EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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Committee for Medicinal Products for Human Use (CHMP)

CHMP assessment report

Atazanavir Krka

International non-proprietary name: atazanavir

Procedure No. EMEA/H/C/004859/0000

Note

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

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List of abbreviations

AESI	AEs of special interest
AGP	α1-acid glycoprotein
ANOVA	Analysis of variance
ANSM	National Agency for the Safety of Medicine and Health Products
AP	Applicant's Part (or Open Part) of a ASMF
API	Active Pharmaceutical Ingredient
AR	Assessment Report
ASM	Active Substance Manufacturer
ASMF	Active Substance Master File = Drug Master File
ATV	Atazanavir
AUC	Area Under the plasma Concentration
AUC0-inf	Area Under the plasma Concentration-time curve from time zero to infinity
AUC0-t	Area Under the plasma Concentration-time curve from time zero to t hours
BP	British Pharmacopoeia
CEP	Certificate of Suitability of the European Pharmacopoeia
Cmax	maximum plasma concentration
CMS	Concerned Member State
CoA	Certificate of Analysis
CRO	Certified Research Organisation
CRS	Chemical Reference Substance (official standard)
CV	Coefficient of Variation
DMF	Drug Master File = Active Substance Master File
DP	Decentralised (Application) Procedure
EMA	European Madicines Agency
ERA	Enviromental Risk Assessment
EU	European Union
GCP	Good Clinical Practice
ICH	International Conference on Harmonisation
IPC	In-process control
IR	Infrared
IS-normalized MF	Internal Standard-normalised Matrix Factor
ISR	Incurred Sample Reanalysis
IU	International Units
K2EDTA	dipotassium ethylenediaminetetraacetic acid
LC-MS/MS	liquid chromatography coupled with tandem mass spectrometry
LLOQ	Lower Limit of Quantification
LOA	Letter of Access
LOD	Limit of Detection
LOQ	(1) Limit of Quantification, (2) List of Questions
LOQ	Limit of Quantification
LoQ	List of Questions
MA	Marketing Authorisation
MA	Marketing Authorisation
MAA	Marketing Authorization Application
MAH	Marketing Authorisation holder
MS	Mass Spectrometry
ND	Not detected
NLT	Not less than
NMR	Nuclear Magnetic Resonance
NMT	Not more than
OOS	Out of Specifications
PDE	Permitted Daily Exposure
Ph. Eur.	European Pharmacopoeia
PK	pharmacokinetic
PL	Patient Leaflet
QC	Quality Control (samples)
QOS	Quality Overall Summary
RH	Relative Humidity

RMS	Reference Member State
RP	Restricted Part (or Closed Part) of a ASMF
RRT	Relative retention time
RSD	Relative standard deviation
SmPC	Summary of Product Characteristics
SOP	Standard Operating Procedure
STD	Standard Deviation
t1/2	terminal elimination half-life
TDM	Therapeutic Drug Monitoring
tmax	time to maximum plasma concentration
TTC	Threshold of toxicological concern
USP/NF	United States Pharmacopoeia/National Formulary
UV	Ultraviolet
XRD	X-Ray Diffraction

1. Background information on the procedure

1.1. Submission of the dossier

The applicant KRKA, d.d., Novo mesto submitted on 8 March 2018 an application for marketing authorisation to the European Medicines Agency (EMA) for Atazanavir Krka, 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 22 June 2017.

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, as defined in Article 10 (2)(a) of Directive 2001/83/EC, 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 Krka capsules, 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".

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.

The chosen reference product is:

Medicinal product which is or has been authorised in accordance with Union provisions in force for not less than 10 years in the EEA:

- Product name, strength, pharmaceutical form: Reyataz
- Marketing authorisation holder: Bristol-Myers Squibb Pharma EEIG
- Date of authorisation: 02-03-2004
- Marketing authorisation granted by:
  - Union
- Marketing authorisation number: EU/1/03/267/003-004, EU/1/03/267/005-006, EU/1/03/267/008-010

Medicinal product authorised in the Union/Members State where the application is made or European reference medicinal product:

- Product name, strength, pharmaceutical form: Reyataz
- Marketing authorisation holder: Bristol-Myers Squibb Pharma EEIG
- Date of authorisation: 02-03-2004
- Marketing authorisation granted by:
  - Union
- Marketing authorisation number: EU/1/03/267/003-004, EU/1/03/267/005-006, EU/1/03/267/008-010

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

- Product name, strength, pharmaceutical form: Reyataz, 300mg, capsule, hard
- Marketing authorisation holder: Bristol-Myers Squibb Pharma EEIG
- Date of authorisation: 02-03-2004

- Marketing authorisation granted by:
  - Union
- Marketing authorisation number: EU/1/03/267/008-010
- Bioavailability study number: 2017-4324

Information on paediatric requirements

Not applicable

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

1.2. Steps taken for the assessment of the product

The Rapporteur appointed by the CHMP was:

Rapporteur: Tomas Boran

The application was received by the EMA on	8 March 2018
The procedure started on	29 March 2018
The Rapporteur's first Assessment Report was circulated to all CHMP members on	18 June 2018
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC members on	2 July 2018
The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on	26 July 2018
The applicant submitted the responses to the CHMP consolidated List of Questions on	14 September 2018
The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on	22 October 2018
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	31 October 2018
The CHMP agreed on a list of outstanding issues in writing and/or in an oral explanation to be sent to the applicant on	15 November 2018
The applicant submitted the responses to the CHMP List of Outstanding Issues on	19 December 2018
The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP members on	16 January 2019
The CHMP, in the light of the overall data submitted and the scientific	31 January 2019

discussion within the Committee, issued a positive opinion for granting a marketing authorisation to Atazanavir Krka on	

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 optimised (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.

The product atazanavir 150, 200 and 300 mg, hard capsules was developed as a generic equivalent to the innovator´s product Reyataz (atazanavir) 300 mg, hard capsules. The active substance of this product is atazanavir sulfate. The innovator´s product was authorised in EU on 2.3.2004. The marketing authorization holder is Bristol-Myers Squibb Pharma EEIG, UK.

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 hard 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 sulfate) as active substance.

Other ingredients are:

Capsule contents: lactose monohydrate, crospovidone (type A), magnesium stearate

Capsule shell cap (150 mg and 200 mg): titanium dioxide (E171), yellow ferric oxide (E172), red ferric oxide (E172), gelatine

Capsule shell body (150 mg and 300 mg): titanium dioxide (E171), gelatine

Printing ink (150 mg and 200 mg): shellac, black ferric oxide (E172), potassium hydroxide

Capsule shell body (200 mg): titanium dioxide (E171), yellow ferric oxide (E172), red ferric oxide (E172), gelatine

Capsule shell cap (300 mg): titanium dioxide (E171), yellow ferric oxide (E172), red ferric oxide (E172), black ferric oxide (E172), gelatine

Printing ink (300 mg): shellac, titanium dioxide (E171), potassium hydroxide.

The product is available in HDPE tablet container with child-resistant tamper evident PP with desiccant closure as described in section 6.5 of the SmPC.

2.2.2. Active substance

General information

The chemical name of atazanavir sulfate 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 $C_{38}H_{54}N_6O_{11}S$. It has a relative molecular mass of 802.93 and the following structure:

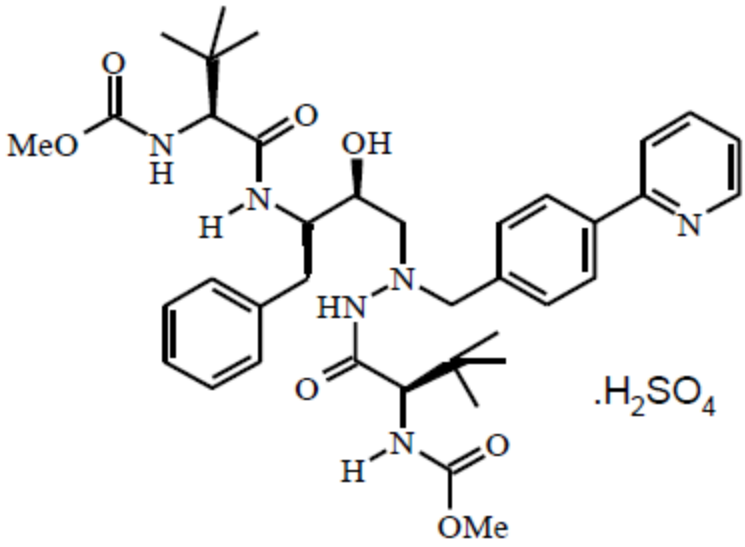

Figure 1: active substance structure

The chemical structure of the active substance was elucidated by a combination of high resolution mass spectrometry (HRMS), mass spectroscopy, NMR spectroscopy (^{1}H NMR), IR spectroscopy, UV spectroscopy and identification by HPLC. The solid state properties of the active substance were measured by X-Ray diffraction.

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 that originate in the starting materials and synthesis. Enantiomeric purity of the active substance is controlled routinely by specific optical rotation and by the HPLC method in the active substance specifications.

Polymorphism for atazanavir sulphate has been recorded in literature. The manufacturing process consistently produces the required form (Form-A or Type-I) 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

The information on atazanavir sulphate is provided according to the Active Substance Master File (ASMF) procedure. 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 multiple manufacturers are responsible for different steps of the active substance production. Atazanavir sulfate is synthesised in a convergent process in six main steps using well-defined starting materials with acceptable specifications. Each intermediate is

provided by two suppliers using different synthetic routes which was supported by data and found acceptable. One of the starting materials was re-defined during the procedure at the request of CHMP in order to ensure that critical steps and enough of the synthetic process are included in the dossier, thereby ensuring the quality of the active substance throughout its life cycle.

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 double LDPE bags which comply with the EC directive 2002/72/EC and EC 10/2011 as amended. These are stored inside a triple laminated sunlight barrier which is heat-sealed and placed in a HDPE container.

Specification

The active substance specification includes tests for appearance, solubility in MeOH and water (Ph. Eur.), identification (IR, HPLC, sulfate test), water content (KF), sulfated ash (Ph. Eur.), sulfate content (in house), specific optical rotation (Ph. Eur.), enantiomeric purity (isocratic HPLC), impurities (HPLC), assay (HPLC), residual solvents (GC) and other product specific requirements.

Impurities are all limited to below the qualification threshold according to ICH Q3A. Potential genotoxic impurities have limits either in accordance with ICH M7 Note 7 or TTC.

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 five production and one pilot scale batches of the active substance tested by the finished product manufacturer are provided. Additional supportive data on numerous batches of different sizes tested by the active substance manufacturer were also provided. The results are within the specifications and consistent from batch to batch.

Stability

Stability data from 21 active substance batches of different scales from the proposed manufacturer stored in the intended commercial package for up to 60 months under long term conditions (25 ºC / 60% RH), for up to 60 months under intermediate conditions (30 ºC / 65% RH) and for up to 6 months under accelerated conditions (40 ºC / 75% RH) according to the ICH guidelines were provided. Photostability testing following the ICH guideline Q1B was performed on two batches. Results on stress conditions (acid, base, peroxide, heat and light) were also provided.

The following parameters were tested*:* appearance, water content (KF), specific optical rotation (Ph. Eur.), enantiomeric purity (isocratic HPLC), impurities (HPLC), assay (HPLC) and microbiological. The parameters tested are the same as for release. The analytical methods used were the same as for release and were stability indicating.

All tested parameters were within the specifications. Forced degradation studies revealed that there is significant appearance of known impurities. The active substance is not sensitive to light.

The stability results indicate that the active substance manufactured by the proposed supplier is sufficiently stable. The stability results justify the proposed retest period of 60 months 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 yellowish-white to yellow-white powder. Atazanavir 150 mg capsules are size no. 1, the body of the capsule is white or almost white colour, the cap of the capsule is brownish-orange colour. The capsule cap is imprinted with black mark A150. Atazanavir 200 mg capsules are size no. 0, the body and the cap of the capsule are brownish-orange colour. The capsule cap is imprinted with black mark A200. Atazanavir 300 mg capsules are size no. 00, the body of the capsule is white or almost white colour, the cap of the capsule is dark brown colour. The capsule cap is imprinted with white mark A300. These characteristics are considered sufficient to distinguish different capsule strengths.

The aim of pharmaceutical development was to develop a product essentially similar with the originator product (i.e. reference product) and to design a product of specified quality and its manufacturing process to consistently deliver the intended performance of the product, e.g. easily manufactured, stable formulation in proposed packaging.

Atazanavir sulphate is known to exhibit polymorphism as it is described in literature but the commercial process produces exclusively a non-solvated, highly crystalline form designed as form A.

According to the reference product, Reyataz's EPAR, atazanavir sulphate undergoes polymorphic transition during the wet granulation operation and polymorphic transition (from highly crystalline form A to less crystalline hydrate form) during the granulation is crucial for *in vitro* dissolution profiles. Based on the data presented regarding the finished product manufacturing process, it was shown that that the process is well-defined and the polymorphic transition is consistent in every batch.

Atazanavir is poorly soluble substance according to the BCS (class II); hence its particle size might affect dissolution behaviour and biopharmaceutical characteristics of the medicine. However, the effect of particle size on dissolution rate is less pronounced due to polymorphic transition of active ingredient which occurs during the wet granulation phase. Nevertheless, the effect of particle size on dissolution behaviour was evaluated and a particle size limits were established.

Development of the finished product was based on qualitative and quantitative composition of the reference product. Differences compared to the reference product's formulation were appropriately justified.

Formulation development was based on the highest strength and the other two strengths were prepared as dose proportional (same qualitative and quantitative composition of the capsulating mixture and proportionally reduced capsule filling weight).

To establish bioequivalence between Krka's atazanavir formulation and Reyataz a single dose bioequivalence study under fed conditions was performed. The reference product is to be taken with food. Therefore, the bioequivalence study was performed under the same conditions. The pharmacokinetics of atazanavir are dose proportional in the dosing range. For such cases a bioequivalence study using the highest strength is recommended which is 300 mg in this case. The 200 mg and 150 mg strengths were manufactured by the same manufacturing process, the qualitative composition of the strengths is the same and the composition the capsule content is quantitatively proportional. Appropriate *in vitro* dissolution data have been provided for all strengths. Therefore, a biowaiver for lower strengths was considered justified. Furthermore, the reference batches used in the study were representative for the reference formulation. The BEQ batch used in the study has the same composition and has been manufactured on the same type of equipment as the one to be marketed.

Additional dissoulution data was generated at the request of the CHMP. . Similarity of dissolution profiles between 300 mg, 200 mg and 150 mg has been demonstrated.

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 discriminatory power of the dissolution method has been demonstrated with regards to changes in composition and manufacturing process parameters.

At the request of CHMP the limit for dissolution was revised in order to ensure the satisfactory control of the finished product.

The primary packaging is HDPE tablet container with child-resistant tamper evident PP with desiccant closure. The material complies 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 11 main steps: sieving, mixing, granulating, drying and sieving of granulate, IPC of granulate, sieving, blending, IPC of capsulating mixture, capsulating, IPC of capsules and 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 shown in Table 5 include appropriate tests for this kind of dosage form: appearance (visually), water (Ph. Eur.), uniformity of dosage units – mass variation (Ph. Eur.), identification of atazanavir (HPLC, DAD), impurities (in house), dissolution (Ph. Eur.), content of atazanavir (in house) and microbiological quality (Ph. Eur.).

To evaluate the presence of elemental impurities in the finished product, a risk assessment in line with ICHQ3D guideline was performed using component approach. The results showed that elemental impurities are set in accordance with ICH Q3D. It was concluded that there is no need to specify any elemental impurities in final product in line with ICHQ3D guideline.

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 3 commercial scale batches of each capsule strength confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification.

The finished product is released on the market based on the approved specifications, through traditional final product release testing.

Stability of the product

Stability data from 3 commercial scale batches of each strength of the finished product stored for up to 12 months under long term conditions (25 ºC / 60% RH) and for up to 6 months and under accelerated

conditions (40 ºC / 75% RH) according to the ICH guidelines were provided. The batches of medicinal product are identical to those proposed for marketing and were packed in the primary packaging representative to that proposed for marketing.

Samples were tested for appearance, water, uniformity of dosage units – mass variation, identification of atazanavir, impurities, dissolution, content of atazanavir and microbiological purity. The analytical procedures used are stability indicating. Neither significant changes nor trends have been observed. Nevertheless, since the pharmaceutical form is gelatine capsule a temperature limit according to the Ph. Eur. Monograph for Capsules 'Store at a temperature not exceeding 30°C' is justified.

In addition, one batch of each of the capsule strengths batches was exposed to light as defined in the ICH Guideline on Photostability Testing of New Drug Substances and Products. No significant changes of tested parameters have been observed.

The results of the in use stability studies have been provided.

Based on available stability data, the proposed shelf-life of 2 years when stored below 30 °C in the container tightly closed in order to protect from moisture as stated in the SmPC (section 6.3) are acceptable. Shelf life after first opening is 2 months, stored below 25 °C.

Adventitious agents

It is confirmed that the lactose 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.

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

Not applicable.

2.3. Non-clinical aspects

2.3.1. Introduction

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. 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.

Therefore, the CHMP agreed that no further non-clinical studies are required.

2.3.2. Pharmacology, Pharmacokinetics and Toxicology

The non-clinical overview has been written by *(confidential information deleted)*, an independent researcher in Krka d.d., Novo mesto, Slovenia. The overview is dated on March 2018. The report refers to 56 references up to year 2017.

The CHMP considers that the non-clinical overview on the pre-clinical pharmacology, pharmacokinetics and toxicology is adequate.

No novel excipients are used. The qualitative composition of the Atazanavir Krka and the originator Reyataz is same. Quantitatively, the products differ in amount of magnesium stearate. Justification focusing on paediatric population has been provided. From toxicological perspective there are no concerns regarding the used excipients.

Adequate discussion regarding to impurity profile, residual solvents and degradants was provided. Impurity profile of Atazanavir Krka product and the originator are comparable. Limits for elemental impurities in the drug product are below the permitted daily exposures based on ICH Q3D.

The instructions on use of the compounds during pregnancy and lactation and preclinical safety data contained in the proposed SmPC reflect the characteristics of the substances and are fully in line with the SmPC of the reference product Reyataz (PI: EMEA/H/C/000494 -WS/1292, updated on 21/03/2018).

2.3.3. Ecotoxicity / environmental risk assessment

No Environmental Risk Assessment studies were submitted. This was justified by the applicant as the introduction of Atazanavir Krka hard capsules 150 mg, 200 mg, 300 mg manufactured by Krka 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. Thus, the ERA is expected to be similar.

2.3.4. Conclusion on the non-clinical aspects

A non-clinical overview on the pharmacology, pharmacokinetics and toxicology for atazanavir hard capsules 150 mg, 200 mg, 300 mg 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 (T_{max} 2.5 h) and demonstrates nonlinear pharmacokinetics, resulting in greater than dose-proportional increases in bioavailability (AUC and C_{max}) 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.

2.4.2. Pharmacokinetics

The applicant has submitted one single dose bioequivalence study *(confidential information deleted)* under fed condition in support of this application.

Bioequivalence study *(confidential information deleted)***:**

Title of Study:

A Single-Dose, Comparative Bioavailability Study of Two Formulations of Atazanavir 300 mg Capsules under Fed Conditions.

The objective of this study was to evaluate the comparative bioavailability between atazanavir 300 mg capsules, hard (manufactured by *(confidential information deleted)*) and Reyataz (atazanavir) 300 mg hard capsules (MAH: Bristol-Myers Squibb Pharma EEIG, United Kingdom, EU) after a single-dose in healthy subjects under fed conditions.

Methods

Sponsor	Krka, d. d., Novo mesto Šmarješka Cesta 6 8501 Novo mesto
CRO	**Clinical Facility:** Pharma Medica Research Inc. 4770 Sheppard Avenue East Toronto, Ontario, Canada, M1S 3V6 **Clinical Laboratory Facility:** Alpha Laboratories Incorporated 1262 Don Mills Road Toronto, Ontario, Canada, M3B 2W7 **Bioanalytical, Pharmacokinetic and Statistical Facility:** Pharma Medica Research Inc. 6100 Belgrave Road Mississauga, Ontario, Canada, L5R 0B7
Protocol identification No.	2017-4324
Study initiation date:	September 23, 2017
Study completion date:	October 30, 2017
Principal investigator	*(confidential information deleted)*
Date of the study protocol Date of the study report	July 28, 2017 (version 1) January 2018
Analytical Phase Dates	October 06, 2017 - October 24, 2017
Date of the Analytical Report	December 14, 2017

Date of the Validation Report	Method Validation Report: January 2012 Latest Amendment No. 5: September 2017

Study design

This was an open-label, single-dose, randomised, two-period, two-treatment, two sequence, crossover study to evaluate the comparative bioavailability of atazanavir in healthy male and female subjects under fed conditions.

According to the EMA Guidance (CPMP/EWP/QWP/1401/98 Rev.1 Cor**) the design of the study is considered adequate. The test product is immediate release formulation; therefore a single dose bioequivalence study is appropriate.

Test and reference products

Atazanavir Krka 300 mg manufactured by *(confidential information deleted)*, (batch No. 82460717, manufacturing date; exp. Date January 2018) has been compared to Reyataz 300 mg manufactured by (Batch No. AAN4140, exp. Date March 2018).

Table 6: Test and reference product information

Product Characteristics	Test product	Reference Product
Name	Atazanavir 300 mg capsules, hard	Reyataz® (atazanavir) 300 mg hard capsules
Strength	300 mg	300 mg
Dosage form	hard capsules	hard capsules
Manufacturer	[redacted]	
Batch number	82460717	AAN4140
Batch size (Biobatch)	120, 000 capsules	
Measured content(s)[1] (% of label claim)	99.3 %	99.9 %
Commercial Batch Size	120, 000 capsules	
Expiry date (Retest date)	January 2018	03.2018
Location of Certificate of Analysis	Appendix 16.1.6	Appendix 16.1.6
Member State where the reference product is purchased from:		Austria
This product was used in the following trials:	17-558	17-558

[1] List for each active substance for fixed combinations

Population studied

Sample size determination

In-house data indicated a coefficient of variation (CV) for atazanavir C_{max} of approximately 28%. Assuming a 30% intra-subject variability and a difference between the treatment means of 5% or less, the necessary sample size for a 90% probability of the 90% CI of the treatment means ratio to be within the 80.00 to 125.00% range was estimated to be 52 subjects.

Six (6) extra subjects were included into the study to account for potential dropouts. Therefore, 58 subjects were enrolled into this study. Only volunteers who were dosed were considered enrolled.

Fifty-eight (58) subjects were enrolled in the study and 56 subjects completed the study. Fifty-seven (57) subjects received the test product (Treatment A) and 57 subjects received the reference product (Treatment B). The subjects were healthy volunteers between 23 – 55 years of age with body mass index (BMI) between 20,3 – 29,5 kg/m^2. Overall 33 subjects were of White race, 9 Asian, 15 Black or African American and 1 American Indian/Alaska Native.

There were 2 discontinued subjects:

Subject *(confidential information deleted)* – was withdrawn from the study prior to period 2 due to non-compliance (positive THC test)

Subject *(confidential information deleted)* – was withdrawn from the study prior to period 2 due to adverse event (electrocardiogram QT prolonged)

Concomitant medication

There were no concomitant medications used during this study.

Protocol deviations

Subject *(confidential information deleted)* - consumed a caffeine-containing drink approximately 24 hours prior to Period 2 drug administration.

Subject *(confidential information deleted)* - One check-in blood sample was centrifuged 1 minute late.

Subject *(confidential information deleted)* - was to be excluded from the statistical dataset due to low concentrations of the reference product; however, the subject was included in the statistical dataset due to the Sponsor's request.

Analytical methods

Atazanavir was analysed by the validated LC/MS/MS method at the Bioanalytical Laboratory of Pharma Medica Research Inc. The method involved a protein precipitation extraction. *(confidential information deleted)*

Total number of subject samples analysed was two thousand, three hundred and seventy-four (2374). Subjects 09 and 55 were dismissed from the study prior to Period 2. These subjects were excluded from the PK analysis. The samples were received from the Pharma Medica Research Inc. Clinical Facility in good condition and were stored at -25 ± 10 °C along with the quality control samples.

Study sample assays were supported by assay performance data generated at the time of analysis. A minimum of sixteen (16) QC samples (four at each concentration level) were included in each analytical batch. The results of inter-day QC samples accuracy and precision were 100.6% - 103.5% and 2.3% - 3.7%CV, respectively.

Two (2) plasma samples from 2374 study samples were repeated for atazanavir. At least 2/3 of the total samples selected for ISR evaluation met the percent difference criteria of ≤20.0% between original and re-assayed concentrations as outlined in the Guideline on Bioanalytical Method Validation.

The method was validated before initiation of study samples analyses. The following parameters were addressed: linearity and calibration curve range, sensitivity, precision and accuracy, selectivity in the presence of endogenous components of normal, lipaemic and haemolysed plasma, selectivity in the presence of concomitant medication including hormonal contraceptives, carry-over test, extraction recovery of both the analyte and the internal standard, matrix effect, dilution integrity accuracy and precision, stability of analyte and internal standard in the stock and working solutions, short-term and long-term stability in the biological matrix, freeze-thaw stability in human plasma and stability of extracted samples. Each validation parameter was assessed. The validation results were acceptable and in line with the requirements of the Guideline on Bioanalytical Method Validation.

The stability results demonstrated that atazanavir and internal standard were stable under the conditions of study samples collection, shipment, treatment and analysis. The longest storage period of the study samples was covered by the long-term stability data at -25 ± 10 °C.

Pharmacokinetic variables

The following PK parameters/observations were estimated for atazanavir using a non-compartmental approach in SAS (version 9.4):

- AUC_t: The area under the analyte concentration versus time curve, from time zero (0) to the time of the last measurable analyte concentration (t), as calculated by the linear trapezoidal method,
- AUC_{inf}: The area under the analyte concentration versus time curve from time zero to infinity. $AUC_{inf} = AUC_t + C_t/K_{el}$, where C_t is the last measurable analyte concentration,
- C_{max}: Maximum measured analyte concentration over the sampling period,
- T_{max}: Time of the maximum measured analyte concentration over the sampling period,
- K_{el}: The apparent first-order elimination rate constant,
- T_{half}: The apparent elimination half-life,
- AUC_t/AUC_{inf}: The ratio of AUC_t to AUC_{inf},
- TLIN: Start time for linear regression,
- LQCT: Last quantifiable concentration time,
- R: Correlation coefficient obtained from regression analysis.

K_{el}, T_{half}, and AUC_{inf} parameters would not be estimated for concentration-time profiles where the terminal linear phase was not clearly defined. Individual and mean plasma concentration versus time curves were plotted.

Statistical methods

Statistical analysis was performed on quality assured data from subjects in the statistical dataset. The PROC GLM procedure from SAS (version 9.4) was used. Analysis of variance (ANOVA) was performed on log-transformed AUC_t, AUC_{inf}, and C_{max} parameters. The significance of the sequence, period, treatment, and subject (sequence) effects (all fixed) was tested.

Using the same statistical model, the least-squares-means, the differences between the treatments least-squares-means, and the corresponding standard errors of these differences were estimated for log-transformed AUC_t, AUC_{inf}, and C_{max} parameters. Based on these statistics, the ratios of the geometric means for treatments and the corresponding 90% CIs were calculated.

Based on the log-transformed parameters, bioequivalence between the test and reference product was considered met if the 90% CIs of the relative mean plasma atazanavir AUC_t and C_{max} of the test to reference products were between 80.00 and 125.00%.

Results

Fifty-eight (58) subjects were enrolled in the study and 56 subjects completed the study. Fifty-seven (57) subjects received the test product (Treatment A) and 57 subjects received the reference product (Treatment B).

Table 7: Pharmacokinetic parameters for atazanavir (non-transformed values)

Pharmacokinetic parameter	Test		Reference	
	arithmetic mean	SD	arithmetic mean	SD
$AUC_{(0-t)}$	6867.60	4029.30	6595.90	3714.90
$AUC_{(0-\infty)}$	7222.80	4214.10	6907.70	3884.80
C_{max}	1297.30	694.00	1276.70	613.20
T_{max}*	4.00	(2.00 – 10.00)	4.00	(2.50 – 8.05)
AUC_{0-t}	area under the plasma concentration-time curve from time zero to t hours (ng*h/mL)			
$AUC_{0-\infty}$	area under the plasma concentration-time curve from time zero to infinity (ng*h/mL)			
C_{max}	maximum plasma concentration (ng/mL)			
T_{max}	time for maximum concentration (* median, range)			

Table 8: Statistical analysis for atazanavir (ln-transformed values)

Pharmacokinetic parameter	Geometric Mean Ratio Test/Reference	Confidence Intervals	CV%*
$AUC_{(0-t)}$	101.80%	(85.12%, 121.74%)	61
C_{max}	96.95%	(82.65%, 113.72%)	54
$AUC_{(0-\infty)}$	103.30%	(87.94%, 121.34%)	54
* estimated from the Residual Mean Squares			

The test product, atazanavir 300 mg capsules, hard (Manufacturer: *(confidential information deleted)*), exhibited equivalent rate and extent of absorption to the reference product, Reyataz (atazanavir) 300 mg hard capsules (Bristol-Myers Squibb Pharma EEIG, United Kingdom, EU), in healthy subjects after a single, oral dose, under fed conditions.

Safety data

Of the 25 AEs, 16 were suspected to be possibly related to the study treatments. Five (5) subjects (8.8% of subjects dosed) receiving Treatment A reported 5 treatment related AEs and 9 subjects (15.8%) receiving Treatment B reported 11 treatment related AEs.

It can be concluded that the two formulations were well tolerated. The reported adverse events are already described in the SmPC of the reference product Reyataz.

No deaths or serious adverse events were reported during the study.

Conclusions

Based on the presented bioequivalence study Atazanavir Krka 300 mg hard capsules are considered bioequivalent with the reference product Reyataz 300 mg hard capsules.

The results of the bioequivalence study with the 300 mg formulation can be extrapolated to the other strengths 150 mg and 200 mg, according to conditions in Guideline on the Investigation of Bioequivalence CPMP/EWP/QWP/1401/98 Rev. 1/Corr*, section 4.1.6.

2.4.3. Pharmacodynamics

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

2.4.4. Discussion on clinical aspects

To support the application, the company has submitted one bioequivalence study. The study was an open-label, single-dose, randomised, two-period, two-treatment, two sequence, crossover study between Atazanavir Krka 300 mg capsules, hard (manufactured by *(confidential information deleted)*) and Reyataz (atazanavir) 300 mg hard capsules (MAH: Bristol-Myers Squibb Pharma EEIG, United Kingdom, EU) in healthy subjects under fed conditions.

2.4.5. Conclusions on clinical aspects

Based on the presented bioequivalence study Atazanavir Krka 300 mg hard capsules are considered bioequivalent with the reference product Reyataz 300 mg hard capsules under fed condition.

The results of Study 2017-4324 with Atazanavir Krka 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.

2.5. Risk management plan

Safety concerns

The list of safety concerns is the same as for originator's atazanavir product. No new risks have been identified for the generic products that are not recognised for the reference product.

Summary of safety concerns	
Important identified risks	PR interval prolongation (both paediatric and adult populations)
	Neprolithiasis with or without alteration of the renal function
	Hyperbilirubinemia
	Severe skin reactions
	Cholelithiasis
	Angioedema
	Immune reconstitution inflammatory syndrome (IRIS)
	Chronic kidney disease
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
	Woman who are breastfeeding

Pharmacovigilance plan

Routine pharmacovigilance activities are considered sufficient. There are no additional PhV activities. However, pregnancy reports will be actively followed-up using Pregnancy Report Forms.

Risk minimisation measures

The safety information in the proposed Product Information is aligned to the reference medicinal product.

Conclusion

The CHMP and PRAC considered that the risk management plan version 0.2 is acceptable.

2.6. 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.

2.7. Product information

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, randomised 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 hard capsule 300 mg of Krka 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 Krka 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.