



NDA 21567/S-027

SUPPLEMENT APPROVAL

Bristol Myers Squibb Company
Attention: Hwei-Gene Wang, PhD
Associate Director, Global Regulatory Strategy
5 Research Parkway, Room 285B, Mailstop 2DW-206
Wallingford, CT 06492

Dear Dr. Wang:

Please refer to your Supplemental New Drug Application (sNDA) dated and received November 16, 2011, 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 amendment dated December 20, 2011 in response to our additional non-safety labeling change request sent on December 14, 2011 via e-mail.

We also refer to our letter dated October 19, 2011, notifying you, under Section 505(o)(4) of the FDCA, of new safety information that we believe should be included in the labeling for antiretroviral products. This information pertains to the risk of the autoimmune disorder as syndromes that can occur in the setting of immune reconstitution with the use of antiretroviral products.

In addition, we refer to non-safety labeling changes in our October 19, 2011 letter for all antiretroviral products based on recent studies demonstrating decreased transmission of HIV when HIV-infected patients or their uninfected partners take antiretroviral medication.

This supplemental new drug application provides for revisions to the labeling for Reyataz® (atazanavir sulfate) 100 mg, 150 mg, 200 mg and 300 mg Capsules, consistent with our October 19, 2011 letter and December 14, 2011 e-mail request, as follows (additions are noted by underline and deletions are noted by ~~striketrough~~).

1. The phrase, “Warnings and Precautions (5.8) ----- (XX/2012)” has been added under the **RECENT MAJOR CHANGES** in the Highlights section of the labeling.
2. The word, “breast-feed” has been revised to “breastfeed” throughout the labeling.
3. The revision date has been revised from October 2011 to XX/201X at the end of the **HIGHLIGHTS** section.

4. The **WARNINGS AND PRECAUTIONS/Immune Reconstitution Syndrome** sub-section has been revised as follows:

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 jirovecii* pneumonia (PCP), or tuberculosis), which may necessitate further evaluation and treatment.

Autoimmune disorders (such as Graves' disease, polymyositis, and Guillain-Barré syndrome) have also been reported to occur in the setting of immune reconstitution; however, the time to onset is more variable, and can occur many months after initiation of treatment.

5. 7.3 **Established and Other Potentially Significant Drug Interactions** section has been revised as follows:

Table 13: 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
<u>HCV Antiviral Agents</u>		
<u>Protease Inhibitors:</u> <u>telaprevir</u>	↓ telaprevir ↑ atazanavir	<u>Concomitant administration of telaprevir and atazanavir/ritonavir resulted in reduced steady-state telaprevir exposure, while steady-state atazanavir exposure was increased.</u>
<u>Other Agents</u>		
HMG-CoA reductase inhibitors: atorvastatin, rosuvastatin	↑ atorvastatin ↑ rosuvastatin	<u>Titrate atorvastatin dose carefully and use the lowest possible necessary dose of atorvastatin or rosuvastatin dose should not exceed 10 mg/day, 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.</u>

Concomitant Drug Class: Specific Drugs	Effect on Concentration of Atazanavir or Concomitant Drug	Clinical Comment
Hormonal contraceptives: ethinyl estradiol and norgestimate or norethindrone	↓ ethinyl estradiol ↑ norgestimate ^c ↑ ethinyl estradiol ↑ norethindrone ^d	<p>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.</p> <p>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.</p> <p>Coadministration of REYATAZ or REYATAZ/ritonavir with other hormonal contraceptives (eg, contraceptive patch, contraceptive vaginal ring, or injectable contraceptives) or oral contraceptives containing progestagens <u>progestogens</u> other than norethindrone or norgestimate, or less than 25 mcg of ethinyl estradiol, has not been studied; therefore, alternative methods of contraception are recommended.</p>

6. The second paragraph of the 7.4 **Drugs with No Observed or Predicted Interactions with REYATAZ** section has been revised as follows:

Based on known metabolic profiles, clinically significant drug interactions are not expected between REYATAZ (atazanavir sulfate) and ~~fluvastatin, pravastatin,~~ dapson, 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 17 and 18 (12.3).]

7. Table 17 and 18 in the **Pharmacokinetics/Drug Interaction Data** sub-section has been revised as follows:

Table 17: 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		
			Ratio	90% CI	90% CI
<u>pitavastatin</u>	<u>4 mg QD for 5 days</u>	<u>300 mg QD for 5 days</u>	<u>1.13</u> <u>(0.96, 1.32)</u>	<u>1.06</u> <u>(0.90, 1.26)</u>	<u>NA</u>
<u>telaprevir</u>	<u>750 mg q8h for 10 days (n=7)</u>	<u>300 mg QD/ritonavir 100 mg QD for 20 days (n=7)</u>	<u>0.85</u> <u>(0.73, 0.98)</u>	<u>1.17</u> <u>(0.97, 1.43)</u>	<u>1.85</u> <u>(1.40, 2.44)</u>

NA = not available.

Table 18: 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}
<u>pitavastatin</u>	<u>4 mg QD for 5 days</u>	<u>300 mg QD for 5 days</u>	<u>1.60</u> (1.39, 1.85)	<u>1.31</u> (1.23, 1.39)	<u>NA</u>
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
<u>rosuvastatin</u>	<u>10 mg single dose</u>	<u>300 mg QD/ritonavir 100 mg QD for 7 days</u>	<u>↑7-fold^o</u>	<u>↑3-fold^o</u>	<u>NA</u>
saquinavir ⁹² (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)
<u>telaprevir</u>	<u>750 mg q8h for 10 days (n=14)</u>	<u>300 mg QD/ritonavir 100 mg QD for 20 days (n=14)</u>	<u>0.79</u> (0.74, 0.84)	<u>0.80</u> (0.76, 0.85)	<u>0.85</u> (0.75, 0.98)

Table 18: 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}
<u>tenofovir</u> ^{PQ}	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) ^{QI}	1.34 (1.20, 1.51)	1.37 (1.30, 1.45)	1.29 (1.21, 1.36)

^O Mean ratio (with/without coadministered drug). ↑ indicates an increase in rosuvastatin exposure.

^{QI} 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.

^{PQ} Note that similar results were observed in a study where administration of tenofovir and REYATAZ was separated by 12 hours.

^{QI} Administration of tenofovir and REYATAZ was temporally separated by 12 hours

8. The second paragraph of the **PATIENT COUNSELING INFORMATION** section has been revised as follows: ~~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. REYATAZ is not a cure for HIV-1 infection and patients may continue to experience illnesses associated with HIV-1 infection, including opportunistic infections. Patients should remain under the care of a physician when using REYATAZ.~~

Patients should be advised to avoid doing things that can spread HIV-1 infection to others.

- **Do not share needles or other injection equipment.**
- **Do not share personal items that can have blood or body fluids on them, like toothbrushes and razor blades.**

- **Do not have any kind of sex without protection.** Always practice safe sex by using a latex or polyurethane condom ~~or other barrier method~~ to lower the chance of sexual contact with semen, vaginal secretions, or blood.
- **Do not breastfeed.** ~~We do~~ It is not known if REYATAZ can be passed to your baby in your breast milk and whether it could harm your baby. Also, mothers with HIV-1 should not breastfeed because HIV-1 can be passed to the baby in the breast milk.

9. Patient Information:

- a. The “**Does REYATAZ cure HIV or AIDS?**” section has been revised as follows: **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. **REYATAZ does not cure HIV infection or AIDS and you may continue to experience illnesses associated with HIV-1 infection, including opportunistic infections. You should remain under the care of a doctor when using REYATAZ.**

Avoid doing things that can spread HIV-1 infection.

- **Do not share needles or other injection equipment.**
 - **Do not share personal items that can have blood or body fluids on them, like toothbrushes and razor blades.**
 - **Do not have any kind of sex without protection.** Always practice safe sex by using a latex or polyurethane condom ~~or other barrier method~~ to lower the chance of sexual contact with semen, vaginal secretions, or blood.
- b. The third bulleted paragraph in the “**What should I tell my healthcare provider before I take REYATAZ?/Tell your healthcare provider:**” section has been revised as follows:

If you are breastfeeding, ~~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.~~ **Do not breastfeed.** ~~We do~~ It is not known if REYATAZ can be passed to your baby in your breast milk and whether it could harm your baby. Also, mothers with HIV-1 should not breastfeed because HIV-1 can be passed to the baby in the breast milk.

10. The revision date section has been revised as follows:

1246226~~XXB~~0

Rev Month Year ~~October 2011~~

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 the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>. Content of labeling must be identical to the enclosed labeling (text for the package insert, text for the patient package insert), with the addition of any labeling changes in pending “Changes Being Effectuated” (CBE) supplements, as well as 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, as well as annual reportable changes and annotate each change. To facilitate review of your submission, provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should provide appropriate annotations, including supplement number(s) and annual report date(s).

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
Office of Prescription Drug Promotion (OPDP)
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 Office of Prescription Drug Promotion (OPDP), see <http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm>.

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, call Kyong Hyon, Safety Regulatory Project Manager, at (301) 796-0734.

Sincerely,

{See appended electronic signature page}

Kendall A. Marcus, MD
Deputy Director for Safety
Division of Antiviral Products
Office 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/

KENDALL A MARCUS
02/17/2012