Bristol-Myers Squibb Submits New Drug Application to U.S. FDA for a Fixed-Dose Combination Tablet of Atazanavir Sulfate with Cobicistat for People Living with HIV-1

Release Date: Monday, April 14, 2014 8:00 am EDT

Terms:

Dateline City: PRINCETON, N.J.

Atazanavir sulfate capsules are available as Reyataz®

PRINCETON, N.J.--(BUSINESS WIRE)--Bristol-Myers Squibb Company (NYSE:BMY) announced today the submission of a new drug application (NDA) on April 4, 2014 to the U.S. Food and Drug Administration (FDA) for a fixed-dose combination of atazanavir sulfate, a protease inhibitor marketed as Reyataz®, and cobicistat, an investigational pharmacokinetic enhancer, or boosting agent, that can increase the level of certain HIV-1 medicines in the blood and make them more effective.

Bristol-Myers Squibb is seeking approval of the fixed-dose combination tablet for use in combination with other antiretroviral agents for the treatment of HIV-1 infection. If approved, atazanavir sulfate and cobicistat could offer patients living with HIV-1 a single tablet that eliminates the need to take a boosting agent in a separate tablet. Cobicistat is being developed by Gilead Sciences, Inc.

Approximately 245,000 patients in the U.S. have been treated with Reyataz since its launch in 2003, nearly twice that of any other protease inhibitor launched since that time. Reyataz is currently used in combination with other antiretroviral agents and is most commonly used with ritonavir, a pharmacokinetic enhancer. A once-daily therapy, Reyataz is indicated for the treatment of HIV-1 infection in treatment-naive and treatment-experienced adult patients and pediatric patients six years of age or older.

"Bristol-Myers Squibb is committed to enhancing our existing regimens, as well as developing new therapies to make HIV treatment simpler for patients," said Brian Daniels, M.D., senior vice president, Global Development and Medical Affairs, Bristol-Myers Squibb. "The submission of this NDA represents an important step forward in our efforts to provide patients with new options for Reyataz treatment."

Reyataz is the only protease inhibitor that has been evaluated with cobicistat in a prospective, randomized, Phase III double-blind clinical trial (Gilead’s Study 114), which compared the efficacy and safety of cobicistat-boosted Reyataz (atazanavir sulfate) versus ritonavir-boosted Reyataz in treatment-naïve adult patients for 48 weeks. Study 114 may support the clinical use of atazanavir and cobicistat together.

"Adhering to HIV treatment regimens can be challenging for some patients, and if the prescribed medications are not taken properly, it could result in treatment failure," said Calvin J. Cohen, M.D., MPH, director of research, Community Research Initiative of New England and internist, Harvard Vanguard Medical Associates. "If approved by the FDA, a once-daily, fixed-dose combination of atazanavir sulfate and cobicistat would offer patients living with HIV-1 another treatment option."

In October 2011, Bristol-Myers Squibb announced a licensing agreement with Gilead for the development and commercialization of a once-daily, single tablet fixed-dose combination product of atazanavir sulfate and Gilead's cobicistat. Under the terms of the agreement, Bristol-Myers Squibb and its affiliates are responsible for the formulation, manufacturing, registration, distribution and commercialization of the atazanavir sulfate and cobicistat fixed-dose combination product worldwide. Gilead retains sole rights for the manufacture, development and commercialization of cobicistat as a stand-alone product and for use in combination with other agents.

About Bristol-Myers Squibb’s HIV Research Portfolio

For more than 20 years, Bristol-Myers Squibb has focused on discovering, developing and delivering innovative medicines to help meet the needs of patients living with HIV-1 and continues to pursue advances in treatment, for both children and adults with HIV-1. Studies are ongoing for new treatments including an HIV-1 attachment inhibitor (BMS-663068), an HIV-1 maturation inhibitor (BMS-955176) and an anti-PD-L1 (BMS-936559).

INDICATION and IMPORTANT SAFETY INFORMATION about REYATAZ (atazanavir sulfate) 200mg/300mg Capsules:

INDICATION:

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

- In Study 045, REYATAZ/ritonavir and lopinavir/ritonavir were similar for the primary efficacy measure of time-averaged difference in change from baseline in HIV RNA. This study was not large enough to reach a definitive conclusion that REYATAZ/ritonavir and lopinavir/ritonavir are equivalent on the secondary efficacy measure of proportions below the HIV RNA lower limit of detection.

- The number of baseline primary protease inhibitor mutations affects virologic response to REYATAZ/ritonavir.

**IMPORTANT SAFETY INFORMATION:**

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

- **Contraindicated Drugs:** Concomitant use of REYATAZ is contraindicated in patients with severe hepatic impairment (Child-Pugh class C). Use REYATAZ with caution in patients with moderate hepatic impairment (Child-Pugh class B) due to the potential for more frequent or severe hepatotoxicity, including hepatotoxicity that may be life-threatening.

- **Cardiac Conduction Abnormalities:** PR interval prolongation may occur in some patients. Atrioventricular (AV) conduction abnormalities were asymptomatic and generally limited to first-degree AV block. There have been reports of second-degree AV block and other conduction abnormalities. Use REYATAZ with caution in patients with preexisting conduction system disease or when administered with other drugs that may prolong the PR interval (including beta-blockers other than atenolol, diltiazem, verapamil, and digoxin), especially drugs metabolized by CYP3A. When used with REYATAZ, a 50% dose reduction of diltiazem should be considered, and ECG monitoring is recommended.

- **Rash** (all grades, generally mild-to-moderate maculopapular skin eruptions, regardless of causality) occurred in approximately 20% of patients treated with REYATAZ in controlled clinical trials. Cases of Stevens-Johnson syndrome, erythema multiforme, and toxic skin eruptions, including drug rash, eosinophilia and systemic symptoms (DRESS) syndrome, have been reported. Discontinue REYATAZ if severe rash develops.

- **Hyperbilirubinemia:** Reversible, asymptomatic elevations in indirect (unconjugated) bilirubin occurred in most patients treated with REYATAZ. There are no long-term safety data for patients with persistent elevations in total bilirubin >5 times upper limit of normal. Alternative antiretroviral therapy may be considered if jaundice or scleral icterus present cosmetic concerns.

- **Hepatotoxicity:** Use REYATAZ (atazanavir sulfate) with caution in patients with hepatic impairment because atazanavir concentrations may be increased. Patients with hepatitis B or C infection or marked elevations in transaminases are at risk of further transaminase elevations or hepatic decompensation. In these patients, hepatic laboratory testing should be performed before and during REYATAZ therapy.

- **Nephrolithiasis and cholelithiasis** have been reported during postmarketing surveillance in HIV-infected patients receiving REYATAZ. Some patients required hospitalization and some had complications. If signs or symptoms of nephrolithiasis and/or cholelithiasis occur, consider temporary interruption or discontinuation of therapy.

- New onset or exacerbation of diabetes mellitus and hyperglycemia have been reported in patients treated with protease inhibitor therapy. A causal relationship has not been established.

- **Immune reconstitution syndrome** has been reported in patients treated with combination antiretroviral therapy, including REYATAZ. 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.

- **Redistribution and/or accumulation of body fat** have been seen in patients receiving antiretroviral therapy. A causal relationship has not been established.

- **Increased bleeding** has been reported in patients with hemophilia type A and B treated with protease inhibitors.

- Various degrees of cross-resistance among protease inhibitors have been observed.

- The most common moderate or severe adverse reactions were as follows, regardless of causality:
  - **In treatment-naive adult patients** (≥2%): nausea (4-14%), jaundice/scleral icterus (5-7%), rash (3-7%), headache (1-6%), abdominal pain (4%), vomiting (3-4%), peripheral neurologic symptoms (<1-4%), diarrhea (1-
3%), insomnia (<1-3%), and dizziness (<1-2%).

- **In treatment-experienced adult patients** (≥2%): jaundice/scleral icterus (9%), myalgia (4%), diarrhea (3%), nausea (3%), depression (2%), and fever (2%).

- **In pediatric patients** (≥5%): cough (21%), fever (18%), jaundice/scleral icterus (15%), rash (14%), vomiting (12%), diarrhea (9%), headache (8%), peripheral edema (7%), extremity pain (6%), nasal congestion (6%), oropharyngeal pain (6%), wheezing (6%), and rhinorrhea (6%).

- REYATAZ (atazanavir sulfate) should be used with caution in patients with mild to moderate hepatic impairment. REYATAZ should not be used in patients with severe hepatic impairment (Child-Pugh Class C). REYATAZ/ritonavir has not been studied in patients with hepatic impairment and is not recommended.

- REYATAZ should not be used in treatment-experienced patients with end-stage renal disease managed with hemodialysis.

Please see accompanying Full Prescribing Information here.

About Bristol-Myers Squibb

Bristol-Myers Squibb is a global biopharmaceutical company whose mission is to discover, develop and deliver innovative medicines that help patients prevail over serious diseases. For more information, please visit [http://www.bms.com](http://www.bms.com) or follow us on Twitter at [http://twitter.com/bmsnews](http://twitter.com/bmsnews).

Bristol-Myers Squibb Forward Looking Statement

This press release contains “forward-looking statements” as that term is defined in the Private Securities Litigation Reform Act of 1995 regarding the research, development and commercialization of pharmaceutical products. Such forward-looking statements are based on current expectations and involve inherent risks and uncertainties, including factors that could delay, divert or change any of them, and could cause actual outcomes and results to differ materially from current expectations. No forward-looking statement can be guaranteed. Among other risks, there can be no guarantee that the combination therapy mentioned will receive regulatory approval or, if approved, that it will become a commercially successful product. Forward-looking statements in this press release should be evaluated together with the many uncertainties that affect Bristol-Myers Squibb’s business, particularly those identified in the cautionary factors discussion in Bristol-Myers Squibb’s Annual Report on Form 10-K for the year ended December 31, 2013 in our Quarterly Reports on Form 10-Q and our Current Reports on Form 8-K. Bristol-Myers Squibb undertakes no obligation to publicly update any forward-looking statement, whether as a result of new information, future events or otherwise.

Language:

English

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