LÄKEMEDELSVERKET
MEDICAL PRODUCTS AGENCY

Public Assessment Report
Scientific discussion

Atazanavir Teva
(atazanavir)

SE/H/1398/01-03/DC

This module reflects the scientific discussion for the approval of Atazanavir Teva. The procedure was finalised on 2015-09-22. For information on changes after this date please refer to the module 'Update'.

Postadress/Postal address: P.O. Box 26, SE-751 03 Uppsala, SWEDEN
Besöksadress/Visiting address: Dag Hammarskjölds väg 42, Uppsala
Telefon/Phone: +46 (0)18 17 46 00 Fax: +46 (0)18 54 85 66
Internet: www.mpa.se E-mail: registrator@mpa.se

I. INTRODUCTION

The application for Atazanavir Teva, 150 mg, 200 mg and 300 mg, capsule, hard is a generic application made according to Article 10(1) of Directive 2001/83/EC. The applicant, Teva Sweden AB, applies through the Decentralised Procedure with Sweden acting as reference member state (RMS) and the following member states as concerned member states (CMS):

CMS 150 mg: BE, DE, DK, FI, FR, IE, IS, IT, LT, LV, MT, NL, PL, PT, RO and UK
CMS 200 mg: BE, DE, DK, ES, FI, FR, IE, IS, IT, LT, LV, MT, NL, NO, PL, PT, RO and UK
CMS 300 mg: BE, DE, DK, EE, ES, FI, FR, IE, IS, IT, LT, LV, MT, NL, NO, PL, PT, RO and UK

The reference medicinal product chosen for the purposes of establishing the expiry of the data protection period is Reyataz, 150 mg and 200 mg, capsule, hard authorised in the community (centralised procedure) since 2004, with Bristol-Myers Squibb Pharma EEIG as marketing authorisation holder.
The reference product used in the bioequivalence study is Reyataz, 300 mg, capsule, hard from Germany with Bristol-Myers Squibb Pharma EEIG as marketing authorisation holder.

For approved indications, see the Summary of Product Characteristics.

For recommendations to the marketing authorisation not falling under Article 21a/22 of Directive 2001/83 and conditions to the marketing authorisation pursuant to Article 21a or 22 of Directive 2001/83/EC to the marketing authorisation, please see section VI.

II. QUALITY ASPECTS

II.1 Drug Substance

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

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

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 studies confirm the retest period.

II.2 Medicinal Product

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

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

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

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.

Safety specification

Summary table of safety concerns as approved in RMP

Summary of safety concerns	
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.
The application is therefore recommended for approval.

List of recommendations not falling under Article 21a/22 of Directive 2001/83 in case of a positive benefit risk assessment

N/A

List of conditions pursuant to Article 21a or 22 of Directive 2001/83/EC

N/A

VII. APPROVAL

The Decentralised procedure for Atazanavir Teva, 150 mg, 200 mg and 300 mg, capsule, hard was positively finalised on 2015-09-22.

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Public Assessment Report – Update

Scope	Procedure number	Product Information affected	Date of start of the procedure	Date of end of procedure	Approval/ non approval	Assessment report attached
						Y/N (version)

Postadress/Postal address: P.O. Box 26, SE-751 03 Uppsala, SWEDEN
Besöksadress/Visiting address: Dag Hammarskjölds väg 42, Uppsala
Telefon/Phone: +46 (0)18 17 46 00 Fax: +46 (0)18 54 85 66
Internet: www.mpa.se E-mail: registrator@mpa.se