COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Atazanavir Sandoz 100 mg, 150 mg, 200 mg, 300 mg, hard capsules

(atazanavir sulphate)

NL/H/4117/001-004/DC

Date: 23 July 2019

This module reflects the scientific discussion for the approval of Atazanavir Sandoz. The procedure was finalised at 19 September 2018. 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 Sandoz 100 mg, 150 mg, 200 mg, 300 mg, hard capsules from Sandoz B.V.

The product 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 (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 Sandoz 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 100 mg, 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 Germany, France (only the 150 mg , 200 mg, and 300 mg strength), Ireland, Latvia (only the 200 mg and 300 mg strength), Poland, Portugal, Romania, and 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 Sandoz is a hard capsule:
100 mg strength - opaque, blue and white capsule printed with white ink, with "100 mg" on the cap.
150 mg strength - opaque, blue and powder blue capsule printed with white ink, with "150 mg" on the cap.
200 mg strength - opaque, blue capsule printed with white ink, with "200 mg" on the cap.

300 mg strength - opaque red and blue capsule printed with white ink, with “300 mg” on the cap.

The capsules contain as active substance 100 mg, 150 mg, 200 mg or 300 mg of atazanavir as sulphate.

The hard capsules are packed in Aluminium-OPA/Alu/PVC unit dose perforated blisters and high-density polyethylene (HDPE) bottles closed with child-resistant polypropylene closure.

The excipients are:
Capsule content - lactose monohydrate, crospovidone (type A) (E1202), colloidal anhydrous silica (E551), magnesium stearate (E470b)
Capsule shell - gelatin, titanium dioxide (E171), indigotine (E132), red iron oxide (E172) (300 mg strength only)
Printing ink, white - shellac, titanium dioxide (E171), propylene glycol (E1520)

The tablet strengths are dose proportional with respect to the capsule content.

II.2 Drug Substance

The active substance is atazanavir sulphate, an established active substance that is not described in the European Pharmacopoeia (Ph.Eur.). A monograph for atazanavir sulphate is available in the WHO International Pharmacopoeia and a USP monograph for atazanavir sulphate is pending. The active substance shows a pH dependant aqueous solubility over the physiological pH range, which is very poor especially at higher pH values. The active substance is manufactured as polymorphic Form A, but undergoes complete conversion to the Form C during the drug product manufacturing process. The structure of atazanavir sulphate incorporates four stereogenic centres and the drug substance is manufactured as the pure S,S,S,S-enantiomer.

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 comprises five chemical transformation steps. The first two steps, where the starting materials are introduced, include the manufacturing process of the two intermediates used subsequently in the third step. Two further isolated intermediates are produced in steps III and IV while in last step a salt formation occurs. Another starting material is introduced in step IV. No class 1 organic solvents or heavy metal catalysts are

used in the process. The active substance has been adequately characterised and acceptable specifications have been adopted for the solvents and reagents.

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 five full scale batches.

Stability of drug substance

Stability data on the active substance have been provided for five full scaled batches stored at 25°C/60% RH (24 months for 3 batches, 9 months for 1 batch and 6 month for 1 batch) and for 3 full scaled batches at 40°C/75% RH (6 months). No clear trends or changes were seen in any of the tested stability indicating parameters at both storage conditions. A retest period of 36 months without any special storage precautions is granted.

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 explained. The main development studies performed concerned the characterisation of the reference products, optimisation of the formulation and manufacturing process, dissolution method development and performance of comparative *in vitro* dissolution studies.

A bioequivalence study has been performed with the 300 mg product versus the 300 mg reference product. The 300 mg batch used in the study was manufactured according to the finalised composition and manufacturing process at a scale representative for the commercial product. A biowaiver for the 100 mg, 150 mg and 200 mg products was claimed and supported by *in vitro* dissolution studies at three pHs. The pharmaceutical development of the product has been adequately performed.

Manufacturing process

The manufacturing process mainly consists of wet granulation, blending and lubrication, capsule filling and packaging. The manufacturing process has been adequately validated according to relevant European guidelines. Process validation data on the product has been presented for three commercial scale batches per strength. The product is manufactured using conventional manufacturing techniques.

Control of excipients

The excipients comply with the Ph.Eur. or meet the requirements of Regulation 231/2012 (indigotine and red iron oxide). 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, identity of atazanavir and colourants, uniformity of mass, uniformity of dosage units, related substances, dissolution, assay and microbiological quality. The release and shelf-life limits are identical with exception of the related substances limits. 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 production scaled and one smaller batch per strength from the proposed production site have been provided, demonstrating compliance with the specification.

Stability of drug product
Stability data on the product have been provided on three production scaled batches and one smaller batch per strength stored at 25°C/60% RH (18 months), 30°C/65% RH (12 months, part of the batches) and 40°C/75% RH (6 months). The conditions used in the stability studies are according to the ICH stability guideline. The batches were stored in the proposed packaging. Photostability studies were performed in accordance with ICH recommendations and showed that the product stable when exposed to light.

For the three lower strengths a significant decrease in dissolution leading to out-of-specification results was observed after 6 months storage at accelerated conditions (for the 100 mg and 150 mg strength in both the blisters and bottles and for the 200 mg strength only in bottles). No out-of-specification results were observed at the long-term and intermediate storage conditions in any of the tested parameters.

On basis of the data submitted, a shelf-life was granted of 24 months. The labelled storage conditions are 'Do not store above 30°C'.

In use stability data have been provided demonstrating that the 100 mg, 150 mg and 200 mg products remain stable for two months and the 300 mg product remains stable for one month after first opening of the container with declared storage conditions of "Do not store above 30°C".

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies
Lactose monohydrate, magnesium stearate and gelatin are the materials of animal origin used in the drug product. Scientific data and 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 Sandoz 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 Sandoz 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 Sandoz 300 mg hard capsules (Sandoz B.V., The Netherlands) is compared with the pharmacokinetic profile of the reference product Reyataz 300 mg hard

capsules (Bristol-Myers Squibb Pharma EEIG, United Kingdom) in the presence of low-dose of Norvir (ritonavir) 100 mg film-coated tablets (AbbVie Ltd, 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

For 100 mg, 150 mg and 200 mg capsule strengths a biowaiver is accepted based on the bioequivalence study with the highest strength of 300 mg:

- The strengths have been manufactured by the same manufacturing process
- The compositions are qualitatively similar and quantitatively dose proportional
- Furthermore the MAH has demonstrated similarity of *in vitro* dissolution at the pH conditions 0.1N HCl, pH 4.5 and pH 6.8 between the additional lower strengths and the strength used for bioequivalence testing (of the test product), as in all cases the 5% percentile of the bootstrapping interval for f2 was > 50.0%.

Bioequivalence study

Design

A single-dose, randomised, two-period, two-treatment, two-sequence, crossover bioequivalence study was carried out under fed conditions in 36 healthy male subjects, aged 19-41 years in the presence of Norvir 100 mg film-coated tablets (AbbVie Ltd, United Kingdom). 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 seven days.

Blood samples were collected pre-dose and at 0.50, 1.00, 1.33, 1.67, 2.00, 2.33, 2.67, 3.00, 3.33, 3.67, 4.00, 4.33, 4.67, 5.00, 5.50, 6.00, 8.00, 10.00, 12.00, 16.00, 24.00, 36.00, 48.00 and 72.00 hours after administration of the products.

The design of the study is acceptable. As atazanavir sulphate must be taken with food, a study under fed conditions is required.

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 suffering from tonsillitis (fever, cough and cold, body ache) and hence was withdrawn from the study during the washout after period 1. Another subject did not report to the clinical facility for period 2 check-in and hence he was considered as 'dropout' from the study. Three subjects experienced vomiting during period 2 before two times the median

T_{max} and hence were withdrawn from the study. Therefore 31 subjects were eligible for pharmacokinetic analysis.

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

Treatment N=31	AUC_{0-t} (ng.h/ml)	$AUC_{0-\infty}$ (ng.h/ml)	C_{max} (ng/ml)	t_{max} (h)	$t_{1/2}$ (h)
Test	64208 ± 13783	67498 ± 14740	4672 ± 962	3.3 (1.3 – 4.7)	16.5 ± 3.6
Reference	63722 ± 12326	66992 ± 13251	4631 ± 790	3.3 (1.7 – 4.3)	16.7 ± 3.7
***Ratio (90% CI)**	1.01 (0.98 - 1.04)	--	1.01 (0.97 - 1.04)	--	--

$AUC_{0-\infty}$ 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

**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 Sandoz 300 mg hard capsules is considered bioequivalent with Reyataz 300 mg capsules.

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 Sandoz.

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

Important identified risks	• PR interval prolongation (both paediatric and adult populations) • Nephrolithiasis with or without alteration of the renal function • Hyperbilirubinemia • Severe skin reactions

	• Cholelithiasis • Angioedema • Immune reconstitution inflammatory syndrome (IRIS)
Important potential risks	• QT prolongation • Kernicterus • Acute renal failure (adults) • Interstitial nephritis • Lack of efficacy due to unboosted ATV "off label use"
Missing information	• Hepatic impairment • Pregnancy • Paediatric patients <3 months of age • Geriatric patients • Women who are breastfeeding

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 Azatanavir Mylan (content) and Ivabradine 5 mg and 7.5 mg film-coated tablets (lay out). 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 Sandoz 100 mg, 150 mg, 200 mg, 300 mg, hard capsules has a proven chemical-pharmaceutical quality and is a generic form of Reyataz 100 mg, 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 Sandoz with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 19 September 2018.

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