COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Atazanavir Accord 150 mg, 200 mg, 300 mg, hard capsules

(atazanavir sulphate)

NL/H/4246/001-003/DC

Date: 4 September 2019

This module reflects the scientific discussion for the approval of Atazanavir Accord 150 mg, 200 mg, 300 mg hard capsules. The procedure was finalised at 20 March 2019. For information on changes after this date please refer to the 'steps taken after finalisation' at the end of this PAR.

List of abbreviations

ASMF	Active Substance Master File
CMD(h)	Coordination group for Mutual recognition and Decentralised procedure for human medicinal products
CMS	Concerned Member State
EDMF	European Drug Master File
EDQM	European Directorate for the Quality of Medicines
EEA	European Economic Area
ERA	Environmental Risk Assessment
ICH	International Conference of Harmonisation
MAH	Marketing Authorisation Holder
Ph.Eur.	European Pharmacopoeia
PL	Package Leaflet
RH	Relative Humidity
RMP	Risk Management Plan
SmPC	Summary of Product Characteristics
TSE	Transmissible Spongiform Encephalopathy

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for Atazanavir Accord 150 mg, 200 mg, 300 mg, hard capsules from Accord Healthcare B.V.

The product, 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 (see SmPC section 4.2).

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).

The choice of Atazanavir Accord in treatment experienced adult and paediatric patients should be based on individual viral resistance testing and the patient's treatment history (see SmPC sections 4.4 and 5.1).

A comprehensive description of the indications and posology is given in the SmPC.

This decentralised procedure concerns a generic application claiming essential similarity with the innovator product Reyataz 150 mg, 200 mg and 300 mg hard capsules which has been registered in the EEA through a centralised procedure (EU/1/03/267) by Bristol-Myers Squibb Pharma EEIG since 2 March 2004.

The concerned member states (CMS) involved in this procedure were Bulgaria (150 strength), Cyprus (150 mg and 300 mg strength), Czech Republic, Germany, Denmark (200 mg and 300 mg strength), Spain, Finland (200 mg and 300 mg strength), Croatia, Ireland (200 mg and 300 mg strength), Italy (200 mg and 300 mg strength), Norway (200 mg and 300 mg strength), Poland, Portugal, Romania, Sweden (200 mg and 300 mg strength), Slovenia, and the United Kingdom.

The marketing authorisation has been granted pursuant to Article 10(1) of Directive 2001/83/EC.

II. QUALITY ASPECTS

II.1 Introduction

Atazanavir Accord is a hard capsule.
150 mg strength - off white to pale yellow coloured granular powder filled in hard gelatin capsules with green opaque cap imprinted with "H" in black colour and light green opaque body imprinted with "A6" in black colour.

200 mg hard capsules - off white to pale yellow coloured granular powder filled in hard gelatin capsules with green opaque cap imprinted with “H” in black colour and light green opaque body imprinted with “A7” in black colour.
300 mg hard capsules - off white to pale yellow coloured granular powder filled in hard gelatin capsules with orange opaque cap imprinted with “H” in black colour and green opaque body imprinted with “A8” in black colour.

The capsules contain as active substance 150 mg, 200 mg or 300 mg of atazanavir as sulphate.

The hard capsules are packed in OPA/Aluminium/PVC-Aluminium blisters and high-density polyethylene (HDPE) bottles closed with a child-resistant polypropylene screw cap with pulp liner.

The excipients are:
Capsule content – lactose monohydrate, crospovidone (E1202), magnesium stearate (E470b)
Capsule shell – gelatin (E441), brilliant blue FCF (E133), iron oxide black (E172) (150 mg strength), iron oxide yellow (E172), titanium dioxide (E171), sunset yellow FCF (E110) (200 mg and 300 mg strength), erythrosine (E127) (300 mg strength)
Black ink – shellac (E904), iron oxide black (E172), potassium hydroxide (E525)

The three capsule strengths are dose proportional.

II.2 Drug Substance

The active substance is atazanavir sulphate, an established active substance that is described in the European Pharmacopoeia (Ph.Eur.). The active substance is slightly soluble in water, freely soluble in ethanol (96%) and practically insoluble in heptane. Different polymorphic forms exist. The polymorphic form A (type I) is used in the manufacturing process of the finished product. Atazanavir sulphate is not hygroscopic and has four chiral centres.

The Active Substance Master File (ASMF) procedure is used for the active substance. The main objective of the ASMF procedure, commonly known as the European Drug Master File (EDMF) procedure, is to allow valuable confidential intellectual property or ‘know-how’ of the manufacturer of the active substance (ASM) to be protected, while at the same time allowing the applicant or marketing authorisation holder (MAH) to take full responsibility for the medicinal product, the quality and quality control of the active substance. Competent Authorities/EMA thus have access to the complete information that is necessary to evaluate the suitability of the use of the active substance in the medicinal product.

<u>Manufacturing process</u>
The manufacturing process of atazanavir sulphate is adequately described. It is divided into the manufacturing of the intermediate consisting of four steps and the manufacturing of the final drug substance consisting of three stages. The drug substance starting materials are

adequately defined. No class 1 solvents are used in the manufacturing process of atazanavir sulphate.

Quality control of drug substance
The active substance specification is considered adequate to control the quality. Batch analytical data demonstrating compliance with this specification have been provided for two batches.

Stability of drug substance
Stability data of thirteen batches of the drug substance have been submitted and assessed. The stability studies are carried out under ICH conditions. During both accelerated and long term conditions none of the tested parameters showed significant changes or up- or downward trends. All results are within the specification. The available stability results are comparable between the two sites. Based on the data submitted, a retest period could be granted of 60 months with storage condition 'Preserve in tight, light resistant containers and store at 25°C, excursions permitted between 15°C and 30°C'.

II.3 Medicinal Product

Pharmaceutical development
The product is an established pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines. The choice of excipients is justified and their functions are explained. The same excipients as present in the reference product were selected. Formulation development mainly consisted of reference product characterisation, optimisation of formulation with regard to the quantities of the selected excipients and optimisation of the wet granulation manufacturing process.

A bioequivalence study has been performed with the 300 mg product strength. A biowaiver of strengths for the 150 mg and 200 mg strengths is applied.

Manufacturing process
The manufacturing process consists of sifting, dry mixing, wet granulation, drying, sifting and milling, prelubrication, lubrication, capsule filling and packing. The process is considered to be a standard manufacturing process. The manufacturing process has been adequately validated according to the relevant European guidelines. Process validation data have been presented for three production scale batches of each capsule strength.

Control of excipients
The excipients comply with the Ph.Eur. requirements. These specifications are acceptable.

Quality control of drug product
The finished product specifications are adequate to control the relevant parameters for the dosage form. The specification includes tests for description, identification, water content, average weight of filled capsule, average net fill content, lock length, dissolution, uniformity of dosage units, related compounds, assay and microbiological quality. Limits in the

specification have been justified and are considered appropriate for adequate quality control of the product.

Satisfactory validation data for the analytical methods have been provided. Batch analytical data from three batches of each capsule strength from the proposed production site have been provided, demonstrating compliance with the specification.

Stability of drug product

Stability data on the drug product have been provided for three batches of each capsule strength stored at accelerated (40°C/75% RH) for six months and long term (25°C/60% RH) for 24 months. The product was stored in the proposed packaging. No significant changes or up- or downward trends in the tested parameters were observed for the product at the tested stability conditions and all results remained well within the specifications. The drug product was shown to be photostable, as no significant changes were observed in the tested parameters when one batch of each capsule strength was directly exposed to UV and fluorescent light.

Based on the provided stability data, a shelf-life was granted of 24 months, without specific storage conditions, can be granted. No additional storage conditions or in-use shelf-life are necessary, based on the results obtained during the 24 months in-use stability study of the proposed product.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies

Except for lactose monohydrate, no materials derived from animal and/or human origin are used in the manufacture of the proposed drug product. Scientific data and/or certificates of suitability issued by the EDQM have been provided and compliance with the Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via medicinal products has been satisfactorily demonstrated.

II.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the member states consider that Atazanavir Accord has a proven chemical-pharmaceutical quality. Sufficient controls have been laid down for the active substance and finished product.

No post-approval commitments were made.

III. NON-CLINICAL ASPECTS

III.1 Ecotoxicity/environmental risk assessment (ERA)

Since Atazanavir Accord is intended for generic substitution, this will not lead to an increased exposure to the environment. An environmental risk assessment is therefore not deemed necessary.

III.2 Discussion on the non-clinical aspects

This product is a generic formulation of Reyataz which is available on the European market. Reference is made to the preclinical data obtained with the innovator product. A non-clinical overview on the pharmacology, pharmacokinetics and toxicology has been provided, which is based on up-to-date and adequate scientific literature. The overview justifies why there is no need to generate additional non-clinical pharmacology, pharmacokinetics and toxicology data. Therefore, the member states agreed that no further non-clinical studies are required.

IV. CLINICAL ASPECTS

IV.1 Introduction

Atazanavir sulphate is a well-known active substance with established efficacy and tolerability. A clinical overview has been provided, which is based on scientific literature. The overview justifies why there is no need to generate additional clinical data. Therefore, the member states agreed that no further clinical studies are required.

For this generic application, the MAH has submitted one bioequivalence study, which is discussed below.

IV.2 Pharmacokinetics

The MAH conducted a bioequivalence study in which the pharmacokinetic profile of the test product Atazanavir Accord 300 mg, hard capsules (Accord Healthcare B.V., Netherlands) is compared with the pharmacokinetic profile of the reference product Reyataz 300 mg hard capsules (Bristol-Myers Squibb, Pharma EEIG, United Kingdom).

The choice of the reference product in the bioequivalence study has been justified. The formula and preparation of the bioequivalence batch is identical to the formula proposed for marketing.

Biowaiver
A biowaiver request for the additional strengths 150 mg and 200 mg is applicable.

The following pre-requisites for a biowaiver for the additional 150 and 200 mg strengths based on the bioequivalence study with the highest strength 300 mg are met:

- all different strengths have been manufactured by the same manufacturing process

- the composition of the different strengths is qualitatively similar and quantitatively dose-proportional.
- based on the provided data, similarity among the three strengths of the test product can be considered shown at the three required physiological pHs.

As such, the waiver for the additional strengths is considered acceptable.

Bioequivalence study

Design

An open label, randomized, two- treatment, two-sequence, two- period, single oral dose, cross-over bioequivalence study was carried out under fasted conditions in 56 healthy male subjects, aged 19-44 years. Each subject received a single dose (300 mg) of one of the two atazanavir formulations. The tablet was orally administered with 240 ml water 30 minutes after the actual start time of a high-fat, high-calorie breakfast. There were two dosing periods, separated by a washout period of five days.

Blood samples were collected at 0.5, 1, 1.33, 1.67, 2, 2.3, 2.7, 3, 3.3, 3.7, 4, 4.3, 4.7, 5, 5.3, 5.7, 6, 6.5, 7, 8, 10, 12, 16, 20, 24, 36, 48 and 72 hours after administration of the products.

The design of the study is acceptable. The procedures followed for a fed study are according to the bioequivalence guideline. The composition of the meal is in line with the recommended high fat (approximately 50 percent of total caloric content of the meal) and high-calorie (approximately 800-1000 kcal) meal, consisting of approximately 150, 250, and 500-600 kcal from proteins, carbohydrate and fats, respectively. The sampling times are sufficient. A washout period of five days is considered appropriate.

Analytical/statistical methods

The analytical method has been adequately validated and is considered acceptable for analysis of the plasma samples. The methods used in this study for the pharmacokinetic calculations and statistical evaluation are considered acceptable.

Results

One subject was withdrawn in Period-II due to medical grounds (i.e. fever with chills and colds). Therefore, 55 subjects were eligible for pharmacokinetic analysis.

Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of atazanavir under fed conditions.

Treatment N=55	**AUC_{0-t}** (ng.h/ml)	**$AUC_{0-\infty}$** (ng.h/ml)	**C_{max}** (ng/ml)	**t_{max}** (h)
Test	12203 ± 5658	12445 ± 5727	2229 ± 870	3.00 (1.67– 5.67)
Reference	12833 ± 5762	13165 ± 6035	2295 ± 750	3.00 (1.67– 5.67)
***Ratio**	0.90 (0.85 – 0.96)	0.90 (0.85 – 0.95)	0.92 (0.83 – 1.00)	--

(90% CI)				

$AUC_{0-\infty}$	area under the plasma concentration-time curve from time zero to infinity
AUC_{0-t}	area under the plasma concentration-time curve from time zero to t hours
C_{max}	maximum plasma concentration
t_{max}	time for maximum concentration
$t_{1/2}$	half-life
CV	coefficient of variation

**ln-transformed values*

Conclusion on bioequivalence study

The 90% confidence intervals calculated for AUC_{0-t}, $AUC_{0-\infty}$ and C_{max} are within the bioequivalence acceptance range of 0.80 – 1.25. Based on the submitted bioequivalence study Atazanavir Accord is considered bioequivalent with Reyataz.

The MEB has been assured that the bioequivalence study has been conducted in accordance with acceptable standards of Good Clinical Practice (GCP, see Directive 2005/28/EC) and Good Laboratory Practice (GLP, see Directives 2004/9/EC and 2004/10/EC).

IV.3 Risk Management Plan

The MAH has submitted a risk management plan, in accordance with the requirements of Directive 2001/83/EC as amended, describing the pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to Atazanavir Accord.

Table 2. Summary table of safety concerns as approved in RMP

Important identified risks	• PR interval prolongation • Nephrolithiasis • Hyperbilirubinaemia • Severe skin reactions • Cholelithiasis • Angioedema • Immune reconstitution inflammatory syndrome (IRIS) • Chronic kidney disease (CKD)
Important potential risks	• QT prolongation • Kernicterus • Acute renal failure (adults) • Interstitial nephritis • Lack of efficacy due to unboosted ATV 'off label use
Missing information	• Pregnancy • Geriatrics

The member states agreed that routine pharmacovigilance activities and routine risk minimisation measures are sufficient for the risks and areas of missing information.

IV.4 Discussion on the clinical aspects

For this authorisation, reference is made to the clinical studies and experience with the innovator product Reyataz. No new clinical studies were conducted. The MAH demonstrated through a bioequivalence study that the pharmacokinetic profile of the product is similar to the pharmacokinetic profile of this reference product. Risk management is adequately addressed. This generic medicinal product can be used instead of the reference product.

V. USER CONSULTATION

A user consultation with target patient groups on the package leaflet (PL) has been performed on the basis of a bridging report making reference to Atazanavir Teva 150 mg, 200 mg and 300 mg hard capsules (SE/H/1398/001-003/DC) and Levetiracetam Hetero 750 mg film-coated tablets (PT/H/515/001-004/DC). The bridging report submitted by the MAH has been found acceptable; bridging is justified for both content and layout of the leaflet.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Atazanavir Accord 150 mg, 200 mg, 300 mg, hard capsules has a proven chemical-pharmaceutical quality and is a generic form of Reyataz 150 mg, 200 mg, 300 mg hard capsules. Reyataz is a well-known medicinal product with an established favourable efficacy and safety profile.

Bioequivalence has been shown to be in compliance with the requirements of European guidance documents.

The Board followed the advice of the assessors.

There was no discussion in the CMD(h). Agreement between member states was reached during a written procedure. The member states, on the basis of the data submitted, considered that essential similarity has been demonstrated for Atazanavir Accord with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 20 March 2019.

STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

Procedure number*	Scope	Product Information affected	Date of end of procedure	Approval/ non approval	Summary/ Justification for refuse