U.S. Food and Drug Administration Approves Bristol-Myers Squibb’s Evotaz™ (atazanavir and cobicistat) for the Treatment of HIV-1 Infection in Adults

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- Evotaz is the first and only protease inhibitor pharmacoenhanced by cobicistat that is supported by comparative Phase III clinical trial data
- Evotaz is the only protease inhibitor pharmacoenhanced by cobicistat with virologic failure rates as low as 6% [HIV-1 RNA ≥50 copies/mL at 48 weeks: 6% Evotaz arm; 4% Reyataz® (atazanavir)/ritonavir arm]*

PRINCETON, N.J.--(BUSINESS WIRE)--Bristol-Myers Squibb Company (NYSE:BMY) announced today that the U.S. Food and Drug Administration (FDA) has approved Evotaz (atazanavir 300 mg and cobicistat 150 mg) tablets in combination with other antiretroviral agents for the treatment of HIV-1 infection in adults. Evotaz is coformulated to be one pill, once-daily, combining the protease inhibitor atazanavir, which is marketed as Reyataz (atazanavir 200 mg/300 mg) capsules, and cobicistat, a pharmacokinetic enhancer marketed by Gilead Sciences, Inc. Today’s approval offers patients living with HIV an innovative treatment option that delivers proven suppression (HIV-1 RNA <50 copies/mL, 85% Evotaz arm; 87% Reyataz/ritonavir arm) through 48 weeks.

The use of Evotaz in patients who have previously received HIV medication should be guided by their baseline resistance to protease inhibitors. Evotaz and Reyataz do not cure HIV-1 infection or AIDS. Evotaz is contraindicated in patients with previously demonstrated clinically significant hypersensitivity (e.g., Stevens-Johnson syndrome, erythema multiforme, or toxic skin eruptions) to any of the product components and in combination with certain drugs. See Evotaz full contraindications in the Important Safety Information section below.

As a dedicated partner to the HIV community for more than 20 years, Bristol-Myers Squibb continues to discover and develop innovative therapies to meet the needs of a broad range of patients living with HIV. There are approximately 50,000 new cases of HIV each year, with an estimated 1.1 million people living with the condition in the U.S. While many are diagnosed and undergoing treatment, only one quarter are virally suppressed, demonstrating the continued need for additional treatments to help patients achieve viral suppression.

“We are pleased to provide physicians and patients with an important new option to treat HIV; atazanavir with cobicistat delivers sustained efficacy and safety through 48 weeks, as demonstrated through its rigorous clinical development plan, including a head-to-head Phase III trial,” said Murdo Gordon, Head of Worldwide Markets, Bristol-Myers Squibb. “Evotaz increases the possibility of providing HIV suppression by combining reduced pill burden with a low rate of virologic failure (6% Evotaz arm; 4% Reyataz/ritonavir arm) and zero protease inhibitor mutations.” In the Evotaz arm, zero patients developed tenofovir-associated resistance K65R; two patients developed emtricitabine resistance M184V. In the Reyataz/ritonavir arm, zero resistance was observed.

Evotaz is the first and only protease inhibitor pharmacoenhanced by cobicistat that is supported by comparative Phase III trial data (Gilead Sciences, Inc.’s Study 114). The randomized, double-blind clinical trial (N=692) evaluated the efficacy and safety of Reyataz 300 mg with cobicistat 150 mg (the components of Evotaz) (n=344) versus Reyataz 300 mg with ritonavir 100 mg (Reyataz/ritonavir) (n=348), another pharmacokinetic enhancing agent, in combination with emtricitabine/tenofovir disoproxil fumarate in treatment-naive adults. Patients had a baseline estimated CrCL >70mL/min, a mean baseline plasma HIV-1 RNA of 4.8 log10 copies/mL, and a mean baseline CD4+ cell count of 352 cells/mm. At 48 weeks, 85% of patients in the Evotaz arm achieved HIV-1 RNA levels of <50 copies/mL compared to 87% of patients in the Reyataz/ritonavir arm. Low rates of virologic failure (HIV-1 RNA ≥50 copies/mL: 6% Evotaz arm; 4% Reyataz/ritonavir arm) were observed at 48 weeks, making Evotaz the only protease inhibitor pharmacoenhanced with cobicistat with virologic failure rates as low as 6%.

In the study, zero protease inhibitor resistance was detected through 48 weeks. No patients developed tenofovir-associated resistance, and two patients in the Evotaz arm developed emtricitabine-associated resistance. Various degrees of resistance and cross-resistance have been observed among protease inhibitors; however, resistance to atazanavir may
not preclude the use of other protease inhibitors.

“Maintaining sufficient drug concentrations inhibits viral replication and prevents the development of resistance, which are critical considerations in treating patients with HIV,” said study investigator Joel Gallant, associate medical director of Specialty Services at Southwest CARE Center in Santa Fe, New Mexico, and adjunct professor of medicine in the Division of Infectious Diseases at the Johns Hopkins University School of Medicine. “Pharmacokinetic studies and a large clinical trial have demonstrated that we can expect the same atazanavir drug levels and clinical efficacy from Evotaz as with ritonavir-boosted Reyataz with one less pill.”

Evotaz demonstrated a safety profile comparable to Reyataz/ritonavir: The most common moderate to severe adverse events in the Evotaz and Reyataz/ritonavir arm were: rash (5%, 4%); jaundice (5%, 3%); ocular iterus (3%, 1%); nausea (2%, 2%). There were similar low rates of discontinuation due to adverse events (AEs) with Evotaz as compared to Reyataz/ritonavir (7% and 7%, respectively).

Additional research confirmed that Evotaz is bioequivalent to the co-administration of its components, Reyataz and cobicistat, when given with a light meal.

In October 2011, Bristol-Myers Squibb announced a licensing agreement with Gilead for the development and commercialization of a once-daily, fixed-dose combination product of atazanavir and cobicistat, now named Evotaz. Under the terms of the agreement, Bristol-Myers Squibb and its affiliates are responsible for the formulation, manufacturing, registration, distribution and commercialization of the Evotaz 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 Reyataz (atazanavir)

Since the approval of Reyataz, a component of Evotaz, in July 2003, more than 7 million prescriptions have been filled in the US* for once-daily administration, with or without ritonavir as part of an HIV-1 regimen.

Reyataz is indicated in combination with other antiretroviral agents for the treatment of HIV-1 infection in patients 3 months and older weighing at least 10 kg. Reyataz is not recommended for use in pediatric patients less than 3 months due to the risk of kernicterus. Use of Reyataz with ritonavir in treatment-experienced patients should be guided by the number of baseline primary protease inhibitor resistance substitutions. Reyataz is contraindicated in patients with previously demonstrated clinically significant hypersensitivity (e.g., Stevens-Johnson syndrome, erythema multiforme or toxic skin eruptions) to any of the product components. See Reyataz full contraindications in the Important Safety Information section below.

For more information, please visit www.reyatazhcp.com.

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).

INDICATIONS for Evotaz (atazanavir and cobicistat) and Reyataz® (atazanavir)

Evotaz is a fixed dose combination of atazanavir and cobicistat, and is indicated for use with other antiretroviral agents for the treatment of HIV-1 infection in adults.

Reyataz is indicated in combination with other antiretroviral agents for the treatment of HIV-1 infection in adults, and for patients 3 months and older weighing at least 10 kg.

LIMITATIONS OF USE

* Use of Evotaz or Reyataz/ritonavir in treatment-experienced patients should be guided by the number of baseline primary protease inhibitor resistance substitutions

* Reyataz is not recommended for use in patients less than 3 months due to the risk of kernicterus

IMPORTANT SAFETY INFORMATION for EVOTAZ and REYATAZ

CONTRAINDICATIONS

EVOTAZ and REYATAZ are contraindicated:

* In patients with previously demonstrated clinically significant hypersensitivity (e.g., Stevens-Johnson syndrome, erythema multiforme, or toxic skin eruptions) to any of the product components

* When coadministered with drugs highly dependent on CYP3A or UGT1A1 for clearance and for which elevated plasma concentrations of the interacting drugs are associated with serious and/or life-threatening events. The following are contraindicated with EVOTAZ and REYATAZ: alfuzosin, rifampin, irinotecan, triazolam, orally administered midazolam, dihydroergotamine, ergotamine, methylergonovine, cisapride, St. John's wort (Hypericum perforatum), lovastatin, simvastatin, pimozone, sildenafil when used for pulmonary arterial hypertension, indinavir, nevirapine. Additionally, EVOTAZ IS contraindicated with: dronedarone, ranolazine, lurasidone, colchicine in patients with renal and/or hepatic impairment. Additionally, REYATAZ IS contraindicated with ergonovine

* When coadministered with drugs that strongly induce CYP3A and may lead to lower exposure and loss of efficacy of EVOTAZ and REYATAZ
WARNINGS AND PRECAUTIONS

The following Warnings & Precautions are associated with EVOTAZ (atazanavir and cobicistat) and REYATAZ (atazanavir):

- **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. There is limited clinical experience in patients with preexisting conduction system disease such as marked first degree AV block or second or third degree AV block. Consider ECG monitoring in these patients.

- **Rash:** Cases of Stevens-Johnson syndrome, erythema multiforme, and toxic skin eruptions, including drug rash, eosinophilia, and systemic symptoms (DRESS) syndrome, have been reported in patients receiving atazanavir. Discontinue if severe rash develops. Mild-to-moderate maculopapular skin eruptions have also been reported, and generally did not require discontinuation of treatment.

- **Nephrolithiasis and cholelithiasis:** Have been reported during postmarketing surveillance in HIV-infected patients receiving atazanavir. 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.

- **Hepatotoxicity:** Patients with hepatitis B or C viral infections 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 therapy.
  - **EVOTAZ** is not recommended in patients with **hepatic impairment**
  - **REYATAZ/ritonavir** is not recommended in patients with **hepatic impairment**
  - **REYATAZ** is not recommended for patients with **severe hepatic impairment**

- **Hyperbilirubinemia:** Reversible, asymptomatic elevations in indirect (unconjugated) bilirubin occurred in most patients treated with atazanavir. 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.

- **Immune reconstitution syndrome:** Has been reported in patients treated with combination antiretroviral therapy, including atazanavir. Autoimmune disorders (such as Graves’ disease, polymyositis, and Guillain-Barre 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.

- **Diabetes mellitus/hyperglycemia:** New onset of diabetes, exacerbation of preexisting diabetes, and hyperglycemia have been reported in postmarketing surveillance in HIV-infected patients treated with protease inhibitor therapy. A causal relationship has not been established.

- **Fat Redistribution** or accumulation of body fat including central obesity, dorsocervical fat enlargement (buffalo hump), peripheral wasting, breast enlargement, and “cushingoid appearance” have been seen in patients receiving antiretroviral therapy. A causal relationship has not been established.

- **Hemophilia:** Increased bleeding has been reported in patients with hemophilia type A and B treated with protease inhibitors. A causal relationship has not been established.

**EVOTAZ (atazanavir and cobicistat): ADDITIONAL WARNINGS AND PRECAUTIONS**

- **Effects on Serum Creatinine:** Cobicistat decreases estimated creatinine clearance (CrCl) by inhibiting the tubular secretion of creatinine without affecting actual renal glomerular function. This effect should be considered when interpreting changes in estimated CrCl in patients initiating EVOTAZ, particularly in patients with medical conditions or receiving drugs needing monitoring with estimated CrCl. Prior to initiating therapy with EVOTAZ, assess estimated CrCl. Dosage recommendations are not available for drugs that require dosage adjustment in cobicistat-treated patients with renal impairment. Consider alternative medications that do not require dosage adjustments in patients with renal impairment. Patients who experience a confirmed increase in serum creatinine of greater than 0.4 mg/dL from baseline should be closely monitored for renal safety.

- **New onset or worsening renal impairment when used with tenofovir disoproxil fumarate:** Renal impairment, including cases of acute renal failure and Fanconi syndrome, has been reported when cobicistat was used with tenofovir disoproxil fumarate (tenofovir DF).
  - Coadministration of EVOTAZ and tenofovir DF is not recommended in patients who have an estimated creatinine clearance below 70 mL/min.
  - When EVOTAZ is used with tenofovir DF, evaluate baseline and perform routine monitoring of estimated CrCl, urine glucose, and urine protein. Measure serum phosphorus in patients at risk for renal impairment.
  - Coadministration of EVOTAZ and tenofovir DF in combination with concomitant or recent use of a nephrotoxic agent is not recommended.

- **Risk of Serious Adverse Reactions or Loss of Virologic Response Due to Drug Interactions:** Coadministration of EVOTAZ with medications that are metabolized by CYP3A may lead to increased exposures of these medications, which may increase the risk of clinically significant adverse reactions (including life-threatening or fatal reactions). Coadministration of EVOTAZ with CYP3A inducers may lead to lower exposure of atazanavir and cobicistat and loss of efficacy of atazanavir and possible resistance. The potential for drug interactions prior to and during EVOTAZ therapy should be considered, review concomitant medications and monitor patients for adverse reactions.

- **Antiretrovirals that are NOT Recommended:** EVOTAZ is not recommended in combination with other antiretroviral drugs that require CYP3A inhibition to achieve adequate exposures (e.g. other HIV protease inhibitors or...
elvitegravir) because dosing for such combinations has not been established; coadministration may lead to loss of therapeutic effect and development of resistance

EVOTAZ is not recommended in combination with products containing the individual components of EVOTAZ (atazanavir or cobicistat) or in combination with ritonavir containing products

REYATAZ: ADDITIONAL WARNING AND PRECAUTION

- Patients with Phenylketonuria: Phenylalanine can be harmful to patients with phenylketonuria (PKU). REYATAZ oral powder contains phenylalanine (a component of aspartame). REYATAZ capsules do not contain phenylalanine
- Resistance/cross resistance in various degrees have been observed among protease inhibitors

MOST COMMON MODERATE OR SEVERE ADVERSE REACTIONS

EVOTAZ (atazanavir and cobicistat), regardless of causality:

- In treatment-naive adults (≥2%): nausea (2%), ocular icterus (3%), jaundice (5%), rash (5%)

REYATAZ (atazanavir), regardless of causality:

- In treatment-naive adults (≥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 adults (≥2%): jaundice/scleral icterus (9%), myalgia (4%), diarrhea (3%), depression (2%), and fever (2%)
- In pediatric patients taking the capsule formulation (≥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 rhinorrea (6%)
- In pediatric patients taking the oral powder formulation: the adverse reactions were generally similar to that observed in clinical studies of REYATAZ in pediatric patients taking the capsule formulation

DRUG INTERACTIONS

EVOTAZ: Coadministration of EVOTAZ and the following drugs is not recommended

- efavirenz, etravirine, ritonavir, boceprevir, telaprevir, simprevir, apixaban, rivaroxaban, dabigatran etexilate (in specific renal impairment groups), voriconazole, salmeterol, avanafil, inhaled or nasal corticosteroids that are metabolized by CYP3A
- when EVOTAZ is coadministered with tenofovir DF and an H2-receptor antagonist in treatment-experienced patients
- proton pump inhibitors in treatment-experienced patients

REYATAZ: Coadministration of REYATAZ and the following drugs is not recommended

- salmeterol
- when REYATAZ is coadministered with ritonavir: boceprevir, other HIV protease inhibitors, voriconazole
- when REYATAZ is coadministered without ritonavir: carbamazepine, phenytoin, phenobarbital, bosentan, buprenorphine
- in treatment-experienced patients: proton pump inhibitors or efavirenz
- in patients with renal or hepatic impairment: cholecine

See Table 5 of the EVOTAZ Full Prescribing Information, and Table 16 of the REYATAZ Full Prescribing Information for additional established and potentially significant Drug Interactions, and related dose modification recommendations.

EVOTAZ and REYATAZ: Use in Renal Impairment

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

Please click here for the EVOTAZ full prescribing information
Please click here for the REYATAZ full prescribing information

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 or follow us on Twitter at 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 Evotaz 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.

*Includes patients who had HIV-1 RNA ≥ 50 copies/mL in the Week 48 window; patients who discontinued early due to lack of efficacy; patients who discontinued for reasons other than an adverse event, death, or loss of efficacy and at the time of discontinuation had HIV-1 RNA ≥ 50 copies/mL

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