COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Atazanavir Teva 150 mg, 200 mg and 300 mg, hard capsules (atazanavir)

NL/H/5710/001-003/DC

Date: 24 February 2023

This module reflects the scientific discussion for the approval of Atazanavir Teva 150 mg, 200 mg and 300 mg, hard capsules. The procedure was finalised on 22 September 2015 in Sweden (SE/H/1398/01-03/DC). After a transfer on 21 October 2022, the current RMS is the Netherlands. 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
CEP	Certificate of Suitability to the monographs of the European Pharmacopoeia
CHMP	Committee for Medicinal Products for Human Use
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
EMA	European Medicines Agency
ICH	International Conference of Harmonisation
MAH	Marketing Authorisation Holder
Ph.Eur.	European Pharmacopoeia
PL	Package Leaflet
RH	Relative Humidity
RMP	Risk Management Plan
RMS	Reference Member State
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 Teva 150 mg, 200 mg and 300 mg, hard capsules from Teva Nederland B.V.

For the indication and posology of the product, see the current Summary of Product Characteristics (SmPC).

This decentralised procedure concerns a generic application claiming essential similarity with the innovator product Reyataz 150 mg and 200 mg, hard capsule from Bristol-Myers Squibb Pharma EEIG, which has been registered in the European Union since 2 March 2004 under the centralized procedure EU/1/03/267.

The concerned member states (CMS) involved in this procedure were: Belgium, Germany, Denmark, Estonia (only for 300 mg), Finland, France, Ireland, Iceland, Italy, Lithuania, Latvia, Malta, the Netherlands, Norway (only for 200 & 300 mg), Poland, Portugal, Romania, Spain (only for 200 & 300 mg) 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

The structure of the drug substance has been adequately proven and its physico-chemical properties are sufficiently described.

II.2 Drug Substance

Manufacturing process

The manufacture of the drug substance has been adequately described and satisfactory specifications have been provided for starting materials, reagents and solvents.

Quality control of drug substance

The drug substance specification includes relevant tests and the limits for impurities and degradation products have been justified. The analytical methods applied are suitably described and validated.

Stability of drug substance

Stability studies confirm the retest period.

II.3 Medicinal Product

Manufacturing process
The manufacturing process has been sufficiently described and critical steps identified.

Control of excipients
The medicinal product is formulated using excipients listed in section 6.1 in the Summary of Product Characteristics.

Quality control of drug product
The tests and limits in the specification are considered appropriate to control the quality of the finished product in relation to its intended purpose.

Stability of drug product
Stability studies have been performed and data presented support the shelf life and special precautions for storage claimed in the Summary of Product Characteristics, sections 6.3 and 6.4.

III. NON-CLINICAL ASPECTS

III.1 Discussion on the non-clinical aspects

Since this product has been shown to be essentially similar and refer to a product approved based on a full application with regard to preclinical data, no further such data have been submitted or are considered necessary.

IV. CLINICAL ASPECTS

IV.1 Pharmacokinetics

There are no data on absolute oral bioavailability of atazanavir. Following multiple oral doses of atazanavir 300 mg once daily with ritonavir 100 mg once daily with food to HIV infected patients, maximal plasma concentrations occur at approximately 2.5 hours. Concomitant food intake increases the C_{max} and AUC and decreases the coefficient of variation of AUC and C_{max} and therefore atazanavir should be administered with food. The pharmacokinetics is non-linear. There was a more than dose-proportional increase in AUC and C_{max} in fasted and fed healthy volunteers after 200-800 mg atazanavir. The mean half-life is 12 hours at steady state (in HIV-infected adult patients) following a dose of 300 mg daily together with ritonavir 100 mg daily with a light meal.

Bioequivalence study and biowaiver
Design
Bioequivalence was evaluated in one single-dose, two-way crossover study conducted in 59 healthy volunteers, comparing Atazanavir, 300 mg, hard capsules, manufactured by PLIVA

Croatia Ltd., Croatia with Reyataz 300 mg, hard capsules, by Bristol-Myers Squibb Pharma EEIG from the German market under fed conditions (high-fat high-calorie meal). Test and reference product were co-administered with 100 mg ritonavir in accordance with SmPC recommendations. The study was conducted at Pharma Medica Research Inc, Toronto, Ontario, Canada between 13th and 22nd July 2013. Blood samples were collected pre-dose and up to 48 hours post-dose. The study design is considered acceptable.

Analytical/statistical methods
Plasma concentrations of atazanavir were determined with an adequately validated achiral LC/MS/MS method.

Results
For AUC_{0-t} and C_{max} the 90% confidence interval for the ratio of the test and reference products fell within the conventional acceptance range of 80.00-125.00%.

Conclusion on bioequivalence study and biowaiver:
From a pharmacokinetic point of view, absence of studies with the additional strengths 150 and 200 mg is acceptable, as the pharmacokinetics of atazanavir is non- linear with a more than dose-proportional increase in AUC and C_{max} between 200 mg and 800 mg. The biowaiver is also acceptable from a quality perspective.

IV.2 Discussion on the clinical aspects

Since this product has been shown to be essentially similar and refer to a product approved based on a full application with regard to clinical efficacy/safety data, no further such data have been submitted or are considered necessary.

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 Teva.

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

Important identified risks	• PR interval prolongation • Hyperbilirubinaemia • Nephrolithiasis • Severe skin reactions • Cholelithiasis
Important potential risks	• QT prolongation • Kernicterus • Acute renal failure (adults) • Angioedema • Interstitial nephritis

	• Immune reconstitution inflammatory syndrome (IRIS)

Missing information	• Pregnancy
	• Hepatic impairment
	• Paediatric population:
	  ○ Safety data in paediatric patients <6 years (<15 kg)
	  ○ Limited safety data in children 6 years to less than 18 years of age.

Pharmacovigilance Plan
Routine pharmacovigilance is suggested and no additional pharmacovigilance activities are proposed by the applicant, which is endorsed.

Risk minimisation measures
Routine risk minimisation is suggested and no additional risk minimisation activities are proposed by the applicant, which is endorsed.

Summary of the RMP
The RMP is approved.

V. USER CONSULTATION

The package leaflet has been evaluated via a user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC. The language used for the purpose of user testing the PIL was English. The results 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.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

The quality of the generic product, Atazanavir Teva, is found adequate. There are no objections to approval of Atazanavir Teva, from a non-clinical and clinical point of view. Bioequivalence between the test and reference product has been adequately demonstrated. The product information is acceptable. Therefore, the decentralised procedure for Atazanavir Teva 150 mg, 200 mg and 300 mg, hard capsules was positively finalised on 22 September 2015.

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
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