23 June 2016
EMA/503216/2016
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Atazanavir Mylan

International non-proprietary name: atazanavir

Procedure No. EMEA/H/C/004048/0000

Note

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

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Table of contents

List of abbreviations

AAS	Atomic Absorption Spectrometry
AEs	Adverse events
AP	Applicant's part
ANOVA	Analysis of variance
ASMF	Active substance master file
AUC_{0-t}	Area Under the Curve from time zero to time of last measurable concentration
$AUC_{0-\infty}$	Area Under the Curve from time zero to time infinite
BA	Bioavailability
BCS	Biopharmaceutics Classification System
BE	Bioequivalence
CEP	Certificate of Suitability of the EP
CHMP	Committee for Medicinal Products for Human use
CI	Confidence interval
C_{max}	Maximum measured plasma concentration over the time span specified
C_{min}	Minimum measured plasma concentration over the time span specified
COA	Certificate of Analysis
CV	Coefficient of variation
CYP	Cytochrome P450 isoenzymes
EC	European Commission
ECG	Electrocardiogram
EPAR	European Assessment Report
ERA	Environmental Risk Assessment
EU	European Union
GC	Gas Chromatography
GCP	Good clinical practice
GLP	Good laboratory practice
HDPE	High Density Polyethylene
HPLC	High performance liquid chromatography
ICH	International Conference on Harmonisation of Technical Requirements for Registration of

	Pharmaceuticals for Human Use
IPC	In-process control
IR	Infrared
IS	Internal standard
K_{el}	Elimination Rate Constant
K_3EDTA	Tri Potassium Ethylene Diamine Tetra Acetic Acid
KF	Karl Fischer titration
LDPE	Low density polyethylene
LOQ	Limit of Quantification
MAH	Marketing Authorisation holder
NMR	Nuclear Magnetic Resonance
OPA	*ortho*-phthalaldehyde
PE	Polyethylene
Ph. Eur.	European Pharmacopoeia
PK	Pharmacokinetics
PP	Polypropylene
PVC	Polyvinyl chloride
QC	Quality control
RH	Relative humidity
RP	Restricted part
rpm	Rotations Per Minute
RSD	Relative standard deviation
SmPC	Summary of product characteristics
SOP	Standard Operating Procedure
T1/2	Plasma Elimination Half-Life
TLC	Thin layer chromatography
Tmax	Time of the maximum measured plasma concentration
TSE	Transmissible Spongiform Encephalopathy
TTC	Threshold of toxicological concern
UV	Ultraviolet
XRPD	X-Ray Powder Diffraction

1. Background information on the procedure

1.1. Submission of the dossier

The applicant MYLAN S.A.S. submitted on 23 December 2014 an application for Marketing Authorisation to the European Medicines Agency (EMA) for Atazanavir Mylan, through the centralised procedure under Article 3 (3) of Regulation (EC) No. 726/2004– 'Generic of a Centrally authorised product'. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 24 July 2014.

The application concerns a generic medicinal product as defined in Article 10(2)(b) of Directive 2001/83/EC and refers to a reference product for which a Marketing Authorisation is or has been granted in the Union on the basis of a complete dossier in accordance with Article 8(3) of Directive 2001/83/EC.

The applicant applied for the following indication:

> *Atazanavir Mylan, co-administered with low dose ritonavir, is 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 (see sections 4.4 and 5.1).*
>
> *The choice of Atazanavir Mylan in treatment experienced adult and paediatric patients should be based on individual viral resistance testing and the patient's treatment history (see sections 4.4 and 5.1).*

The legal basis for this application refers to:

Generic application (Article 10(1) of Directive No 2001/83/EC).

The application submitted is composed of administrative information, complete quality data and a bioequivalence study with the reference medicinal product Reyataz instead of non-clinical and clinical unless justified otherwise.

Information on paediatric requirements

Not applicable

The chosen reference product is:

- Medicinal product which is or has been authorised in accordance with Community provisions in accordance with Community provisions in force for not less than 6/10 years in the EEA:
- Product name, strength, pharmaceutical form: Reyataz, 100 mg/150 mg/200 mg/300 mg, hard capsules
- Marketing authorisation holder: Bristol Myers Squibb Pharma EEIG
- Date of authorisation: 02-03-2004
- Marketing authorisation granted by:
  - Union

- Medicinal product authorised in the Community/Members State where the application is made or European reference medicinal product:
- Product name, strength, pharmaceutical form: Reyataz, 100 mg/150 mg/200 mg/300 mg, hard capsules

- Marketing authorisation holder: Bristol Myers Squibb Pharma EEIG
- Date of authorisation: 02-03-2004
- Marketing authorisation granted by:
  - Union
- Union Marketing authorisation number:
  - 100 mg: EU/1/03/267/001, EU/1/03/267/002
  - 150 mg: EU/1/03/267/003, EU/1/03/267/004
  - 200 mg: EU/1/03/267/005, EU/1/03/267/006
  - 300 mg: EU/1/03/267/008, EU/1/03/267/009, EU/1/03/267/010

■ Medicinal product which is or has been authorised in accordance with Community provisions in force and to which bioequivalence has been demonstrated by appropriate bioavailability studies:

- Product name, strength, pharmaceutical form: Reyataz, 300 mg, hard capsules
- Marketing authorisation holder: Bristol Myers Squibb Pharma EEIG
- Date of authorisation: 02-03-2004
- Marketing authorisation granted by:
  - Union
- Union Marketing authorisation number:
  - 300 mg: EU/1/03/267/010
- Bioavailability study number(s): 14-VIN-255

Licensing status

The product was not licensed in any country at the time of submission of the application.

1.2. Steps taken for the assessment of the product

The Rapporteur appointed by the CHMP was:

Rapporteur: Karsten Bruins Slot

- The application was received by the EMA on 23 December 2014.
- The procedure started on 21 January 2015.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 10 April 2015.
- The PRAC Rapporteur's RMP Assessment Report was circulated to all CHMP and PRAC members on 27 April 2015.
- During the meeting on 21 May 2015, the CHMP agreed on the consolidated List of Questions to be sent to the applicant. The final consolidated List of Questions was sent to the applicant on 22 May 2015.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 21 August 2015.
- The Rapporteur circulated the Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 25 September 2015.

- The PRAC Rapporteur's RMP Assessment Report was circulated to all CHMP and PRAC members on 29 September 2015.
- During the CHMP meeting on 22 October 2015, the CHMP agreed on a List of outstanding issues to be addressed by the applicant.
- The applicant submitted the responses to the CHMP consolidated List of Outstanding Issues on 22 December 2015.
- The PRAC Rapporteur's RMP Assessment Report was circulated to all CHMP and PRAC members on 19 January 2016.
- The Rapporteur circulated the Assessment Report on the applicant's responses to the List of Outstanding Issues to all CHMP members on 21 January 2016.
- During the CHMP meeting on 28 January 2016, the CHMP agreed on the second List of outstanding issues to be addressed by the applicant.
- The applicant submitted the responses to the second CHMP consolidated List of Outstanding Issues on 24 March 2016.
- The PRAC Rapporteur's RMP Assessment Report was circulated to all CHMP and PRAC members on 04 April 2016.
- The Rapporteur circulated the Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 07 April 2016.
- During the CHMP meeting 28 April 2016, the CHMP agreed on the third List of outstanding issues to be addressed by the applicant.
- The applicant submitted the responses to the third CHMP consolidated List of Outstanding Issues on 24 May 2016.
- The Rapporteur circulated the Assessment Report on the applicant's responses to the List of Outstanding Issues to all CHMP members on 02 June 2016.
- During the meeting on 23 June 2016, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a Marketing Authorisation to Atazanavir Mylan.

2. Scientific discussion

2.1. Introduction

AIDS is a chronic, potentially life-threatening condition caused by the human immunodeficiency virus (HIV). By damaging immune system, HIV interferes with body's ability to fight the organisms that cause disease.

HIV is a sexually transmitted infection. It can also be spread by contact with infected blood, or from mother to child during pregnancy, childbirth or breast-feeding.

There's no cure for HIV/AIDS, but there are medications that can dramatically slow the progression of the disease. These medicinal products have reduced AIDS deaths in many developed nations. But HIV continues

to decimate populations in Africa, Haiti and parts of Asia. HIV is transmitted through direct contact of a mucous membrane or the bloodstream with a bodily fluid containing HIV, such as blood, semen, vaginal fluid, pre-seminal fluid, and breast milk. This transmission can involve anal, vaginal or oral sex, blood transfusion, contaminated hypodermic needles, exchange between mother and baby during pregnancy, childbirth, breastfeeding or other exposure to one of the above bodily fluids.

Introduction of HIV protease inhibitors (PIs) within antiretroviral therapy, in association with nucleoside reverse transcriptase inhibitors (NRTIs), started a new era in the battle against HIV and enabled the construction of highly active antiretroviral therapy (HAART), which dramatically decreased mortality in HIV-infected populations in developed countries. Further and substantial improvements occurred with the addition of a low dose of the PI ritonavir to another PI in order to increase plasma levels of the latter (i.e. 'boosting' strategy, denoted by '/r' following the PI), to reduce inter-individual variability in plasma concentrations and increase the overall potency of the regimens) (Focà E et al., 2012).

The long-term efficacy of ritonavir boosted PI regimens, several toxicity events were related to ritonavir and/or to the increased plasma drug concentrations of the PIs given in association These events may occur either in the short term or in the long term, and include gastrointestinal disturbances, lipid profile alterations, insulin resistance and central body fat accumulation. An alternative booster using molecules such as cobicistat did not significantly improve the tolerability profile) Therefore, we still need to assess whether a PI-based option without any boosting is a feasible option in selected conditions, where potency and genetic barrier against the emergence of RAMs are not compromised and toxicity tolerability profiles of the regimen are optimized.. (Focà E et al., 2012).

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

Atazanavir (Reyataz) was the first once-daily PI approved for the treatment of HIV-infected patients and has been used in clinical practice since 2003) (Focà E et al., 2012) Atazanavir (ATV) is the newest protease inhibitor (PI) approved for use in highly active antiretroviral therapy (HAART) (Busti AJ et al., 2006) Atazanavir is a selective and potent inhibitor of the HIV-1 protease (Deeks ED et al., 2012).

Atazanavir is co-administered with low dose ritonavir and indicated for the treatment of HIV-1 infected adult and paediatric patients 6 years of age and older in combination with other antiretroviral products. The recommended dose in adults is 300 mg once daily taken with ritonavir 100 mg once daily and with food. Paediatric patients are dosed based on body weight.

This application is for a generic form of Atazanavir capsules in strengths of 150 mg, 200 mg and 300 mg and applies for the indication of the reference product. This is an abridged application submitted under Article 10.1 of Directive 2001/83/EC. An abridged application is appropriate since the product in this application is essentially similar to the existing product REYATAZ (Atazanavir sulfate) 300 mg capsules form the originator of BRISTOL-MYERS SQUIBB PHARMA EEIG. The active ingredient and the route of administration are the same for both products.

2.2. Quality aspects

2.2.1. Introduction

The finished product is presented as hard capsules containing 150, 200 or 300 mg of atazanavir as active substance.

Other ingredients are:

Capsule contents: lactose monohydrate, crospovidone, magnesium stearate

Capsule shell cap (150 mg): iron oxide red (E172), titanium dioxide (E171), patent blue V (E131), gelatin

Capsule shell body (150 mg): titanium dioxide (E171), patent blue V (E131), gelatin

Capsule shell cap (200 mg): titanium dioxide (E171), indigo carmine (E132), gelatin

Capsule shell body (200 mg): iron oxide yellow (E172), titanium dioxide (E171), patent blue V (E131), gelatin

Capsule shell cap (300 mg): iron oxide yellow (E172), iron oxide red (E172), titanium dioxide (E171), gelatin

Capsule shell body (300 mg): iron oxide red (E172), titanium dioxide (E171), patent blue V (E131), gelatin

Printing ink: shellac, propylene glycol, concentrated ammonia solution, iron oxide black (E172), potassium hydroxide.

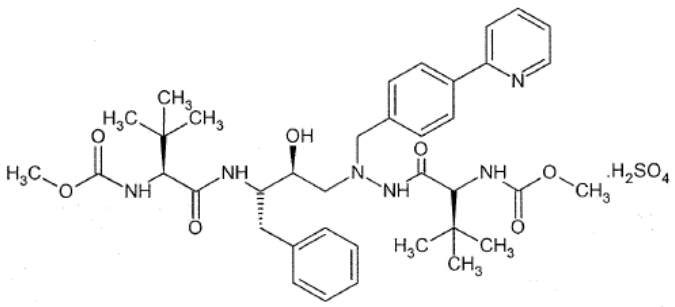
The product is available in OPA/Aluminium/PVC – Aluminium blisters and HDPE bottles with polypropylene screw caps as described in section 6.5 of the SmPC.

2.2.2. Active substance

General information

The information on atazanavir sulphate is provided according to the Active Substance Master File (ASMF) procedure.

The chemical name of atazanavir sulphate 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 sulphate corresponding to the molecular formula $C_{38}H_{54}N_6O_{11}S$ and a relative molecular mass of 802.9 g/mol. It has the following structure:



The structure of the active substance was elucidated by a combination of ^{1}H and ^{13}C NMR spectroscopy, IR spectroscopy, UV spectroscopy, mass spectrometry and elemental analysis. The polymorphic form was characterised by XRPD and shown to be equivalent to that published in the patent literature.

The active substance is a white to pale yellow, slightly hygroscopic, crystalline powder with pH dependent aqueous solubility. It is slightly soluble at acidic pH, solubility increasing as pH decreases, but practically insoluble at neutral pH. Since atazanavir has low solubility (BCS class II), control of polymorphic form and particle size are critical to ensuring a consistent performance *in vivo*.

Atazanavir contains four chiral centres. Three originate in amino acid-derived starting materials and the fourth is generated under substrate control during the process. Enantiomeric purity of the active substance is controlled routinely by specific optical rotation and diastereomers can be detected by the HPLC method.

Polymorphism has been observed for atazanavir sulphate with four polymorphic forms having been identified. The manufacturing process consistently produces the required form (Form A) which will be routinely tested in batches of active substance.

There is no monograph of atazanavir sulphate in the European Pharmacopoeia.

Manufacture, characterisation and process controls

Detailed information on the manufacturing of the active substance has been provided in the restricted part of the ASMF and it was considered satisfactory.

One source of active substance is used although five manufacturers are responsible for different steps of its production. Atazanavir sulphate is synthesized in a convergent process in nine main steps using well-defined starting materials with acceptable specifications. The starting materials were re-defined during the procedure at the request of CHMP in order to ensure that critical steps (in particular, those generating mutagens and vital to control of stereochemistry) and enough of the synthetic process are included in the dossier, thereby ensuring the quality of the active substance throughout its life cycle. As a result of this, additional manufacturers were added to the dossier and the QP declaration was updated. Initially, the revised QP declaration could not be accepted as the audit reports requested by CHMP were not available, resulting in a further major objection. The applicant carried out new audits and after providing the reports, the QP declaration was deemed acceptable.

Adequate in-process controls are applied during the synthesis. The specifications and control methods for intermediate products, starting materials and reagents have been presented.

The characterisation of the active substance and its impurities are in accordance with the EU guideline on chemistry of new active substances. Potential and actual impurities were well discussed with regards to their origin and characterised. The origin, fate and purge of mutagenic impurities have been described. Elemental impurities are controlled by several tests in the active substance specification.

The active substance is packaged in an anti-static LDPE bag with PP seal which comply with the EC directive 2002/72/EC and EC 10/2011 as amended. These are stored inside a black PE bag which is placed in a heat-sealed triple laminated aluminium bag containing a silica gel desiccant, all placed in a HDPE drum.

Specification

The active substance specification includes tests for appearance, solubility in MeOH (Ph. Eur.), identity (IR, HPLC, sulfate test), assay (HPLC), impurities (HPLC), residual solvents (GC), water content (KF), heavy metals (Ph. Eur.), sulphated ash (Ph. Eur.), palladium content (AAS), specific optical rotation (Ph. Eur.), polymorphic form (XRPD) and particle size distribution (laser diffraction).

Impurities are all limited to below the qualification threshold according to ICH Q3A. Limits for mutagenic impurities have been set in line with the TTC as described in ICH M7. The analytical methods used have been adequately described and non-compendial methods appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used for assay and impurities testing has been presented.

Batch analysis data on three production scale batches of the active substance are provided. The results are within the specifications and consistent from batch to batch.

Stability

Stability data on three production scale batches of atazanavir sulphate from the proposed manufacturer stored in the intended commercial package for up to 12 months under long term conditions (25°C / 60% RH) and for up to 3 months under accelerated conditions (40°C/ 75% RH) according to the ICH guidelines were provided. The following parameters were tested: appearance; identity; water content; specific optical rotation; polymorphic form; related substances; assay. The analytical methods used were the same as for release and are stability indicating. Under accelerated conditions, one impurity was above the specification limit in one batch after 3 months. Total impurities and assay remained within specification. All other tested parameters were well within specification at all time-points under both sets of conditions and no significant trends were observed.

Forced degradation studies were carried out in solution and in the solid state. Solid atazanavir sulphate degraded when exposed to heat at 105^{o}C. In solution, significant degradation was observed in the presence of acid, base and peroxide. Photostability testing following the ICH guideline Q1B was also performed on one batch and the active substance shown not to be photosensitive.

The stability results indicate that the active substance manufactured by the proposed supplier is sufficiently stable. The stability results justify the proposed retest period in the proposed container.

2.2.3. Finished medicinal product

Description of the product and pharmaceutical development

The finished product is an immediate release hard gelatin capsule containing a white to pale yellow powder. The capsules are imprinted with MYLAN and ARxxx where xxx denotes the strength of the capsule in mg. The different strength capsules are also distinguishable based on their colour.

The aim of development was to develop a generic version of the reference product, Reyataz hard capsules, with equivalent performance in clinical use. Other requirements were for a robust and scalable manufacturing process and suitable stability in the commercial pack.

Atazanavir sulphate is highly permeable but poorly soluble in aqueous media and is thus BCS class II. Batches with smaller particle size dissolve faster and the particle size distribution is thus carefully controlled. It also has poor flow properties. Although multiple polymorphic forms are known, the commercial form is thermodynamically stable. It is also stable when combined with the proposed excipients as demonstrated by a series of binary compatibility studies.

Given the poor flow and solubility properties, a granulation approach was adopted. The excipients chosen for the capsule contents are qualitatively the same as in the reference product. The relative amounts of each excipient were varied in order to afford the desired dissolution and disintegration characteristics. Comparative dissolution studies between the optimised formulation and the reference product were carried out across the physiological pH range and in the quality control (QC) medium and the profiles found to be similar. The generic and originator product also have similar impurity profiles.

Bioequivalence was demonstrated between 300 mg Reyataz and Atazanavir Mylan capsules. Other strengths biowaiver was considered justified as the generic product strengths are dose proportional in terms of the capsule contents, manufactured using the same process and manufacturer, and exhibit similar dissolution profiles across the physiological pH range and in the QC medium.

Atazanavir sulphate only fully dissolves in acidic aqueous media and therefore, an acidic medium was chosen for the dissolution method. Other parameters such as apparatus and rotation speed were then optimised in order to afford a discriminatory method. The discriminatory power was demonstrated by testing batches made with coarser grade active substance or excess granulation fluid which was shown to produce slower-dissolving granules. The granulation process was optimised in order to provide a consistent product with appropriate dissolution characteristics and also to allow efficient processing. Different parameters in the granulation step and subsequent milling and blending operations were investigated and suitable set-points chosen.

All excipients are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur. standards. There are no novel excipients used in the finished product formulation. The list of excipients is included in section 6.1 of the SmPC and in paragraph 2.1.1 of this report.

The primary packaging is OPA/aluminium/PVC – aluminium blisters or HDPE bottles with polypropylene screw caps. The materials comply with Ph. Eur. and EC requirements. The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product.

Manufacture of the product and process controls

The manufacturing process consists of five main steps: blending of intra-granular excipients and granulation; drying and milling of granules; blending with extra-granular excipients; encapsulation; packaging. The process is considered to be a standard manufacturing process.

Major steps of the manufacturing process have been validated by a number of studies. It has been demonstrated that the manufacturing process is capable of producing the finished product of intended quality in a reproducible manner. The in-process controls are adequate for this type of manufacturing process and pharmaceutical form.

Product specification

The finished product release specifications are appropriate for this kind of dosage form and include tests for appearance, identification (UV, TLC), colour identification (colour reaction), dissolution (Ph. Eur.), uniformity of dosage units (Ph. Eur.), assay (HPLC), water content (KF), degradation products (HPLC) and microbiological quality (Ph. Eur.). The specification for the other strengths is identical other than the description, colour identification and assay (actual amounts).

The analytical methods used have been adequately described and appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used for assay and impurities testing has been presented.

Batch analysis results are provided for three pilot scale batches of final blend, each sub-divided and filled into capsules of each strength, confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification.

Stability of the product

Stability data of three pilot scale batches of finished product stored for up to 12 months under long term conditions (25ºC / 60% RH) and for up to 6 months under accelerated conditions (40ºC / 75% RH) according to the ICH guidelines were provided. The batches of Atazanavir Mylan are identical to and were packed in the primary packaging as those proposed for marketing. Samples were tested for appearance, water content, degradation products, dissolution, assay and microbiological quality. The analytical procedures used are stability indicating. No significant trends were observed to any of the measured parameters under long term conditions. Under accelerated conditions, an increase in impurity content was noted, although the observed levels were still within specification after 6 months. In addition, one batch of 300 mg capsules was exposed to light as defined in the ICH Guideline on Photostability Testing of New Drug Substances and Products. Atazanavir Mylan is not photosensitive.

In-use stability studies have been commenced on two batches of 300 mg capsules from early after manufacture to simulate use of an HDPE bottle containing 90 tablets throughout its usage period (once daily posology). All measured parameters were within specifications after the 90 day period, thus the proposed in-use shelf life after first opening in the SmPC (section 6.3) is justified. The study will be repeated on batches from near the end of shelf life once they become available. A bulk storage study was carried out on both final blend and filled capsules (1 batch of each strength) in LDPE bags inside a triple laminated secondary bag containing desiccant for up to 90 days. The applicant committed to repeat the study on a second batch of each strength. In addition, studies were carried out on capsules in a simulated bulk shipment pack under long term (up to 12 months) and accelerated conditions (up to 6 months) in order to support the shipment of capsules to a different site for re-packaging. These studies show the capsules to be stable in this packaging format and a shelf-life of 12 months in the bulk shipment pack is acceptable.

Based on available stability data, the proposed shelf-life of 18 months stored at less than 25^{o}C as stated in the SmPC (section 6.3) is acceptable.

Adventitious agents

It is confirmed that the lactose used in Atazanivir Mylan is produced from milk from healthy animals in the same condition as those used to collect milk for human consumption and that the lactose has been prepared

without the use of ruminant material other than calf rennet according to the Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents Via Human and veterinary medicinal products.

Gelatine obtained from bovine sources is used in the product. Valid TSE CEP from the suppliers of the gelatine used in the manufacture is provided.

All other excipients are of vegetable origin.

2.2.4. Discussion on chemical, and pharmaceutical aspects

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way. Data has been presented to give reassurance on viral/TSE safety.

2.2.6. Recommendations for future quality development

In the context of the obligation of the MAHs to take due account of technical and scientific progress, the CHMP recommends the following points for investigation:

- The applicant should carry out an additional in-use stability study using a batch near the end of its shelf-life.
- The applicant should carry out an additional bulk storage study on an additional batch of each capsule strength.

2.3. Non-clinical aspects

2.3.1. Pharmacology

Atazanavir (ATV) is an azapeptide human immunodeficiency virus-1 (HIV-1) protease inhibitor, indicated for co-administration with low dose ritonavir, in the treatment of HIV-1 infected adults and paediatric patients 6 years of age and older in combination with other antiretroviral medicinal products (Reyataz SPC 2014).

Protease inhibitors (PIs) prevent the formation of mature virions by blocking the processing of viral Gag-Pol proteins in HIV-1 infected cells (Safrin 2012). Gag and Gag-Pol gene products are translated into precursor proteins as HIV virions mature. These proteins are post-translationally processed by HIV protease to become structural elements of the core of future viral particles. Protease inhibitors prevent the cleavage of the Gag-

Pol polyprotein resulting in the production of immature, non-infectious viral particles. This action effectively terminates the propagation of infection.

In vitro pharmacodynamic studies showed ATV had similar potency for inhibiting the HIV-1 protease compared to other PI's but higher potency in inhibiting the growth of HIV-1 infected cells for most strains and cell types tested. ATV maintained effectiveness in 88% of the clinical isolates tested from patients with resistance to other PI's. In most cases, when ATV was combined with other PI's or reverse transcriptase inhibitors an additive effect was seen with no antagonistic anti-HIV activity or enhanced cytotoxic effects.

Safety pharmacology studies showed no adverse effects on respiratory or central nervous function in rats or dogs but in one study in dogs sinus bradycardia and PR/QRS/QT prolongation was observed. In vitro studies suggested effects on ion currents (HERG, sodium and calcium) and action potential in Purkinje fibres, but only at significantly higher concentrations than are observed in the clinic.

2.3.2. Pharmacokinetics

In vitro, ATV had Caco-2 permeability consistent with its bioavailability in humans, but was susceptible to secretion via P-glycoproteins and OATP transporters. ATV was moderately protein bound in all species (~86-93%) bound human α-1 acid glycoprotein (88.7 %) and partitioned into human red blood cells (30%) in vitro. Radiolabeled studies in rats showed significant tissue distribution with the highest levels occurring in the liver, large intestine and stomach (tissue to plasma ratio > 10) following a single oral dose. Twenty-four hours after administration no single tissue contained more than 1% of the dosed radioactivity. Relative elimination in faeces and urine was not described. Metabolism of ATV occurs primarily in the liver by the action of CYP3A4 resulting in, mono- and di-oxygenated, glucuronidated, N-aklylated and dehydrogenated species.

Three potentially reactive metabolites were identified following incubation of ATV in human liver microsomes, two of these were also observed in mouse faeces.

Significant drug interactions have been observed clinically, most due to competition for CYP3A4 metabolism. Concomitant ritonavir is clinically indicated to exploit "boosted" ATV pharmacokinetics due to ritonavir's higher affinity for CYP3A4. Numerous drugs from a variety of drug classes are not recommended for use with ATV. Ritonavir boosted ATV is contraindicated with CYP3A4 substrates with a narrow therapeutic index; including, astemizole, terfenadine, cisapride, pimozide, quinidine, bepridil, triazolam, orally administered midazolam, and ergot alkaloids, particularly ergotamine and dihydroergotamine.

Studies in rat indicated significant alterations in plasma protein binding and pharmacokinetics in models of obesity and hyperlipidaemia.

2.3.3. Toxicology

ATV was well tolerated following a single oral dose of 400 mg/kg in mice with lethality occurring at 800 mg/kg. Rats tolerated 1600 mg/kg without any overt clinical effects. Repeat dose studies in mice, rats and dogs indicated that the liver was a common target organ of toxicity and was dose and duration of treatment-proportional. No other significant toxicities were noted. In the 6-month rat study, liver toxicity was observed at the lowest dose tested, 100 mg/kg. In the 9-month dog study the NOAEL for liver toxicity was 10 mg/kg in both males and females.

In assays interrogating adverse effects on bilirubin, lipid or glucose processing, ATV had either no effect or a diminished effect compared to other PI's tested at similar concentrations.

Genotoxicity tests indicated that ATV was clastogenic in vitro but in vivo tests were negative. ATV was not mutagenic in the definitive Ames reverse mutation assay. In vitro ATV caused chromosomal aberrations in human lymphocytes. In vivo ATV did not induce micronuclei in bone marrow, DNA damage in duodenum, or unscheduled DNA repair in liver at plasma and tissue concentrations exceeding those that were clastogenic in vitro. In 2-year carcinogenicity studies in mice and rats only female mice showed an increased incidence of any neoplasm. The benign hepatocellular adenomas seen in female mice were attributed to single-cell necrosis (only seen in female mice) and thought to have no relevance in humans at intended therapeutic exposures.

No significant teratological findings were reported from studies in pregnant rats or rabbits.

Reduced fertility was observed in rats when both males and females received ATV but did not affect fertility when only one mate received drug (1400 mg/kg). No adverse embryonic or foetal effects occurred in rats or rabbits at maternally toxic doses up to 1920 or 60 mg/kg, respectively.

2.3.4. Ecotoxicity/environmental risk assessment

No Environmental Risk Assessment (ERA) was submitted. This was justified by the applicant as the introduction of Atazanavir Mylan manufactured by Mylan, is considered unlikely to result in any significant increase in the combined sales volumes for all atazanavir containing products and the exposure of the environment to the active substance. Therefore, the ERA is expected to be similar and not increased.

2.3.5. Conclusion on the non-clinical aspects

A non-clinical overview on the pharmacology, pharmacokinetics and toxicology has been provided. The pharmacology, pharmacokinetics and toxicology data as well known for atazanavir and thus new non-clinical data are not required. The non-clinical aspects of the SmPC are in line with the SmPC of the reference product. The impurity profile has been discussed and was considered acceptable.

2.4. Clinical aspects

2.4.1. Introduction

This is an application for hard capsules containing atazanavir sulfate. To support the marketing authorisation application the applicant conducted a bioequivalence study with two-treatment, two-sequence, two-period crossover design under fed conditions. This study was the pivotal study for the evaluation.

GCP

The Clinical trials were performed in accordance with GCP as claimed by the applicant.

The applicant has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

Exemption

The bioequivalence study was performed using the highest strength of 300 mg, claiming that all conditions regarding biowaiver as described in the Guideline on the Investigation of Bioequivalence have been fulfilled,. A biowaiver has been requested for the additional strengths of 150 mg and 200 mg.

Atazanavir is rapidly absorbed after oral administration (Tmax 2.5 h) and demonstrates nonlinear pharmacokinetics, resulting in greater than dose-proportional increases in bioavailability (AUC and Cmax) over a dose range of 200–800 mg daily. In line with relevant guidelines, the bioequivalence study was conducted on the highest dose (300 mg).

It is considered that the conditions for biowaiver have been fulfilled:

- All the three strengths are manufactured at the same site by the same manufacturer and manufacturing process.
- The qualitative composition of the different strengths is the same.
- The composition of the strengths are quantitatively proportional (except for colouring agents)
- Comparable in vitro dissolution data confirm the adequacy of waiving additional in vivo bioequivalence testing. Dissolution profiles were considered similar as supported by f2 value greater than 50.

Consequently, a biowaiver for the additional strengths is considered acceptable by the CHMP.

Clinical studies

The applicant has submitted one single dose bioequivalence study (Study 14-VIN-255) under fed condition in support of this application.

2.4.2. Pharmacokinetics

Study 14-VIN-255

Study Title: An open label, balanced, randomized, single-dose, two-treatment, two-sequence, two period crossover bioequivalence study of Atazanavir Sulfate Capsules 300 mg of Mylan Laboratories Limited, India and REYATAZ (Atazanavir sulfate) 300 mg Capsules of BRISTOL-MYERS SQUIBB PHARMA EEIG, Uxbridge Business Park, Sanderson Road, Uxbridge UB8 1DH, Vereinigtes konigreich (Mfg. By. BRISTOL-MYERS SQUIBB S.R.L, Italy) in adult healthy subjects under fed condition.

Methods

Study design

The study was designed as an open label, balanced, randomized single-dose, two-treatment, two-sequence, two-period crossover bioequivalence study in healthy, adult, human subjects under fed condition.

Following overnight fasting, the subjects received a high-fat, high-calorie breakfast (approximately 800 to 1000 calories) to be finished 30 minutes prior to administration of the drug formulation. A standard meal was received at about 4, 8 and 12 hours after dosing, as well.

A washout period of 8 days was kept between two consecutive dosing periods and was sufficient for complete elimination of the administered drug from the body. The terminal elimination half-life of atazanavir sulfate is approximately 7 hours.

After drug administration, a total of 21 venous blood samples were collected at pre-dose, and 0.25, 0.50, 0.75, 1.00, 1.25, 1.50, 1.75, 2.00, 2.25, 2.50, 3.00, 3.50, 4.00, 5.00, 6.00, 8.00, 10.00, 12.00, 16.00 and 24.00 hours post dose.

The study site was responsible for protocol development, study coordination, clinical and pharmacokinetic and statistical analysis, reporting of data and audit of the study in compliance with the protocol and SOPs.

Test and reference products

Test product (T)

Formulation	:	Atazanavir Sulfate Capsules 300 mg
Manufactured By	:	Mylan Laboratories Limited H-12 & H-13, MIDC, Waluj Industrial Area, Aurangabad-431136, Maharashtra, India.
Batch No.	:	2006559
Manufacturing Date	:	May 2014
Expiry Date	:	Apr 2016
Mode of Administration	:	One capsule was administered orally in sitting posture with 240mL of dosing water followed by thorough mouth check using torch and disposable spatula.

Reference product (R)

Formulation	:	REYATAZ® 300 mg Hartkapseln/Atazanavir
Manufactured by	:	BRISTOL-MYERS SQUIBB PHARMA EEIG, Uxbridge Business Park, Sanderson Road, Uxbridge UB8 1DH, Vereinigtes konigreich
Batch No.	:	4C85378
Manufacturing Date	:	NA
Expiry Date	:	Nov 2015

The applicant has confirmed that the composition and manufacturing process of the test product formulation used in the bio-equivalence study and proposed for commercial supplies to European Economic Area is the same.

Population studied

Main inclusion criteria

Healthy, willing, volunteers of age between 18 and 45 years (both inclusive) were selected on the basis of laboratory evaluations during screening, medical history, clinical examination (including vital signs, physical examination and systemic examination), Chest X-ray (PA view), ECG recordings, Urine pregnancy test (only for female subjects.

Determination of sample size

Based on Literature and sponsor's in-house estimate the maximum intra-subject variability observed among primary pharmacokinetic parameters was found to be 34.

Hence, considering the CV of 34 the following estimates were considered for the computation of sample size:

T/R ratio = 95-105%

Intra-Subject C.V (%) ~ 34 %

Significance Level = 5 %

Power >= 90%

Bioequivalence Limits = 80.00-125.00 %

Based on the above estimate, a sample size of 66 subjects was sufficient to establish bioequivalence between the formulations with adequate power. However, considering the drop-outs, a sample size of 72 subjects was considered for the study.

Subject disposition

72 healthy, adult Asian males (range 18 to 45 years) were enrolled in the study. Weight of the subjects was within the normal range (Body Mass Index range 18.5 to 30.0 kg/m2) with a minimum of 45 kg.

Two subjects (number 08 and 17) did not report to the clinical facility in Period 2. They were hence withdrawn from the study, and the subjects were not included in the pharmacokinetic analysis. 70 subjects completed both the periods of the study as per protocol.

Three of the 70 subjects were partly excluded from the pharmacokinetic analysis. The applicant has justified the exclusion of subjects, and performed a sensitivity analysis to show that the exclusion of subjects did not alter the overall conclusion of the bioequivalence study.

Analytical methods

The plasma samples of subjects were analysed using HPLC/MS/MS over a validated concentration range of 20.000 to 4000.800 ng/ml for atazanavir. Lopinavir was used as internal standard.

Out of a total of 2982 plasma samples analysed, 119 samples (4.02 %) were re-analysed due to a gradual decrease in IS signal (n=84), quantifiable pre-dose level of atazanavir (n=1) or unacceptable IS response (root cause equipment failure identified) (n=34).

The analytical method was adequately validated, including pre-study and within-study validations.

Incurred samples reanalysis was performed and confirmed reliability of the initial results.

Pharmacokinetic variables

Using the estimated concentration time profile of atazanavir, the following variables were calculated:

Primary variables: Cmax and AUC0-t

Secondary variables: AUC0-∞, Tmax, AUC_%Extrap_obs, t1/2 and Kel

Statistical methods

Statistical comparison of the ln-transformed Cmax, AUC0-t and AUC0-∞ was based on the ANOVA model, and was carried out using SAS® Version 9.2 (SAS Institute Inc., USA). The sequence, treatment, period and sequence effects were included in the model as fixed effects, and subject within sequence as a random effect. All main effects were tested at the 0.10 level of significance using mean square error as the error term.

The 90% CIs of the relative mean of Cmax, AUC0-t and AUC0-∞ of the test and reference formulation for ln-transformed data should be within 80.00% to 125.00% for atazanavir to establish bioequivalence.

Results

Table 1. Pharmacokinetic parameters for atazanavir (non-transformed values)

Pharmacokinetic parameter	Test		Reference	
	arithmetic mean	CV%	arithmetic mean	CV%
$AUC_{(0-t)}$ (hr*ng/mL)	8050.267 ±3989.6257	49.56 %	7934.760 ±4034.3977	50.84 %
$AUC_{(0-\infty)}$ (hr*ng/mL)	8699.454 ±4303.1843	49.46 %	8633.075 ± 4360.8179	50.51 %
C_{max} (ng/mL)	1479.610 ± 678.1085	45.83 %	1566.430 ± 814.4203	51.99 %
T_{max}* (hr)	3.750 (2.25-12.00)	N/A	4.000 (2.25-12.00)	N/A
$T_{1/2}$ (hr)	5.891 ± 5.5399	94.04 %	5.356 ± 1.8847	35.19 %
K_{el} (1/hr)	0.1411 ± 0.04387	31.08 %	0.1434 ± 0.04603	32.09 %
AUC_%Extrap_obs	6.629 ± 8.0467	121.39 %	6.704 ± 6.0171	89.75 %

AUC0-t	area under the plasma concentration-time curve from time zero to t hours
AUC0-∞	area under the plasma concentration-time curve from time zero to infinity
Cmax	maximum plasma concentration
Tmax	time for maximum concentration (* median, range)
T1/2	terminal plasma elimination half life
Kel	elimination rate constant
AUC_%Extrap_obs	Percentage of AUC00-∞ due to extrapolation from Tlast to infinity

Table 2. Statistical analysis for atazanavir (ln-transformed values)

Pharmacokinetic parameter	Geometric Mean Ratio Test/Reference	Confidence Intervals	CV%*
$AUC_{(0-t)}$	102.32 %	92.70 – 112.93 %	35.83
$AUC_{(0-\infty)}$	103.92 %	94.30 – 114.54 %	34.40
C_{max}	95.44 %	85.18 – 106.95 %	41.73

Pharmacokinetic parameter	Geometric Mean Ratio Test/Reference	Confidence Intervals	CV% *
* estimated from the Residual Mean Squares			

The clinical report stated that 3 subjects were excluded from the PK analysis. The potential consequences of the selective exclusion of patient data were noted and new pharmacokinetic analysis was requested without subject 64, but including subjects 24 and 26. In addition, a sensitivity analysis was requested in which all the available results were included.

The applicant provided a scientific rationale and the consequences of including or excluding the subjects # 24, 26 and 64. It was agreed that the calculation of Cmax (primary variable) and tmax (secondary variable) would not be affected by the missing samples at the late time-points.

The applicant has demonstrated that the 90 % CI for T/R of AUC0-t (primary variable) and AUC0-∞ (secondary variable) is within the predefined acceptance criteria (80.00 - 125.00 %) even when subjects # 24 and 26 were included in the calculations.

Although, the three subjects were only excluded in the calculation of certain secondary parameters: $AUC_{0-\infty}$, AUC_%Extrap_obs, $t_{1/2}$ and K_{el}. The primary parameters C_{max} and AUC_{0-t} were always calculated including subjects # 24 and 26. Therefore, the new analysis presented is very similar to the original analysis, and the only result which is different is the ln $AUC_{0-\infty}$ ratio.

The comparison between the original and the new analysis in which subjects # 24 and 26 are included and subject # 64 is excluded (both periods) is shown in Table 3.

Table 3. Comparison of the statistical analysis for atazanavir

Parameter	Original analysis		New analysis	
	Ratio %	CI %	Ratio %	CI %
ln AUC (0-t)	102.32	92.70-112.93	102.32	92.70-112.93
ln AUC (0-∞)	103.92	94.30-114.54	102.58	93.14-112.99
C_{max}	95.44	85.18-106.95	95.44	85.18-106.95

Furthermore, the sensitivity analysis performed including subject # 64, demonstrate that the bioequivalence criteria are still met. It is further noted that the questionable (very low) plasma levels observed for subject # 64 were obtained following administration of the reference product. Therefore, these results should not raise concerns over the bioavailability of the test product.

Safety data

In conclusion, Atazanavir Sulfate Capsule 300 mg was well tolerated by all subjects. Two subjects (number 17 and 44) reported adverse event after administration of the reference product. No significant or serious adverse event occurred during the conduct of the study.

Conclusions

The Test Product (T) (Atazanavir Sulfate Capsules 300 mg of Mylan Laboratories Limited, India) when compared with the Reference Product (R) (REYATAZ (Atazanavir sulfate) 300 mg Capsules of BRISTOL-MYERS SQUIBB PHARMA EEIG, United Kingdom) meets the predefined bioequivalence criteria in terms of rate and extent of absorption after administration of single dose as set in the protocol.

The results of study 14-VIN-255 with 300 mg formulation can be extrapolated to the other strengths 150 mg and 200 mg, according to conditions in the relevant Guidelines.

Based on the presented bioequivalence study Atazanavir Mylan is considered bioequivalent with Reyataz.

2.4.3. Pharmacodynamics

No new pharmacodynamic studies were presented and no such studies are required for this application.

2.4.4. Post marketing experience

No post-marketing data are available. The medicinal product has not been marketed in any country.

2.4.5. Discussion on clinical aspects

Based on the presented bioequivalence study Atazanavir Sulfate Capsules 300 mg of Mylan are considered bioequivalent with REYATAZ 300 mg Capsules.

The results of study 14-VIN-255 with Atazanavir Sulfate Capsules 300 mg can be extrapolated to the other strengths 150 mg and 200 mg, as the conditions for biowaiver in the relevant Guidelines have been met.

2.4.6. Conclusions on clinical aspects

Based on the submitted bioequivalence study results the test product Atazanavir Sulfate Capsule 300 mg of Mylan Laboratories Limited, India and the reference REYATAZ 300 mg Capsules. (MAH: Bristol Myers Squibb Pharma EEIG) are considered bioequivalent in adult healthy subjects under fasting conditions.

The results of study 14-VIN-321 with the 300 mg strength capsule formulation can be extrapolated to Atazanavir Sulfate Capsules 150 mg and 200 mg of Mylan Laboratories Limited, India according to the conditions set in the guideline on the Investigation Bioequivalence CPMP/EWP/QWP/1401/98 Rev 1.

2.5. Risk management plan

Safety concerns

Summary of safety concerns	
Important identified risks	PR interval prolongation (both paediatric and adult populations) Hyperbilirubinaemia

Summary of safety concerns	
	Nephrolithiasis Severe skin reactions Cholelithiasis
Important potential risks	QT prolongation Kernicterus Acute renal failure (adults) Angioedema Interstitial nephritis Immune reconstitution inflammatory syndrome
Missing information	Elderly > 65 years Pregnancy and lactation Hepatic impairment Limited safety data in paediatric patients 6-18 years and <6 years (<15 kg)

Pharmacovigilance plan

As current routine pharmacovigilance activities are sufficient, no additional pharmacovigilance activities are recommended.

Risk minimisation measures

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Important identified risk: PR interval prolongation (both paediatric and adult populations)	• Sections 4.4, 4.5, 4.8 and 4.9 of SPC contain transparent warnings on this risk • Sections 2 and 4 of PL advise patients on this risk • The product is prescription only medicine.	None
Important identified risk: Hyperbilirubinaemia	• Sections 4.4, 4.5, 4.6, 4.8 and 4.9 of SPC contain transparent warnings on this risk • Sections 2 and 4 of PL advise patients on this risk • Restricted distribution of atazanavir	None

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Important identified risk: Nephrolithiasis	• Sections 4.4, and 4.8 of SPC contain transparent warnings on this risk • Sections 2 and 4 of PL advise patients on this risk • The product is prescription only medicine.	None
Important identified risk: Severe skin reactions	• Sections 4.4 and 4.8 of SPC contain transparent warnings on this risk • Sections 2 and 4 of PL advise patients on this risk • The product is prescription only medicine.	None
Important identified risk: Cholelithiasis	• Sections 4.4 and 4.8 of SPC contain transparent warnings on this risk • Section 4 of PL advises patients on this risk • The product is prescription only medicine.	None
Important potential risk: QT prolongation	• Sections 4.4 and 4.8 of SPC contain transparent warnings on this risk • Section 4 of PL advises patients on this risk • The product is prescription only medicine.	None
Important potential risk: Kernicterus	• Section 4.2 of SPC contains transparent warnings on this risk • The product is prescription only medicine.	None
Important potential risk: Acute renal failure (adults)	• Sections 4.2, 4.4 and 5.2 of SPC contain transparent warnings on this risk • Section 2 of PL advises patients on this risk • The product is prescription only medicine.	None
Important potential risk: Angioedema	• Sections 4.8 of SPC contain transparent warnings on this risk • Section 4 of PL advises patients on this risk • The product is prescription only medicine.	None
Important potential risk: Interstitial nephritis	• Section 4.8 of SPC contains transparent warnings on this risk • Section 4 of PL advises patients on this risk	None

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	• The product is prescription only medicine.	
Important potential risk: Immune reconstitution inflammatory syndrome	• Sections 4.4 and 4.8 of SPC contain transparent warnings on this risk • Section 2 of PL advises patients on this risk • The product is prescription only medicine.	None
Missing information: Elderly > 65 years	• Section 5.2 of SPC contains transparent warnings on this risk • The product is prescription only medicine.	None
Missing information: Pregnancy and lactation	• Sections 4.2, and 4.6 of SPC contain transparent warnings on this risk • Section 2 of PL advises patients on this risk • The product is prescription only medicine.	None
Missing information: Hepatic impairment	• Sections 4.2, 4.3, 4.4 and 5.2 of SPC contain transparent warnings on this risk • Section 2 of PL advises patients on this risk • The product is prescription only medicine.	None
Missing information: Limited safety data in paediatric patients 6-18 years and <6 years (<15 kg)	• Sections 4.1, 4.2, 4.4, 4.8 and 5.2 of SPC contain transparent warnings on this risk • Sections 3 and 4 of PL advise patients on this risk • The product is prescription only medicine.	None

Conclusion

The RMP V3.0 is acceptable. No new risks have been identified for the generic products that are not recognised for the reference product and there are no outstanding issues.

2.6. PSUR submission

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

2.7. Pharmacovigilance

Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

2.8. Product information

2.8.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.

3. Benefit-risk balance

This application concerns a generic version of atazanavir sulphate capsule formulation. The reference product Reyataz co-administered with low dose ritonavir, is 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.

No nonclinical studies have been provided for this application but an adequate summary of the available nonclinical information for the active substance was presented and considered sufficient. From a clinical perspective, this application does not contain new data on the pharmacokinetics and pharmacodynamics as well as the efficacy and safety of the active substance; the applicant's clinical overview on these clinical aspects based on information from published literature was considered sufficient.

The bioequivalence study forms the pivotal basis with an open label, balanced, randomized single-dose, two-treatment, two-sequence, two-period crossover design. The study design was considered adequate to evaluate the bioequivalence of this formulation and was in line with the respective European requirements. Choice of dose, sampling points, overall sampling time as well as wash-out period were considered adequate. The analytical method was validated. Pharmacokinetic and statistical methods applied were adequate.

The test formulation of Atazanavir Sulfate capsule 300 mg of Mylan met the protocol-defined criteria for bioequivalence when compared with Reyataz 300 mg capsules. The point estimates and their 90% confidence intervals for the parameters AUC_{0-t},, $AUC_{0-\infty}$, and C_{max} were all contained within the protocol-defined acceptance range of [range, e.g. 80.00 to 125.00%]. Bioequivalence of the two formulations was demonstrated.

A benefit/risk ratio comparable to the reference product can therefore be concluded.

The CHMP, having considered the data submitted in the application and available on the chosen reference medicinal product, is of the opinion that no additional risk minimisation activities are required beyond those included in the product information.

4. Recommendation

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of Atazanavir Mylan in co-administered with low dose ritonavir, is 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 is favourable and therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

Conditions and requirements of the Marketing Authorisation

- **Periodic Safety Update Reports**

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

- **Risk Management Plan (RMP)**

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.