M Perry, MPH
Regulatory Project Manager
Division of Antiviral Products

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/s/

VENESSA M PERRY
01/24/2011

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation IV

FACSIMILE TRANSMITTAL SHEET

DATE: January 21, 2011

To: Heidi Wang, PhD, Associate Director, US Liaison	Venessa M Perry, MPH Regulatory Project Manager
Company: Bristol-Myers Squibb	Division of Antiviral Products
Fax number: 203.677.7435	**Fax number:** 301.796.9883
Phone number: 203.677.7618	**Phone number:** 301.796.4891

Subject: NDA 21-567/S-025

Total no. of pages including cover: 2

Document to be mailed: YES ☑ NO

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Division of Antiviral Drug Products
Food and Drug Administration
Rockville MD 20857

MEMORANDUM OF FACSIMILE CORRESPONDENCE

Date: January 21, 2011

Sponsor: Bristol-Myers Squibb

NDA: 21-567/S-025

Drug: Reyataz ® (atazanavir sulfate) capsules

To: Heidi Wang, PhD, US, Liason

From: Venessa M Perry, MPH, Regulatory Project Manager

Through: Alan Shapiro, M.D., Medical Reviewer
Mary Singer, MD, Medical Team Leader

Subject: NDA 21-567 Reyataz ® (atazanavir sulfate)

The following comments are being conveyed to you on behalf of the clinical review team in reference to your submission dated August 6, 2010 to provide data from AI424182, a study of ATV/RTV in HIV infected pregnant women.

In reference to your email comments of 1/20/11 regarding Section 8.1:

1. We disagree with referring to subject 14-1049 as being of term gestation. In dataset BASEDATA.XPT, gestational ages at delivery were rounded to the nearest values. However, our preference was to use the unrounded values from the dataset TBILI to determine prematurity (< 38 weeks at gestation). As shown in the excerpt below from the TBILI.XPT dataset, subject 14-1049 had a gestational age of 37.57 weeks (i.e. < 38 weeks) at the time of delivery.

EXCERPTED FROM FILE TBILI.XPT

PID	DELD	GES BS	GESDEL	GESDT BS
0014 00049	(b) (6)	23	37.5714286	(b) (6)

2. Three infants had abnormal glucose values not explained by maternal glucose intolerance, difficult delivery, or sepsis: PIDs 5-1011, 5-1026, and 5-1059

MATERIAL SHOULD BE VIEWED AS UNOFFICIAL CORRESPONDENCE. Please feel free to contact me if you have any questions regarding the contents of this transmission at 301-796-4891.

_____

Venessa M Perry, MPH
Regulatory Project Manager
Division of Antiviral Products

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/s/

VENESSA M PERRY
01/21/2011

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation IV

FACSIMILE TRANSMITTAL SHEET

DATE: January 19, 2011

To: Heidi Wang, PhD, Associate Director, US Liaison	Venessa M Perry, MPH Regulatory Project Manager
Company: Bristol-Myers Squibb	Division of Antiviral Products
Fax number: 203.677.7435	**Fax number:** 301.796.9883
Phone number: 203.677.7618	**Phone number:** 301.796.4891

Subject: NDA 21-567/S-025

Total no. of pages including cover: 2

Document to be mailed: YES ☑ NO

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Division of Antiviral Drug Products
Food and Drug Administration
Rockville MD 20857

MEMORANDUM OF FACSIMILE CORRESPONDENCE

Date: January 11, 2011

Sponsor: Bristol-Myers Squibb

NDA: 21-567/S-025

Drug: Reyataz ® (atazanavir sulfate) capsules

To: Heidi Wang, PhD, US, Liason

From: Venessa M Perry, MPH, Regulatory Project Manager

Through: Jenny Zheng, PhD, Clinical Pharmacology Reviewer
Alan Shapiro, M.D., Medical Reviewer
Mary Singer, MD, Medical Team Leader

Subject: NDA 21-567 Reyataz ® (atazanavir sulfate)

The following comments are being conveyed to you on behalf of the clinical review team in reference to your submission dated August 6, 2010 to provide data from AI424182, a study of ATV/RTV in HIV infected pregnant women.

1. Please clarify whether the subject sample #s listed in Run 20 are subject numbers (i.e. how many subjects had samples analyzed in Run20?). Reanalyze the PK data for atazanavir excluding subjects from Run 20 because of the analytical problem associated with this run (subject sample #s 12-44, 12-54, 4-32, 4-43, 4-56, 5-40, 5-41, 5-50, 5-51, and 5-52 were analyzed in Run 20). In addition, please reanalyze the PK data for atazanavir by only excluding the samples from Run 20, and indicate the sampling time of the samples excluded. Please provide a summary table comparing the results with and without exclusion of these subjects/samples.

2. Reanalyze the protein binding data of atazanavir excluding samples from Runs #15, #16 and #26 and compare the difference with or without exclusion of these samples.

Please provide a response by close of business January 20, 2011.

MATERIAL SHOULD BE VIEWED AS UNOFFICIAL CORRESPONDENCE. Please feel free to contact me if you have any questions regarding the contents of this transmission at 301-796-4891.

Venessa M Perry, MPH
Regulatory Project Manager
Division of Antiviral Products

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/s/

VENESSA M PERRY
01/19/2011

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation IV

FACSIMILE TRANSMITTAL SHEET

DATE: January 19, 2011

To: Heidi Wang, PhD, Associate Director, US Liaison	Venessa M Perry, MPH Regulatory Project Manager
Company: Bristol-Myers Squibb	Division of Antiviral Products
Fax number: 203.677.7435	**Fax number:** 301.796.9883
Phone number: 203.677.7618	**Phone number:** 301.796.4891

Subject: NDA 21-567/S-025

Total no. of pages including cover: 2

Document to be mailed: YES ☑ NO

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Division of Antiviral Drug Products
Food and Drug Administration
Rockville MD 20857

MEMORANDUM OF FACSIMILE CORRESPONDENCE

Date: January 11, 2011

Sponsor: Bristol-Myers Squibb

NDA: 21-567/S-025

Drug: Reyataz ® (atazanavir sulfate) capsules

To: Heidi Wang, PhD, US, Liason

From: Venessa M Perry, MPH, Regulatory Project Manager

Through: Jenny Zheng, PhD, Clinical Pharmacology Reviewer
Alan Shapiro, M.D., Medical Reviewer
Mary Singer, MD, Medical Team Leader

Subject: NDA 21-567 Reyataz ® (atazanavir sulfate)

The following comments are being conveyed to you on behalf of the clinical review team in reference to your submission dated August 6, 2010 to provide data from AI424182, a study of ATV/RTV in HIV infected pregnant women.

1. Reanalyze the PK data of atazanavir excluding Subjects # 4, 5, and 12 because of the analytical problem associated with the samples from these subjects. Please provide the summary table comparing the results with exclusion and without exclusion.

2. Reanalyze the protein binding data of atazanavir excluding samples from Runs #15, #16 and #26 and compare the difference with or without exclusion.

Please provide a response by close of business January 20, 2011.

MATERIAL SHOULD BE VIEWED AS UNOFFICIAL CORRESPONDENCE. Please feel free to contact me if you have any questions regarding the contents of this transmission at 301-796-4891.

_____
Venessa M Perry, MPH
Regulatory Project Manager
Division of Antiviral Products

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/s/

VENESSA M PERRY
01/19/2011

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADM NISTRATION

REQUEST FOR DDMAC LABELING REVIEW CONSULTATION

Please send immediately following the Filing/Planning meeting

TO: **CDER-DDMAC-RPM**	FROM: (Name/Title, Office/Division/Phone number of requestor) Venessa M Perry, MPH, RPM OAP/DAVP 301.796.4891

REQUEST DATE	IND NO.	NDA/BLA NO.	TYPE OF DOCUMENTS (PLEASE CHECK OFF BELOW)
8.18.10		21567	

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE (Generally 1 week before the wrap-up meeting)
Reyataz (atazanavir sulfate)	priority	Antiviral	12.30.2010

NAME OF FIRM: Bristol Meyers Squibb company	PDUFA Date:2.6.2011

TYPE OF LABEL TO REVIEW

TYPE OF LABELING:
(Check all that apply)
XX☐ PACKAGE INSERT (PI)
☐ PATIENT PACKAGE INSERT (PPI)
☐ CARTON/CONTAINER LABELING
☐ MEDICATION GUIDE
☐ INSTRUCTIONS FOR USE(IFU)

TYPE OF APPLICATION/SUBMISSION
☐ ORIGINAL NDA/BLA
☐ IND
XX☐ EFFICACY SUPPLEMENT
☐ SAFETY SUPPLEMENT
☐ LABELING SUPPLEMENT
☐ PLR CONVERSION

REASON FOR LABELING CONSULT
☐ INITIAL PROPOSED LABELING
XX☐ LABELING REVISION

EDR link to submission:

This is a new efficacy supplement, NDA 21567/S-025 to provide data from a study of ATV/RTV to support dosing regiments in HIV infected pregnant women. The supplement provides for labeling changes in the dosage and administration section and specific populations. This will be a priority review. The link to the submission is below.

The filing due date is:10/5/2010
PDUFA goal Date is:2/6/2011

EDR Location: \\CDSESUB1\EVSPROD\NDA021567\021567.enx

Please Note: There is no need to send labeling at this time. DDMAC reviews substantially complete labeling, which has already been marked up by the CDER Review Team. The DDMAC reviewer will contact you at a later date to obtain the substantially complete labeling for review.

COMMENTS/SPECIAL INSTRUCTIONS: Dates are tentative at this time.

Mid-Cycle Meeting: [Insert Date]11.6.2010

Labeling Meetings: [Insert Dates]Dec 2010 and Jan 2011 TBD

Wrap-Up Meeting: [Insert Date]1.9.2011

The filing meeting is 9.1.10 2-3 pm bldg 22 rm 6396

SIGNATURE OF REQUESTER Venessa M Perry, MPH

SIGNATURE OF RECEIVER	METHOD OF DELIVERY (Check one) ☐XX eMAIL ☐ HAND

Reference ID: 2892455

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VENESSA M PERRY
01/18/2011

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation IV

FACSIMILE TRANSMITTAL SHEET

DATE: January 11, 2011

To: Lisa Percival, Director, Global Regulatory Strategy	Venessa M Perry, MPH Regulatory Project Manager
Company: Bristol-Myers Squibb	Division of Antiviral Products
Fax number:	**Fax number:** 301.796.9883
Phone number: 203.677.6803	**Phone number:** 301.796.4891

Subject: NDA 21-567/S-025

Total no. of pages including cover: 73

Document to be mailed: ☐ YES ☑ NO

~~DEPARTMENT OF HEALTH & HUMAN SERVICES~~ ~~Public Health Service~~

Division of Antiviral Drug Products
Food and Drug Administration
Rockville MD 20857

MEMORANDUM OF FACSIMILE CORRESPONDENCE

Date: January 11, 2011

Sponsor: Bristol-Myers Squibb

NDA: 21-567/S-025

Drug: Reyataz ® (atazanavir sulfate) capsules

To: Lisa Percival, Director Global Regulatory Strategy

From: Venessa M Perry, MPH, Regulatory Project Manager

Through: Alan Shapiro, M.D., Medical Reviewer
Mary Singer, MD, Medical Team Leader

Subject: NDA 21-567 Reyataz ® (atazanavir sulfate)

The following comments are being conveyed to you on behalf of the clinical review team in reference to your submission dated August 6, 2010 to provide data from AI424182, a study of ATV/RTV in HIV infected pregnant women.

Please find attached the most recent label with recommended changes.

MATERIAL SHOULD BE VIEWED AS UNOFFICIAL CORRESPONDENCE. Please feel free to contact me if you have any questions regarding the contents of this transmission at 301-796-4891.

_____
Venessa M Perry, MPH
Regulatory Project Manager
Division of Antiviral Products

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VENESSA M PERRY
01/13/2011

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation IV

FACSIMILE TRANSMITTAL SHEET

DATE: January 5, 2011

To: Lisa Percival, Director, Global Regulatory Strategy	Venessa M Perry, MPH Regulatory Project Manager
Company: Bristol-Myers Squibb	Division of Antiviral Products
Fax number:	**Fax number:** 301.796.9883
Phone number: 203.677.6803	**Phone number:** 301.796.4891

Subject: NDA 21-567/S-025

Total no. of pages including cover: 2

Document to be mailed: ☐ YES ☑ NO

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Division of Antiviral Drug Products
Food and Drug Administration
Rockville MD 20857

MEMORANDUM OF FACSIMILE CORRESPONDENCE

Date: January 5, 2011

Sponsor: Bristol-Myers Squibb

NDA: 21-567/S-025

Drug: Reyataz ® (atazanavir sulfate) capsules

To: Lisa Percival, Director Global Regulatory Strategy

From: Venessa M Perry, MPH, Regulatory Project Manager

Through: Alan Shapiro, M.D., Medical Reviewer
Mary Singer, MD, Medical Team Leader

Subject: NDA 21-567 Reyataz ® (atazanavir sulfate)

The following comments are being conveyed to you on behalf of the clinical review team in reference to your submission dated August 6, 2010 to provide data from AI424182, a study of ATV/RTV in HIV infected pregnant women.

> **In Table 1 of your December 20, 2010 response to our questions about infants with low glucose values on lab results, we noted a discrepancy that needs clarification. Specifically, you state via a footnote (b) that patient 5-1011 had an SAE and was in the neonatal ward. In our review of the narratives in the CSR and your dataset AESAESTR, no listing or report of an SAE was found for this patient. Please clarify, and provide the narrative summary for our review.**

Please respond back by January 7, 2011.

MATERIAL SHOULD BE VIEWED AS UNOFFICIAL CORRESPONDENCE. Please feel free to contact me if you have any questions regarding the contents of this transmission at 301-796-4891.

_____
Venessa M Perry, MPH
Regulatory Project Manager
Division of Antiviral Products

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/s/

VENESSA M PERRY
01/05/2011

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation IV

FACSIMILE TRANSMITTAL SHEET

DATE: December 16, 2010

To: Lisa Percival, Director, Global Regulatory Strategy	Venessa M Perry, MPH Regulatory Project Manager
Company: Bristol-Myers Squibb	Division of Antiviral Products
Fax number:	**Fax number:** 301.796.9883
Phone number: 203.677.6803	**Phone number:** 301.796.4891

Subject: NDA 21-567/S-025

Total no. of pages including cover: 3

Document to be mailed: ☐ YES ☑ NO

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Division of Antiviral Drug Products
Food and Drug Administration
Rockville MD 20857

MEMORANDUM OF FACSIMILE CORRESPONDENCE

Date: December 7, 2010

Sponsor: Bristol-Myers Squibb

NDA: 21-567/S-025

Drug: Reyataz ® (atazanavir sulfate) capsules

To: Lisa Percival, Director Global Regulatory Strategy

From: Venessa M Perry, MPH, Regulatory Project Manager

Through: Alan Shapiro, M.D., Medical Reviewer
Mary Singer, MD, Medical Team Leader

Subject: NDA 21-567 Reyataz ® (atazanavir sulfate)

The following comments are being conveyed to you on behalf of the clinical review team in reference to your submission dated August 6, 2010 to provide data from AI424182, a study of ATV/RTV in HIV infected pregnant women.

In reviewing your supplement [redacted] (b) (4), it is not apparent how you identified seven infants (three infants born to women treated with REYATAZ/ritonavir 300/100 mg and four infants born to women treated with REYATAZ/ritonavir 400/100 mg) as having a Grade 3-4 bilirubin abnormality. Per the Division of AIDS Toxicity Table for Grading the Severity of Pediatric Adverse Experiences (Appendix 7 of AI424182 protocol), a neonate less than 14 days of age has to have a total bilirubin greater than 20mg/dL (342 mmol/L) to be classified as a Grade 2 (non-hemolytic) or Grade 3 (hemolytic) AE. None of the neonates in the study had a total bilirubin greater than 20mg/L (342 mmol/L). In addition to the seven infants identified as Grade 3-4, there were other infants who had bilirubin laboratory abnormalities with comparable or higher bilirubin values who were not considered to have a Grade 3-4 abnormality (see below).

[redacted] (b) (4)

Please clarify this discrepancy and explain how Grading of hyperbilirubinemia in infants < 14 days of age was done in your analysis. If your Grading of hyperbilirubinemia is in error, please send an erratum for all submitted documents.

Table of Infants with Hyperbilirubin AEs of Grade 3 or Higher and other Infants with Comparable Bilirubin Levels that were not considered Grade 3-4

Infant PID	Maternal ATV/RTV	Hours after Birth for Highest Bilirubin Recorded	Highest Bilirubin Recorded	AE Grading (3 or above) by BMS
-4-1008	300/100	48	10	3
-12-1025	300/100	151.5	15.3	3
-8-1027	300/100	46.6	13	4
-5-1010	300/100	50.8	11.3	None
-5-1020	300/100	51.5	12.2	None
-5-1023	300/100	93.4	12.7	None
-5-1034	300/100	85.3	12.1	None
-8-1024	300/100	59.9	13.5	None
-14-1049	400/100	59	10.8	3
-12-1065	400/100	143.7	11.3	3
-5-1067	400/100	144.5	13.7	4
-12-1054	400/100	140.3	11.4	4
-4-1043	400/100	48.9	14.2	None
-5-1050	400/100	92.8	10.9	None
-12-1068	400/100	97.1	11.7	None

(b) (4)

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_____

Venessa M Perry, MPH
Regulatory Project Manager
Division of Antiviral Products

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/s/

VENESSA M PERRY
12/16/2010

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation IV

FACSIMILE TRANSMITTAL SHEET

DATE: December 7, 2010

To: Lisa Percival, Director, Global Regulatory Strategy	Venessa M Perry, MPH Regulatory Project Manager
Company: Bristol-Myers Squibb	Division of Antiviral Products
Fax number:	**Fax number:** 301.796.9883
Phone number: 203.677.6803	**Phone number:** 301.796.4891

Subject: NDA 21-567/S-025

Total no. of pages including cover: 3

Document to be mailed: ☐ YES ☑ NO

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Division of Antiviral Drug Products
Food and Drug Administration
Rockville MD 20857

MEMORANDUM OF FACSIMILE CORRESPONDENCE

Date: December 7, 2010

Sponsor: Bristol-Myers Squibb

NDA: 21-567/S-025

Drug: Reyataz ® (atazanavir sulfate) capsules

To: Lisa Percival, Director Global Regulatory Strategy

From: Venessa M Perry, MPH, Regulatory Project Manager

Through: Alan Shapiro, M.D., Medical Reviewer
Mary Singer, MD, Medical Team Leader

Subject: NDA 21-567 Reyataz ® (atazanavir sulfate)

The following comments are being conveyed to you on behalf of the clinical review team in reference to your submission dated August 6, 2010 to provide data from AI424182, a study of ATV/RTV in HIV infected pregnant women.

The literature suggests that neonates exposed to protease inhibitors in utero may experience a higher incidence of neonatal hypoglycemia than unexposed infants (Dinsmoor and Forrest, Infect Dis Obstet Gynecol 2002; 10:187–191). In Study AI424182, there were 16 infants who had serum glucose levels < 55mg/dL (indicating hypoglycemia) on Day of Life #1. Of these 16 infants, three had glucose values ranging from 35 to 40 mg/dL and five had glucose values less than 35mg/dL. Only one (PID AI424182-5-1026) of these 16 infants was coded as having hypoglycemia (Grade 1) in the AE dataset. The other 15 neonates were not identified as having an AE of hypoglycemia. In addition to the 16 infants with laboratory identified hypoglycemia, an additional infant (PID AI424182-5-1061) was described as floppy and hypoglycemic (Grade 3) and had a glucose level of 59mg/dL (3.3 mmol/L) which is not considered abnormal for a neonate.

Neonatal hypoglycemia should be diagnosed by the Accu Check method or by a serum sample that is placed on ice immediately or obtained in a special tube designed to prevent glucose hydrolysis during handling. We acknowledge that not all laboratory diagnosed abnormalities are coded as AEs. However, we do need to know how many of the other 15 neonates with glucose levels less than 55 mg/dL had "true" hypoglycemia (i.e. abnormal glucose which was not an artifact of specimen handling) or were symptomatic from the reported low glucose values.

To address our concern about neonatal hypoglycemia, please address the following questions:

1. How were the glucose samples obtained and processed in newborn infants? Please describe collection procedures (venous versus capillary (heel stick blood sampling), collection tubes used, handling (e.g. were samples placed on ice immediately), and time delay from collection to laboratory processing? Were Accu-checks obtained in the delivery room or in the nursery for newborn infants?

2. Please provide adverse event narrative and CSR for the subject PID AI424182-5-1026

3. Did any of the 15 other patients with laboratory diagnosed hypoglycemia have a repeat glucose obtained or have an Accu-check that confirmed the reported results?

4. Were any of the 15 patients with laboratory evidence of hypoglycemia clinically diagnosed with hypoglycemia or treated for hypoglycemia? If yes, please provide adverse event narratives for the hypoglycemic event(s), if available, for any of these 15 patients who were either clinically diagnosed with hypoglycemia and/or treated for hypoglycemia.

5. We have reviewed the safety narrative for subject AI424182-5-106; and are requesting clarification on whether any of the subsequent serum glucose levels obtained from this subject on the first day of life met the definition for neonatal hypoglycemia (serum glucose <55mg/dL [<3.05 mmol/L]); or whether the diagnosis of hypoglycemia made solely on clinical grounds?

In addition, please provide a copy of the Investigator Brochure [IB] for the pregnancy study under review AI424182.

Please provide requested information by December 14, 2010.

MATERIAL SHOULD BE VIEWED AS UNOFFICIAL CORRESPONDENCE. Please feel free to contact me if you have any questions regarding the contents of this transmission at 301-796-4891.

_____
Venessa M Perry, MPH
Regulatory Project Manager
Division of Antiviral Products

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/s/

VENESSA M PERRY
12/07/2010

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION	REQUEST FOR CONSULTATION

TO *(Division/Office)*: **Mail: OSE**			FROM: Venessa M Perry, MPH	
DATE 11.18.10	IND NO.	NDA NO. 21567	TYPE OF DOCUMENT	DATE OF DOCUMENT
NAME OF DRUG Reyataz (Atazanavir sulfate)	PRIORITY CONSIDERATION X		CLASSIFICATION OF DRUG Antiviral	DESIRED COMPLETION DATE

NAME OF FIRM:

REASON FOR REQUEST

I. GENERAL

☐ NEW PROTOCOL	☐ PRE--NDA MEETING	☐ RESPONSE TO DEFICIENCY LETTER
☐ PROGRESS REPORT	☐ END OF PHASE II MEETING	☐ FINAL PRINTED LABELING
☐ NEW CORRESPONDENCE	☐ RESUBMISSION	☐ LABELING REVISION
☐ DRUG ADVERTISING	X☐ SAFETY/EFFICACY	☐ ORIGINAL NEW CORRESPONDENCE
☐ ADVERSE REACTION REPORT	☐ PAPER NDA	☐ FORMULATIVE REVIEW
☐ MANUFACTURING CHANGE/ADDITION	☐ CONTROL SUPPLEMENT	X☐ OTHER *(SPECIFY BELOW)*:
☐ MEETING PLANNED BY		

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
☐ TYPE A OR B NDA REVIEW ☐ END OF PHASE II MEETING ☐ CONTROLLED STUDIES ☐ PROTOCOL REVIEW ☐ OTHER (SPECIFY BELOW):	☐ CHEMISTRY REVIEW ☐ PHARMACOLOGY ☐ BIOPHARMACEUTICS ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

☐ DISSOLUTION	☐ DEFICIENCY LETTER RESPONSE
☐ BIOAVAILABILTY STUDIES	☐ PROTOCOL-BIOPHARMACEUTICS
☐ PHASE IV STUDIES	☐ IN-VIVO WAIVER REQUEST

IV. DRUG EXPERIENCE

☐ PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL	☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
X☐ DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES	☐ SUMMARY OF ADVERSE EXPERIENCE
x☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)	☐ POISON RISK ANALYSIS
☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP	

V. SCIENTIFIC INVESTIGATIONS

☐ CLINICAL	☐ PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS:

This is a new efficacy supplement, NDA 21567/S-025 to provide data from a study of ATV/RTV to support dosing regiments in HIV infected pregnant women. The supplement provides for labeling changes in the dosage and administration section and specific populations. This will be a priority review. The link to the submission is below.

The filing due date is:10/5/2010
PDUFA goal Date is:2/6/2011

EDR Location: \\CDSESUB1\EVSPROD\NDA021567\021567.enx

Request for OSE/Epidemiology to Review GPRD Database for hyperbilirubinemia or consequences thereof in infants and hypoglycemia in infants, as outlined below.

In our review of atazanavir pregnancy supplement NDA 21-567 DARRTS#69, we have concerns about two different abnormalities in infants that can lead to severe consequences:

I. Hyperbilirubinemia

In our review of atazanavir pregnancy supplement, we are concerned about uncongugated hyperbilirubemia in neonates exposed in utero to atazanavir. Hyperbilirubinemia, if mild, can be benign but if elevated (total bilirubin >20mg/dL (SI >342

micromol/L)) can result in toxicity such as hearing loss, developmental delay and in the most severe cases, kernicterus. This concern is even more prominent in prematurely born. The sample size in the submitted study involved 40 atazanavir-exposed infants, and it is our understanding that query of the British GPRD database may help us address our concerns by comparing results for different populations:

1) Normal non-HIV exposed neonates and infants
2) HIV exposed neonates whose mothers were on HIV therapy during pregnancy that did not include a HIV protease inhibitor
3) HIV exposed neonates whose mothers were on HIV therapy during pregnancy that included an HIV protease inhibitor other than atazanavir (e.g. lopinavir/ritonavir, nelfinavir, etc…)
4) HIV exposed neonates whose mothers were on HIV therapy during pregnancy that included the HIV protease inhibitor, atazanavir

FOR EACH OF THE FOUR POPULATIONS LISTED ABOVE ALSO BREAKDOWN THE RESULTS BY:
Prematurely born < 38 weeks of gestation at birth
Term neonates >= 38 weeks of gestation at birth

For these populations, please compare the incidence of
A. Hyperbilirubinemia
B. Receipt of Phototherapy
C. Receipt of Exchange Transfusion

For Neonates that had total bilirubin level >5 mg/dL (SI >85.5 micromol/L) in the first week of life, please compare the incidence of
A. Kernicterus
B. Hearing Loss
C. Developmental Abnormalities

II. Hypoglycemia

In our review of atazanavir pregnancy supplement, we are concerned about post-natal hypoglycemia in neonates exposed in utero to atazanavir. Protease inhibitors like atazanavir have been associated with glucose intolerance in adults. Whether protease-inhibitor associated glucose intolerance is clinically significant in pregnancy has been controversial. In the submitted supplement, we identified 10 infants with significant hypoglycemia by laboratory evaluations. The interpretation of this finding is complicated by the handling of the serum glucose sample. If the obtained glucose sample is not placed on ice and processed immediately or placed in a special grey top tube, the glucose in the laboratory tube can breakdown on its own generating an artificially low value. A common practice in the US and Europe is to obtain a accucheck glucose value and confirm a low glucose value via a STAT specimen sent on ice. Therefore, we believe that querying the GPRD may be helpful to compare the relationship of in utero atazanavir to neonatal hypoglycemia.

The GPRD may use SI units for glucose, in US (SI) values: Grade 1 toxicity in neonates is 50-54mg/dL (SI 2.78 - 3.0 mmol/L); Grade 2 toxicity in neonates is 40- < 50 mg/dL (SI 2.22 - <2.78 mmol/L); Grade 3 toxicity in neonates is 30 - <40mg/dL (SI ; 1.67 - <2.22 mmol/L); Grade 4 toxicity in neonates is <30mg/dL (SI <1.67 mmol/L).

Populations of concern:

1) Normal non-HIV exposed neonates and infants
2) HIV exposed neonates whose mothers were on HIV therapy during pregnancy that did not include a HIV protease inhibitor
3) HIV exposed neonates whose mothers were on HIV therapy during pregnancy that included an HIV protease inhibitor other than atazanavir (e.g. lopinavir/ritonavir, nelfinavir, etc…)
4) HIV exposed neonates whose mothers were on HIV therapy during pregnancy that included the HIV protease inhibitor atazanavir

FOR EACH OF THE FOUR POPULATIONS LISTED ABOVE ALSO BREAKDOWN THE RESULTS BY:
Prematurely born < 38 weeks of gestation at birth
Term neonates >= 38 weeks of gestation at birth
Mothers with glucose intolerance during pregnancy (including gestational diabetes)
Infants weighing more than 4,000 grams at birth.

For these populations, please compare the incidence of
Hypoglycemia first day of life
(if possible) Grade 3-4 hypoglycemia first day of life
Oral glucose administered immediately after delivery

Receipt of IV glucose (dextrose) immediately after delivery	
SIGNATURE OF REQUESTER Venessa M Perry, MPH.	METHOD OF DELIVERY (Check one) XX☐e- MAIL ☐ HAND
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

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/s/

VENESSA M PERRY
11/18/2010

Perry, Venessa

From: Shapiro, Alan
Sent: Tuesday, October 26, 2010 12:22 PM
To: Perry, Venessa
Subject: RE: program request

Venessa:

The best thing is for me to talk with the Statistician since I need to prioritize what I need from them and to come to an understanding of what will be the most useful for my review. What I really need is patient datasets that contains all the information I want to access through jReview.
I will have to make a list of items I would like to be accessed via dataset but not today since I have other obligations.

Thanks

Alan

From: Perry, Venessa
Sent: Tuesday, October 26, 2010 12:15 PM
To: Shapiro, Alan
Subject: FW: program request

FYI- Please advise how you would like to proceed.

Venessa M Perry, MPH
Regulatory Project Manager
FDA/CDER/OND/Division of Antiviral Products
10903 New Hampshire Avenue, Building 22, Room 6377
Silver Spring, MD 20903
301.796.4891 voice
301.796.9883 fax
Venessa.Perry@fda.hhs.gov

From: Percival, Lisa [mailto:Lisa.Percival@bms.com]
Sent: Monday, October 25, 2010 4:54 PM
To: Perry, Venessa
Subject: program request

Hi Venessa,
I spoke with my statistician regarding the safety programs. If FDA needs these programs to be able to be run, then there is some work that's needed to get them to be submission-ready. The programs work by putting the dataset through a macro (or several macros) and then the program output is the table (there is no intermediary dataset). We can provide the programs as-is quickly, but are concerned that they won't work the way that you

need them to work. We can make them submission-ready, but it will take some time. Is there any chance you could prioritize specific ones you want, so that we can do them as needed or clarify the actual intended use of the program?

If this doesn't make sense, then we should probably get my statistician on the phone with Dr. Shapiro because I'm passing along her explanation.

Thanks and regards,
Lisa

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/s/

VENESSA M PERRY
11/08/2010

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR CONSULTATION

TO *(Office/Division)*: Pediatric Maternal Health	FROM (*Name, Office/Division, and Phone Number of Requestor)*: Venessa M Perry, MPH, OAP/DAVP 301.796.4891

DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
10.18.10		21567		10.19.10

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
REYATAZ	PRIORITY	ANTIVIRAL	12/13/10

NAME OF FIRM: BRISTOL MEYERS SQUIBB

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE / ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE-NDA MEETING
- ☐ END-OF-PHASE 2a MEETING
- ☐ END-OF-PHASE 2 MEETING
- ☐ RESUBMISSION
- ☒ SAFETY / EFFICACY
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☒ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☐ OTHER *(SPECIFY BELOW)*:

II. BIOMETRICS

- ☐ PRIORITY P NDA REVIEW
- ☐ END-OF-PHASE 2 MEETING
- ☐ CONTROLLED STUDIES
- ☐ PROTOCOL REVIEW
- ☐ OTHER (SPECIFY BELOW):
- ☐ CHEMISTRY REVIEW
- ☐ PHARMACOLOGY
- ☐ BIOPHARMACEUTICS
- ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE 4 STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL - BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG SAFETY

- ☐ PHASE 4 SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE, e.g., POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

- ☒ CLINICAL
- ☐ NONCLINICAL

COMMENTS / SPECIAL INSTRUCTIONS: NDA 21567/S-025 provides data from a study of the HIV protease inhibitor atazanavir which is usually given in combination with ritonavir (ATV/RTV) to support dosing regiments in HIV infected pregnant women. ATV/RTV is part of a multi-drug regimen to prevent perinatal tramsmission of HIV along with improving the health of the mother who is HIV infected. The submitted study was primarily a PK study with safety in pregnant women to see if increased dosing of ATV in third trimester is needed. As part of the safety analysis, the Applicant examined hyperbilirubunemia among in utero exposed neonates since one of the known side effects of ATV is an unconjugated hyperbilirubinemia that occurs in the majority of patients on this therapy.

The Applicant compared the approved adult regiment of 300mg ATV + 100mg RTV (300/100) with the increased dose of 400mg ATV + 100mg RTV (400/100). No significant PK difference was observed and therefore the Applicant is not recommending a change in dosing.

The Applicant's post-natal follow-up of bilirubin levels was done on the day of delivery (day-of-life 1), day-of-life 3, 5, 7 and week 2. No baby needed an exchange transfusion or had obvious signs of kernicterus. Unfortunately, the frequency of monitoring was done in days not hours and therefore we do not have a good picture of the bilirubin

levels in the first 48 hrs of life. Denver assessments were done at 4 months and 6 months but no newborn hearing assessments were requested as part of the study.

We are asking the Applicant to try to obtain the additional information (e.g. bilirubin levels results based on the time the samples were drawn, details of the abnormal Denver screening results and any newborn audiology results) from patient records.

Questions for PMHS/Pediatrics:

1) Do neonates with in utero exposure to ATV have a higher incidence of neontal hyperbilirubinemia as compared to healthy neonates? If yes, does the increased incidence and/or degree of neonatal hyperbilirubinemia place the ATV exposed neonates at higher risk of bilirubin related complications?

2) Is increased monitoring of bilirubin for exposed infants needed who do not have any obvious risk factors for neonatal hyperbilirubinemia (e.g. Coombs positive)?

3)Given the small sample size (approx 41 infants total) and the incomplete data collection, do we need more data to further define the risk of neonatal hyperbilirubinemia in ATV exposed neonates?

4) Are there other comments or recommendations that PMHS/Pediatrics has for managing the risk(s) of in utero exposure to ATV?

SIGNATURE OF REQUESTOR Venessa M Perry, MPH	METHOD OF DELIVERY (Check one) ☐ DFS ☒ EMAIL ☐ MAIL ☐ HAND
PRINTED NAME AND SIGNATURE OF RECEIVER	PRINTED NAME AND SIGNATURE OF DELIVERER

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/s/

VENESSA M PERRY
10/19/2010

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation IV

FACSIMILE TRANSMITTAL SHEET

DATE: October 12, 2010

To: Lisa Percival, Director, Global Regulatory Strategy	Venessa M Perry, MPH Regulatory Project Manager
Company: Bristol-Myers Squibb	Division of Antiviral Products
Fax number:	**Fax number:** 301.796.9883
Phone number: 203.677.6803	**Phone number:** 301.796.4891

Subject: NDA 21-567/S-025

Total no. of pages including cover: 3

Document to be mailed: ☐ YES ☑ NO

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Division of Antiviral Drug Products
Food and Drug Administration
Rockville MD 20857

MEMORANDUM OF FACSIMILE CORRESPONDENCE

Date: October 12, 2010

Sponsor: Bristol-Myers Squibb

NDA: 21-567/S-025

Drug: Reyataz ® (atazanavir sulfate) capsules

To: Lisa Percival, Director Global Regulatory Strategy

From: Venessa M Perry, MPH, Regulatory Project Manager

Through: Alan Shapiro, M.D., Medical Reviewer
Mary Singer, MD, Medical Team Leader

Subject: NDA 21-567 Reyataz ® (atazanavir sulfate)

The following comments are being conveyed to you on behalf of the clinical review team in reference to your submission dated August 6, 2010 to provide data from AI424182, a study of ATV/RTV in HIV infected pregnant women. In order to better assess the safety of infants exposed to atazanavir in-utero we are requesting the following information:

1. In following neonatal bilirubin levels, it is important to have the bilirubin samples timed by number of hours after birth to accurately gauge the degree of change of bilirubin in the first few days of life. We note that the bilirubin results in your datasets are listed by the day the blood sample was taken with no hours from birth or time of day drawn listed for each sample. Based on this lack of information, two sample taken two calendar days apart could theoretically represent any number of hours from 24.1 – 71.9 depending on the time the samples were drawn. Note the following hypothetical examples:

    a. The first atazanavir exposed infant was born at 10am [redacted] (b) (6) and had bilirubin sample drawn at noon (2 hrs after birth). On the third day of life, a bilirubin sample was taken at 12:01 am on [redacted] (b) (6). The second sample was taken approximately 38 hours from birth.

    b. The second atazanavir exposed infant was also born at 10am on [redacted] (b) (6) and also had bilirubin sample drawn at noon (2 hrs after birth). However on the third day of life [redacted] (b) (6) the bilirubin sample was delayed till 11PM. This second sample was taken approximately 61 hours from birth

Based on the information in the datasets provided, we are not able to accurately calculate the rate of change of bilirubin for either neonate. Therefore, for the first seven days of life for each of the infants in the study, we request that the day and times of every bilirubin sample blood draw be provided along with the age of each infant in hours from birth at the time of each blood draw.

Please provide the information in datasets (.xpt) and tables. Also, provide a line graph of bilirubin (mg/dL) values (y-axis) versus hours from birth (x-axis) for each infant for the first week of life. In addition, provide a summary line graph comparing the bilirubin level vs. hours from birth of all infants for each birth cohort (ATV/RTV: 300/100 versus 400/100) for the first seven days of life.

2. Please analyze and compare the incidence of neonatal hyperbilirubinemia (>5mg/dL) for each of the two birth cohorts (ATV/RTV: 300/100 versus 400/100) for the first seven days of life against the incidence of neonatal hyperbilirubinemia in healthy term infants using the current literature (last five years, if possible). If the data is available, please also compare the results from the two study cohorts against the incidence of neonatal hyperbilirubinemia in HIV exposed infants whose mothers did not receive atazanavir.

3. In your submission, the results of Denver screening tests for ATV exposed infants and description of whether the result was within normal range or abnormal were provided, but details regarding the degree of abnormality were not included. For all infants with abnormal Denver screening results, please provide the exact age at the time of both screenings and the full Denver screening results at each screening, including the milestones met (e.g. sit-head steady and bear weight on legs for gross motor) for each of the four assessment areas (gross motor, language, fine motor-adaptive and personal social) and highlight the milestone(s) not met that indicated an abnormality.

4. One of the most common findings in infants with a history of hyperbilirubenemia toxicity is hearing loss. In the US, newborn screening for hearing abnormalities in the first days of life is common practice but may not be done in other countries. Please provide the results of any hearing screenings and/ or examinations obtained from infants in the study. In presenting these results, provide patient ID, age at each exam or screening, the highest bilirubin level and hours from birth for that level, the hearing results, and the intervention or follow-up obtained for any abnormalities.

We are providing the above information via electronic mail for your convenience. **THIS MATERIAL SHOULD BE VIEWED AS UNOFFICIAL CORRESPONDENCE.** Please feel free to contact me if you have any questions regarding the contents of this transmission at 301-796-4891.

_____

Venessa M Perry, MPH
Regulatory Project Manager
Division of Antiviral Products

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/s/

VENESSA M PERRY
10/13/2010

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 21-567/S-025

FILING COMMUNICATION

Bristol Myers Squibb Company
Attention: Lisa Percival
Director, Global Regulatory Strategy
5 Research Parkway
Room 252A, Mailstop 2CW-506
Wallingford, CT 06492

Dear Ms. Percival:

Please refer to your new drug application (NDA) dated and received August 6, 2010 submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act, for Reyataz ® atazanavir sulfate 100, 150, 200 and 300 mg capsules.

We also refer to your submission dated September 28, 2010.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, in accordance with 21 CFR 314.101(a), this application is considered filed 60 days after the date we received your application. The review classification for this application is **Priority**. Therefore, the user fee goal date is February 4, 2011.

We are reviewing your application according to the processes described in the Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products. Therefore, we have established internal review timelines as described in the guidance, which includes the timeframes for FDA internal milestone meetings (e.g., filing, planning, midcycle, team and wrap-up meetings). Please be aware that the timelines described in the guidance are flexible and subject to change based on workload and other potential review issues (e.g., submission of amendments). We will inform you of any necessary information requests or status updates following the milestone meetings or at other times, as needed, during the process. If major deficiencies are not identified during the review, we plan to communicate proposed labeling and, if necessary, any postmarketing requirement/commitment requests by January 16, 2011.

During our filing review of your application, we identified the following potential review issues:

Clinical Information

1. In addition to the narratives in the CSR, please provide the case report forms (CRFs) for all mothers and infants with SAEs. In addition, please also provide the CRFs for the following subjects (if not covered under the SAE request):

   AI424182-5-23
   AI424182-5-34
   AI424182-5-45
   AI424182-4-1007
   AI424182-8-1018
   AI424182-4-1043
   AI424182-4-1069

2. Please either identify the location of the coding dictionary used for mapping investigator verbatim terms to preferred terms in the submission or provide a copy for the review team. The "coding dictionary" consists of a list of all investigator verbatim terms and the preferred terms to which they were mapped. It is most helpful if this comes in as a SAS transport file so that it can be sorted as needed; however, if it is submitted as a PDF document, it should be submitted in both directions (verbatim -> preferred and preferred -> verbatim).

We are providing the above comments to give you preliminary notice of potential review issues. Our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review. Issues may be added, deleted, expanded upon, or modified as we review the application.

If you have not already done so, you must submit the content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm. The content of labeling must be in the Prescribing Information (physician labeling rule) format.

Please respond only to the above requests for additional information. While we anticipate that any response submitted in a timely manner will be reviewed during this review cycle, such review decisions will be made on a case-by-case basis at the time of receipt of the submission.

REQUIRED PEDIATRIC ASSESSMENTS

We acknowledge receipt of your request for a partial deferral of pediatric studies for this application. Once we have reviewed your request, we will notify you if the partial deferral request is denied.

If you have any questions, please contact Venessa M Perry, MPH, Regulatory Project Manager, at (301) 796-4891.

Sincerely,

{See appended electronic signature page}

Debra Birnkrant, MD
Director
Division of Antiviral Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

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/s/

VENESSA M PERRY
10/04/2010

DEBRA B BIRNKRANT
10/04/2010

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation IV

FACSIMILE TRANSMITTAL SHEET

DATE: September 22, 2010

To: Lisa Percival, Director, Global Regulatory Strategy	Venessa M Perry, MPH Regulatory Project Manager
Company: Bristol-Myers Squibb	Division of Antiviral Products
Fax number:	**Fax number:** 301.796.9883
Phone number: 203.677.6803	**Phone number:** 301.796.4891

Subject: NDA 21-567/S-025

Total no. of pages including cover: 2

Document to be mailed: ☐ YES ☑ NO

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Division of Antiviral Drug Products
Food and Drug Administration
Rockville MD 20857

MEMORANDUM OF FACSIMILE CORRESPONDENCE

Date: September 22, 2010

Sponsor: Bristol-Myers Squibb

NDA: 21-567/S-025

Drug: Reyataz ® (atazanavir sulfate) capsules

To: Lisa Percival, Director Global Regulatory Strategy

From: Venessa M Perry, MPH, Regulatory Project Manager

Through: Alan Shapiro, M.D., Medical Reviewer
Mary Singer, MD, Medical Team Leader

Subject: NDA 21-567 Reyataz ® (atazanavir sulfate)

The following comments are being conveyed to you on behalf of the clinical review team in reference to your submission dated August 6, 2010 to provide data from AI424182, a study of ATV/RTV in HIV infected pregnant women:

> Hemolysis due to maternal-fetal blood type incompatibility (ABO and/or Rh) is a significant cause of jaundice/hyperbilirubinemia in neonates. Please provide the blood types and Coombs results for mother and infants for:
>
> 1) All infants in the study that receive phototherapy
> 2) All infants with jaundice the first day of life
> 3) All infants that had total bilirubin rise by more than 5mg/dL (or 86 µmol/L) per day for one or more days.

We are providing the above information via electronic mail for your convenience. **THIS MATERIAL SHOULD BE VIEWED AS UNOFFICIAL CORRESPONDENCE.** Please feel free to contact me if you have any questions regarding the contents of this transmission at 301-796-4891.

_____
Venessa M Perry, MPH
Regulatory Project Manager
Division of Antiviral Products

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/s/

VENESSA M PERRY
09/23/2010

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation IV

FACSIMILE TRANSMITTAL SHEET

DATE: September 15, 2010

To: Lisa Percival, Director, Global Regulatory Strategy	Venessa M Perry, MPH Regulatory Project Manager
Company: Bristol-Myers Squibb	Division of Antiviral Products
Fax number:	**Fax number:** 301.796.9883
Phone number: 203.677.6803	**Phone number:** 301.796.4891

Subject: NDA 21-567/S-025

Total no. of pages including cover: 2

Document to be mailed: ☐ YES ☑ NO

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Division of Antiviral Drug Products
Food and Drug Administration
Rockville MD 20857

MEMORANDUM OF FACSIMILE CORRESPONDENCE

Date: September 15, 2010

Sponsor: Bristol-Myers Squibb

NDA: 21-567/S-025

Drug: Reyataz ® (atazanavir sulfate) capsules

To: Lisa Percival, Director Global Regulatory Strategy

From: Venessa M Perry, MPH, Regulatory Project Manager

Through: Alan Shapiro, M.D., Medical Reviewer
Sarah Robertson, Pharm.D., Clinical Pharmacology Team Leader
Jenny Zheng, Pharm.D., Clinical Pharmacology Reviewer

Subject: NDA 21-567 Reyataz ® (atazanavir sulfate)

The following comments are being conveyed to you on behalf of the clinical review team in reference to your submission dated August 6, 2010 to provide data from AI424182, a study of ATV/RTV in HIV infected pregnant women:

1. We are reviewing the AESAESTR dataset along with its associated defined file. We note that the majority of the records in AESAESTR dataset do not have an associated AE (e.g. AECRF or PT) and appears to be correlated with study visit rather than a particular AE.

    - Explain how the dataset AESAESTR was constructed and populated in regard to record entry.

    - Explain how new, ongoing, resolving, recurring and resolved AEs are handled in this dataset.

    - Also clarify whether any pre-existing conditions were coded as an AE in the dataset AESAESTR.

2. Please submit all atazanavir and RTV concentration and PK data in the SAS Transport files.

Please submit this information to us by **COB Friday, September 17, 2010**

We are providing the above information via electronic mail for your convenience. **THIS MATERIAL SHOULD BE VIEWED AS UNOFFICIAL CORRESPONDENCE.** Please feel free to contact me if you have any questions regarding the contents of this transmission at 301-796-4891.

Venessa M Perry, MPH
Regulatory Project Manager
Division of Antiviral Products

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-21567	SUPPL-25	BRISTOL MYERS SQUIBB CO	REYATAZ (ATAZANAVIR SULFATE)

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/s/

VENESSA M PERRY
09/16/2010

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR CONSULTATION

TO *(Office/Division)*: Pediatric Maternal Health	FROM (*Name, Office/Division, and Phone Number of Requestor)*: Venessa M Perry, MPH, OAP/DAVP 301.796.4891

DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
8.18.10		21567		8.6.10

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
REYATAZ	PRIORITY	ANTIVIRAL	12/13/10

NAME OF FIRM: BRISTOL MEYERS SQUIBB

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE / ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE-NDA MEETING
- ☐ END-OF-PHASE 2a MEETING
- ☐ END-OF-PHASE 2 MEETING
- ☐ RESUBMISSION
- ☒ SAFETY / EFFICACY
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☒ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☐ OTHER *(SPECIFY BELOW)*:

II. BIOMETRICS

- ☐ PRIORITY P NDA REVIEW
- ☐ END-OF-PHASE 2 MEETING
- ☐ CONTROLLED STUDIES
- ☐ PROTOCOL REVIEW
- ☐ OTHER (SPECIFY BELOW):
- ☐ CHEMISTRY REVIEW
- ☐ PHARMACOLOGY
- ☐ BIOPHARMACEUTICS
- ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE 4 STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL - BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG SAFETY

- ☐ PHASE 4 SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE, e.g., POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

- ☒ CLINICAL
- ☐ NONCLINICAL

COMMENTS / SPECIAL INSTRUCTIONS: This is a new efficacy supplement, NDA 21567/S-025 to provide data from a study of ATV/RTV to support dosing regiments in HIV infected pregnant women. The supplement provides for labeling changes in the dosage and administration section and specific populations. This will be a priority review. The link to the submission is below.

The filing due date is:10/5/2010
PDUFA goal Date is:2/6/2011

EDR Location: \\CDSESUB1\EVSPROD\NDA021567\021567.enx
Please send assign a reveiwer and send to the filing meeting on September 20, 2010 9 am

SIGNATURE OF REQUESTOR Venessa M Perry, MPH	METHOD OF DELIVERY (Check one) ☐ DFS ☒ EMAIL ☐ MAIL ☐ HAND
PRINTED NAME AND SIGNATURE OF RECEIVER	

	PRINTED NAME AND SIGNATURE OF DELIVERER

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-21567	SUPPL-25	BRISTOL MYERS SQUIBB CO	REYATAZ (ATAZANAVIR SULFATE)

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/s/

VENESSA M PERRY
09/03/2010

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADM NISTRATION

REQUEST FOR CONSULTATION

TO *(Division/Office)*:			FROM: Venessa M Perry, MPH	
Mail: OSE				
DATE 8.18.10	IND NO.	NDA NO. 21567	TYPE OF DOCUMENT	DATE OF DOCUMENT
NAME OF DRUG Reyataz (Atazanavir sulfate)	PRIORITY CONSIDERATION X		CLASSIFICATION OF DRUG Antiviral	DESIRED COMPLETION DATE

NAME OF FIRM:

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE/ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE--NDA MEETING
- ☐ END OF PHASE II MEETING
- ☐ RESUBMISSION
- X☐ SAFETY/EFFICACY
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- X☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- X☐ OTHER *(SPECIFY BELOW)*: Filing meeting

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
☐ TYPE A OR B NDA REVIEW ☐ END OF PHASE II MEETING ☐ CONTROLLED STUDIES ☐ PROTOCOL REVIEW ☐ OTHER (SPECIFY BELOW):	☐ CHEMISTRY REVIEW ☐ PHARMACOLOGY ☐ BIOPHARMACEUTICS ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE IV STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL-BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG EXPERIENCE

- ☐ PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

- ☐ CLINICAL
- ☐ PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS:

This is a new efficacy supplement, NDA 21567/S-025 to provide data from a study of ATV/RTV to support dosing regiments in HIV infected pregnant women. The supplement provides for labeling changes in the dosage and administration section and specific populations. This will be a priority review. The link to the submission is below.

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The filing meeting is September 20, 2010 9 am

Please send a representative from DMEPA and DRISK.

SIGNATURE OF REQUESTER Venessa M Perry, MPH.	METHOD OF DELIVERY (Check one) XX☐e- MAIL ☐ HAND
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-21567	SUPPL-25	BRISTOL MYERS SQUIBB CO	REYATAZ (ATAZANAVIR SULFATE)

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/s/

VENESSA M PERRY
09/03/2010

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

NDA 21-567/S-025

PRIOR APPROVAL SUPPLEMENT

Bristol-Myers Squibb Company
Attention: Lisa Percival
Director, Global Regulatory Strategy
5 Research Parkway, Room 252A
Mailstop 2CW-506
Wallingford, CT 06492

Dear Ms. Percival:

We have received your August 6, 2010, supplemental New Drug Application (sNDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product:	Reyataz ® (Atazanavir sulfate, ATV, BMS-232632) capsules 100 mg, 150 mg, 200 mg, 300 mg
NDA Number:	21-567
Supplement number:	025
Date of supplement:	August 6, 2010
Date of receipt:	August 6, 2010

This supplemental application proposes the following change:

- To update the label with the results of Study AI424182 that was conducted in HIV-infected pregnant women using atazanavir with ritonavir.

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on October 5, 2010, in accordance with 21 CFR 314.101(a).

If you have not already done so, promptly submit the content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm. Failure to submit the content of labeling in SPL format may result in a refusal-to-file action under 21 CFR 314.101(d)(3). The content of labeling must conform to the content and format requirements of 21 CFR 201.56-57.

Please cite the application number listed above at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Antiviral Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

If you have questions, please contact me at 301.796.4891 or Venessa. Perry@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Venessa M Perry, MPH
Regulatory Project Manager
Division of Antiviral Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-21567	SUPPL-25	BRISTOL MYERS SQUIBB CO	REYATAZ (ATAZANAVIR SULFATE)

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/s/

VENESSA M PERRY
08/17/2010