17 February 2011
EMA/CHMP/257566/2011
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Reyataz

atazanavir sulphate

Procedure No.: EMEA/H/C/000494/II/0075

Note

Variation assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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CHMP variation assessment report

Type II variation EMEA/H/C/000494/II/0075

Invented name/name:	Reyataz
International non-proprietary name/common name:	atazanavir sulphate
Indication summary (as last approved):	treatment of HIV-1 infection
Marketing authorisation holder:	Bristol-Myers Squibb Pharma EEIG

1. Scope of the variation and changes to the dossier

Scope of the variation:	Update of Summary of Product Characteristics, Annex IIB and Package Leaflet Update of sections 4.3, 4.4 and 4.5 of the SmPC to reflect changes in the drug-drug interactions of ATV and drugs metabolised by CYP3A4, including PDE5 inhibitors, alfuzosin and salmeterol. The PL has been revised accordingly. Update of Annex IIB to delete the DDPS version number.
Rapporteur:	Philippe Lechat
Product presentations affected:	See Annex A to the Opinion
Dossier modules/sections affected:	Modules 1, 2 and 5
Product Information affected:	SmPC, Annex IIB and Package Leaflet (Attachment 1 - changes highlighted)

2. Steps taken for the assessment

Step	Step date
Submission date:	29 November 2010
Start of procedure:	19 December 2010
Rapporteur's preliminary assessment report circulated on:	8 February 2011
CHMP opinion:	17 February 2011

3. Scientific discussion

3.1. Introduction

Reyataz (atazanavir, ATV) is an azapeptide HIV-1 protease inhibitor (PI). This compound selectively inhibits the viral processing of Gag-Pol proteins in HIV-1 infected cells, thus preventing formation of mature virions and infection of other cells. Atazanavir is authorised in the EU only if concomitantly used with ritonavir (RTV) as a pharmacokinetic enhancer ("boosting").

REYATAZ capsules, co-administered with low dose ritonavir, are indicated for the treatment of HIV-1 infected adults and paediatric patients 6 years of age and older in combination with other antiretroviral medicinal products. Based on available virological and clinical data from adult patients, no benefit is expected in patients with strains resistant to multiple protease inhibitors (≥ 4 PI mutations). There are very limited data available from children aged 6 to less than 18 years. The choice of REYATAZ in treatment experienced adult and paediatric patients should be based on individual viral resistance testing and the patient's treatment history.

Reyataz is currently approved as 100 mg, 150 mg, 200 mg and 300 mg capsules of atazanavir as well as a 50 mg/1.5 g oral powder (oral powder containing 1.5 g of powder per levelled measuring spoon, equivalent to 50 mg of atazanavir expressed as free base in a multidose HPDE bottle with a measuring spoon) for use in adults only.

The MAH has submitted a type II variation to update Reyataz SmPC (sections 4.3, 4.4 and 4.5) and Package leaflet (section 2) with new information relative to the drug-drug interactions between ATV and drugs primarily metabolised by CYP3A4, including PDE5 inhibitors (sildenafil, tadalafil, vardenafil), alfuzosin and salmeterol. The PL has been revised accordingly.

3.2. Clinical aspects

Rationale for the proposed change

Atazanavir is an inhibitor of CYP3A4 and UDP glucuronosyltransferase 1A1 (UGT1A1). Coadministration of ATV and drugs primarily metabolized by CYP3A4 or UGT1A1 may result in increased plasma concentrations of the other drug that could increase or prolong its therapeutic effects and its adverse effects. The magnitude of CYP3A4-mediated drug interactions on coadministered drug may change when ATV is coadministered with RTV, also a strong inhibitor of CYP3A4.

Because of these pharmacological properties of ATV, and because ATV is commonly coadministered with RTV, the United States Food and Drug Administration requested that these safety label changes to be applied to the ATV US package insert. A literature search was also conducted by the MAH on the effect of ATV/RTV as well as a CYP3A4 inhibitor, ketoconazole, on several drugs that are known CYP3A4 substrates, including alfuzosin, phosphodiesterase type 5 (PED5) inhibitors (sildenafil, tadalafil, and vardenafil), and salmeterol, using 5 databases (ADIS Clinical Trial Insights, Reactions, Medline, Derwent Drug Files, and Excerpta Medica). Overall, 125 references were obtained that were reviewed for relevancy. After reviewing the available drug-drug interaction data, including the literature data, the MAH has incorporated these necessary changes into the Company Core Data Sheet (CCDS) for ATV.

Based on the above, the MAH have proposed changes to the European Union (EU) PI which are described in the following paragraphs. No supportive study reports have been provided in this application.

Analysis of data submitted

Alfuzosin

Alfuzosin is an alpha1-adrenoreceptor antagonist indicated for the treatment of benign prostatic hyperplasia. Alfuzosin undergoes extensive metabolism by the liver, and CYP3A4 is the principal hepatic enzyme isoform involved in its metabolism. ATV and RTV are both strong inhibitors of CYP3A4.

RTV is currently contraindicated for coadministration with alfuzosin due to the potential increased alfuzosin concentrations that can result in hypotension. Since ATV has to be used in combination with RTV, coadministration of ATV and RTV with alfuzosin may further increase alfuzosin concentrations.

Phosphodiesterase Type 5 Inhibitors

PED5 inhibitors, including sildenafil, tadalafil, and vardenafil, are primarily metabolized by CYP3A4. Coadministration of PDE5 inhibitors with ATV and RTV may cause increased concentrations of the PDE5 inhibitor and result in increased potential for PDE5 inhibitor-associated adverse events (AEs).

- Sildenafil

In the EU sildenafil is sold under 2 brand names for different indications: one is indicated for the treatment of erectile dysfunction and the other one is indicated for the treatment of pulmonary arterial hypertension. Sildenafil metabolism is principally mediated by the cytochrome P450 isoforms 3A4 (major route). Therefore, inhibitors of these isoenzymes may reduce sildenafil clearance. Co-administration of RTV, which is a highly potent P450 inhibitor, at steady state (500 mg twice daily [BID]) with sildenafil (100 mg single dose) resulted in a 300% (4-fold) increase in sildenafil maximum concentration (Cmax) and a 1,000% (11-fold) increase in sildenafil plasma area under the concentration-time curve (AUC). At 24 hours, the plasma levels of sildenafil were still approximately 200 ng/mL, compared to approximately 5 ng/mL when sildenafil was administered alone. This is consistent with RTV's marked effects on a broad range of P450 substrates. Based on these pharmacokinetic (PK) results, coadministration of sildenafil with RTV is not advised (section 4.5 of sildenafil SmPC).

Sildenafil when used for pulmonary arterial hypertension:

Concomitant use of sildenafil with RTV is contraindicated in pulmonary arterial hypertension patients (sildenafil SmPCs). Although a safe and effective dose of sildenafil has not been established for the treatment of pulmonary hypertension when used with ATV/RTV, there is an increased potential for sildenafil-associated AEs (including visual disturbances, hypotension, priapism, and syncope) when sildenafil is coadministered with ATV/RTV due to potentially increased exposures to sildenafil.

Sildenafil when used for the treatment of erectile dysfunction:

Based on the PK results shown above, the sildenafil SmPCs suggest that co-administration of sildenafil with RTV is expected to increase sildenafil concentration, and may result in increased adverse reactions.

- Tadalafil

In the EU, tadalafil is sold under 2 trade names for different indications: one is indicated for the treatment of erectile dysfunction and the other one is indicated for the treatment of pulmonary arterial hypertension. Coadministration of ATV/RTV may substantially increase the plasma concentrations of tadalafil through inhibition of CYP3A4. It has been shown that coadministration of a CYP3A4 inhibitor, ketoconazole, at 200 mg daily increased tadalafil (10 mg) single dose exposure (AUC) 2-fold and Cmax by 15%, relative to the AUC and Cmax values for tadalafil alone. Coadministration of ketoconazole at a

higher dose (400 mg daily) increased tadalafil (20 mg) single dose exposure (AUC) 4-fold and Cmax by 22%. In addition, coadministration of RTV (200 mg BID), which is an inhibitor of CYP3A4, increased tadalafil (20 mg) single dose exposure (AUC) 2-fold with no change in Cmax. Although the effect of ATV/RTV on the exposures of tadalafil has not been directly evaluated, it is expected that coadministration of ATV and a low-dose RTV will substantially increase tadalafil concentrations, and may result in PDE5-associated AEs such as hypotension, visual changes, and priapism.

- Vardenafil

Vardenafil is extensively metabolized by CYP3A4. Although a direct drug interaction study between ATV and vardenafil has not been reported, the following drug interaction data have been presented in the vardenafil SmPC. Coadministration of vardenafil with RTV (600 mg BID) resulted in a 13-fold increase in vardenafil Cmax and a 49-fold increase in vardenafil area under the concentration-time curve from time 0 to 24 hours when coadministered with vardenafil 5 mg. In addition, coadministration of ketoconazole (200 mg), a potent CYP3A4 inhibitor, with vardenafil (5 mg) resulted in a 10-fold increase in vardenafil AUC and a 4-fold increase in vardenafil Cmax.

Although specific interaction studies have not been conducted, it is expected that coadministration of ATV and low-dose RTV will substantially increase vardenafil concentrations, and may result in PDE5-associated AEs such as hypotension, visual changes, and priapism.

- Salmeterol

Salmeterol is a long-acting inhaled beta-agonist indicated for the treatment of asthma and chronic obstructive pulmonary disease. Salmeterol is a substrate of CYP3A4. In a drug interaction study in 20 healthy subjects, coadministration of inhaled salmeterol (50 mcg BID) and oral ketoconazole (400 mg QD) for 7 days resulted in greater systemic exposure to salmeterol (AUC increased 16-fold and Cmax increased 1.4-fold). Three subjects were withdrawn due to beta2-agonist side effects (2 with prolonged QTc and 1 with palpitations and sinus tachycardia). Although there was no statistical effect on the mean QTc, coadministration of salmeterol and ketoconazole was associated with more frequent increases in QTc duration compared with salmeterol and placebo administration.

Although a drug interaction study between ATV and salmeterol has not been reported, based on the inhibitory property of ATV and RTV to the CYP3A4 enzyme, it is expected that concomitant use of salmeterol and ATV/RTV may result in increased cardiovascular AEs associated with salmeterol.

Results and discussion

The CHMP acknowledged that no studies were conducted to assess the potential drug-drug interactions described above, however, given the potential development of safety issues when these drugs are coadministered with ATV + RTV, the data from the literature was deemed relevant for inclusion in the SmPC. A brief discussion on the benefit and risks for the individual compounds follows.

Alfuzosin: The coadministration of alfuzosin with ATV/RTV may be associated with the potential of hypotension and syncope in patients receiving this combination, and in consequence, the potential for injuries. Given that alfuzosin is used for benign prostatic hypertrophy, and that there are other compounds available to the patients with this disease that are not expected to have a drug-drug interaction with ATV/RTV, the MAH proposed to contraindicate the coadministration of these compounds. The CHMP is in agreement with this contraindication.

Phosphodiesterase Type 5 Inhibitors: The drug interaction between PDE5 inhibitors and CYP3A4 inhibitors, including RTV, has been well studied when used for erectile dysfunction, and is included in the ATV CCDS with the recommendation to use with caution and dose adjustment. However, when given for pulmonary hypertension, these compounds, particularly sildenafil, are used at a much higher

dose compared to the dose used for erectile dysfunction. Although a drug-drug interaction study has not been conducted with sildanefil (20 mg three times a day), which is the dose used for pulmonary hypertension, this dose cannot be adjusted without compromising the efficacy of the drug similar to sildanefil when given for erectile dysfunction. The potential clinical AEs with the higher exposure of sildenafil when given for pulmonary hypertension would include hypotension, visual disturbances, and syncope.

Hence, the MAH proposed i) to contraindicate the coadministration of sildenafil when used with ATV/RTV for the treatment of pulmonary arterial hypertension, and ii) to add a warning in the Reyataz SmPC that particular caution should be used when prescribing sildenafil for the treatment of erectile dysfunction in patients receiving ATV with concomitant low-dose RTV, as dose adjustment can be achieved by dose reduction. The CHMP is in agreement with this approach.

Pulmonary hypertension occurs with increased frequency among patients with HIV infection. Although the pathogenesis of HIV-associated pulmonary hypertension remains unknown, it appears to occur independently of other risk factors associated with pulmonary vasculopathy, such as chronic hepatitis C infection and intravenous drug use. Hence, it is important to preserve treatment options for patients who have HIV disease and pulmonary hypertension and are receiving ATV/RTV. Thus, for tadalafil, the MAH proposed a recommendation to use with caution rather than contraindicating, given that dose adjustment is feasible with this compound when coadministered with ATV/RTV. Therefore, a warning statement has been added in the Reyataz SmPC that particular caution should be used when prescribing tadalafil and vardenafil (PDE5 inhibitors) for the treatment of erectile dysfunction in patients receiving ATV with concomitant low-dose RTV. The CHMP endorses the warning statement.

Salmeterol: HIV is an independent risk factor for chronic obstructive pulmonary disease (COPD). Salmeterol is frequently used in the treatment of COPD, and hence, it is important to preserve the option for HIV patients who are receiving ATV/RTV to be able to take salmeterol while being carefully monitored for AEs. Therefore, the MAH proposed to add a warning to the Reyataz SmPC that coadministration of salmeterol and ATV is not recommended. The warning is endorsed by CHMP.

Changes to the Product Information

4.3 Contraindications

- Reyataz was contraindicated to use with the PDE5 inhibitor sildenafil and references to section 4.4 and section 4.5 were included.
- Reyataz was contraindicated to use with alfuzosin.

4.4 Special warnings and precautions for use

- A warning was included for the PDE5 inhibitors used for the treatment of erectile dysfunction, with reference to section 4.5.
- A warning was included that the concomitant use of salmeterol and REYATAZ/ritonavir may result in increased cardiovascular adverse events associated with salmeterol. Co-administration of salmeterol and REYATAZ is not recommended (see section 4.5).

4.5 Interaction with other medicinal products and other forms of interaction

- The contraindication for alfuzosin and sildenafil when used for PAH were reflected in the table.
- Information on tadalafil, Vardenafil and in general on PDE5 inhibitors was included in the table.
- Information on Salmeterol in co-administration with Reyataz was introduced in the table.

Conclusions

Based on literature review the MAH has proposed to update sections 4.3, 4.4 and 4.5 of the SmPC to reflect changes in the drug-drug interactions of ATV and drugs metabolised by CYP3A4, including PDE5 inhibitors, alfuzosin and salmeterol. The PL has been revised accordingly.

The CHMP endorsed the contraindications and the further warnings and information on interaction as proposed by the MAH.

4. Conclusion

On 17 February 2011 the CHMP considered this Type II variation EMEA/H/C/000494/II/0075 to be acceptable and agreed on the amendments to be introduced in the Summary of Product Characteristics, Annex IIB and Package Leaflet.