9 November 2017
EMA/786962/2017
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Darunavir Krka d.d.

International non-proprietary name: darunavir

Procedure No. EMEA/H/C/004891/0000

Note

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

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List of abbreviations

AP	Applicant's Part (or Open Part) of a DMF
API	Active Pharmaceutical Ingredient
AR	Assessment Report
ARV	anti retroviral
ASM	Active Substance Manufacturer
ASMF	Active Substance Master File = Drug Master File
BCS	Biopharmaceutics Classification System
BP	British Pharmacopoeia
CoA	Certificate of Analysis
COBI	cobicistat
CRS	Chemical Reference Substance (official standard)
DAD	Diode array detector
DP	Decentralised (Application) Procedure
DRV	darunavir
DSC	Differential Scanning Calorimetry
EC	European Commission
GC	Gas Chromatography
HDPE	High Density Polyethylene
HIV	human immunodeficiency virus
HPLC	High Pressure Liquid Chromatography
IPC	In-process control test
IR	Infrared
KF	Karl Fischer titration
LDPE	Low density polyethylene
LOD	Limit of Detection
LOQ	Limit of Quantification / Quantitation
LoQ	List of Questions
MA	Marketing Authorisation
MAA	Marketing Authorisation Application
MAH	Marketing Authorisation Holder
MS	Mass Spectrometry
MS	Member State
ND	Not detected
NMR	Nuclear Magnetic Resonance
NMT	Not more than
OOS	Out of Specifications
PDE	Permitted Daily Exposure
PE	Polyethylene
Ph.Eur.	European Pharmacopoeia
PIL	Patient Information Leaflet
PP	Polypropylene
PVA	Polyvinyl alcohol
PVC	Poly vinyl chloride
PXRD	Power X-Ray Diffraction
QC	Quality Control
RH	Relative Humidity
RMP	risk management plan
RMS	Reference Member State
RNA	ribonucleic acid
RP	Restricted Part (or Closed Part) of a DMF
RRT	Relative retention time
RSD	Relative standard deviation
RTV	ritonavir
SmPC	Summary of Product Characteristics
TGA	Thermo-Gravimetric Analysis
TLSB	Triple laminated sunlight barrier
USP	United States Pharmacopoeia
USP/NF	United States Pharmacopoeia/National Formulary
UV	Ultraviolet
XRD	X-Ray Diffraction
HBV	hepatitis B virus

HCV hepatitis C virus

1. Background information on the procedure

1.1. Submission of the dossier

The applicant KRKA, d.d., Novo mesto submitted on 26 June 2017 an application for marketing authorisation to the European Medicines Agency (EMA) for Darunavir 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 10 November 2016.

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 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

Darunavir Krka d.d., co-administered with pharmacokinetic enhancer is indicated in combination with other antiretroviral medicinal products for the treatment of patients with human immunodeficiency virus (HIV-1) infection (see section 4.2).

Darunavir Krka d.d. 400 mg and 800 mg tablets may be used to provide suitable dose regimens for the treatment of HIV-1 infection in adult and paediatric patients from the age of 3 years and at least 40 kg body weight who are:

- antiretroviral therapy (ART)-naïve (see section 4.2).

- ART-experienced with no darunavir resistance associated mutations (DRV-RAMs) and who have plasma HIV-1 RNA < 100,000 copies/ml and CD4+ cell count ≥ 100 cells x 106/l. In deciding to initiate treatment with Darunavir Krka d.d. in such ART-experienced patients, genotypic testing should guide the use of Darunavir Krka d.d. (see sections 4.2, 4.3, 4.4 and 5.1).

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 Prezista 800 mg film-coated tablets 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 Community provisions in force for not less than 6/10 years in the EEA:

- Product name, strength, pharmaceutical form: Prezista 400, 600, 800mg film-coated tablets
- Marketing authorisation holder: Janssen-Cilag International NV
- Date of authorisation: 14-02-2007
- Marketing authorisation granted by:

– Community

- Marketing authorisation number: EU/1/06/380/003, EU/1/06/380/002, EU/1/06/380/007-008

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

- Product name, strength, pharmaceutical form: Prezista 400, 600, 800mg film-coated tablets
- Marketing authorisation holder: Janssen-Cilag International NV
- Date of authorisation: 14-02-2007
- Marketing authorisation granted by:

– Community

- Marketing authorisation number: EU/1/06/380/003, EU/1/06/380/002, EU/1/06/380/007-008

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

- Product name, strength, pharmaceutical form: Prezista
- Marketing authorisation holder: Janssen-Cilag International NV
- Date of authorisation: 14-02-2007
- Marketing authorisation granted by:

– Community

– Marketing authorisation number(s): EU/1/06/380/007-008

- Bioavailability study number(s): CRO: KRS-P8-015 KRKA: 16-495

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.
This application is submitted as a multiple of Darunavir Krka simultaneously being under initial assessment in accordance with Article 82.1 of Regulation (EC) No 726/2004. The submission of this application is due to patent grounds.

Scientific advice

The applicant did not seek scientific advice at the CHMP.

1.2. Steps taken for the assessment of the product

The Rapporteur appointed by the CHMP was:

Rapporteur: John Joseph Borg

- The application was received by the EMA on 26 June 2017
- The procedure started on 14 July 2017.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 14 July 2017.
- The Rapporteur circulated the Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 21 August 2017.
- During the PRAC meeting on 1 September 2017, the PRAC agreed on a PRAC Assessment Overview and Advice to CHMP.
- During the CHMP meeting on 14 September 2017, the CHMP agreed on a list of outstanding issues to be sent to the applicant.
- The applicant submitted the responses to the CHMP consolidated List of Outstanding Issues on 10 October 2017.
- The Rapporteur circulated the Assessment Report on the applicant's responses to the list of outstanding issues to all CHMP members on 25 October 2017.
- The Rapporteur circulated the updated Assessment Report on the applicant's responses to the list of outstanding issues to all CHMP members on 3 November 2017.
- During the meeting on 9 November 2017, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a Marketing authorisation to Darunavir Krka d.d.

2. Scientific discussion

2.1. Introduction

Darunavir is a selective inhibitor of HIV-1 protease. It belongs to the pharmacotherapeutic group: Antiviral for systemic use; Protease inhibitors. Darunavir is used together with low-dose ritonavir and other antiviral medicines to treat adults and children who are infected with human immunodeficiency virus (HIV- 1) and together with cobicistat and other antiviral medicines to treat adults who are infected with human immunodeficiency virus (HIV-1)

The product Darunavir KrKa d.d. , 400, 600 and 800 mg, film coated tablets, manufactured by Krka, d.d., Novo mesto, Slovenia is submitted for approval with generic application according to Article 10 (1) of Directive 2001/83/EC and proposed as essentially similar product to Prezista (darunavir) film-coated tablets (Janssen-Cilag SpA, Italy) registered in EU. The active substances of the above-mentioned medicinal product, darunavir, have been in medicinal use within the Community for almost ten (10) years, with recognized efficacy and an acceptable level of safety.

The first marketing authorization for darunavir was granted on 14.2.2007 in EU via the CAP procedure for Prezista (darunavir) prolonged-release tablets (Janssen-Cilag SpA, Italy). Prezista is available as film-coated tablets (75, 150,300, 400, 600, and 800 mg) and as an oral suspension (100 mg/ml).

The clinical part of this dossier contains a literature review on the main pharmacokinetic, pharmacodynamic and clinical characteristics of darunavir as well as one crossover comparative bioavailability study of single dose darunavir 800 mg tablets in healthy male volunteers showing bioequivalence of Darunavir 800 mg film-coated tablets, manufactured by Krka, d. d., Novo mesto, Slovenia, to Prezista 800 mg film-coated tablets. This is considered standard and sufficient for a generic medicinal product application.

In order to establish bioequivalence between Krka'test formulations and reference formulations, one study (fed state) was performed on the 800 mg strength. Bioequivalence study was conducted according to the Guideline on the Investigation of bioequivalence (CPMP/EWP/QWP/1401/98 Rev 1/ Corr**). The bioequivalence study with Darunavir 800 mg was a Crossover Comparative Bioavailability Study of Single Dose Darunavir 800 mg Tablets in healthy male and female volunteers (fed state).

No request for a BCS biowaivers has been considered necessary or made by the applicant. However a biowaiver for the lower strengths (600 mg and 400 mg) has been applied for on the basis of data according to the Guideline on the Investigation of Bioequivalence, CPMP/EWP/QWP/1401/98 Rev. 1/ Corr **, point 4.1.6 Strength to be investigated.

The below is a summary of the pack size comparison between originator and proposed product.

Pack sizes for the proposed products

For 400mg and 600mg

30 tablets: 1 bottle of 30 film-coated tablets, in a box,
60 tablets: 2 bottles of 30 film-coated tablets, in a box,
90 tablets: 3 bottles of 30 film-coated tablets, in a box,
180 tablets: 6 bottles of 30 film-coated tablets, in a box

For 800mg:

30 tablets: 1 bottle of 30 film-coated tablets, in a box,
90 tablets: 3 bottles of 30 film-coated tablets, in a box.

Pack sizes for the originator:

Prezista 400 mg Film-coated tablet Oral use bottle (HDPE) 60 tablets
Prezista 600 mg Film-coated tablet Oral use bottle (HDPE) 60 tablets
Prezista 800 mg Film-coated tablet Oral use bottle (HDPE) 30 tablets
Prezista 800 mg Film-coated tablet Oral use bottle (HDPE) 90 (3 x 30) Tablets (multipack)

2.2. Quality aspects

2.2.1. Introduction

The finished product is presented as film-coated tablets containing 400 mg, 600 mg and 800 mg of darunavir as active substance.

Other ingredients are:

Tablet core: cellulose microcrystalline, crospovidone, hydroxypropylcellulose, silica colloidal anhydrous, silicified microcrystalline cellulose (cellulose, microcrystalline; silica, colloidal anhydrous) and magnesium stearate (E470b)

Film coating: poly(vinyl alcohol), macrogol, titanium dioxide (E171), talc (E553b), iron oxide, yellow (E172) – only for 400 mg and 600 mg film-coated tablets - and iron oxide red (E172).

The product is available in HDPE bottle with child resistant temper evident PP closure with a desiccant as described in section 6.5 of the SmPC.

2.2.2. Active substance

General information

The chemical name of darunavir is (3R, 3aS, 6aR)-hexahydrofuro [2,3-b]furan-3-yl(1S,2R)-3-[[(4-amino phenyl)sulfonyl](2-methylpropylamino]-1-benzyl-2-hydroxypropyl] carbamate corresponding to the molecular formula **:** $C_{27}H_{37}N_3O_7S$. It has a relative molecular mass of 547.68 g/mol and the following structure:

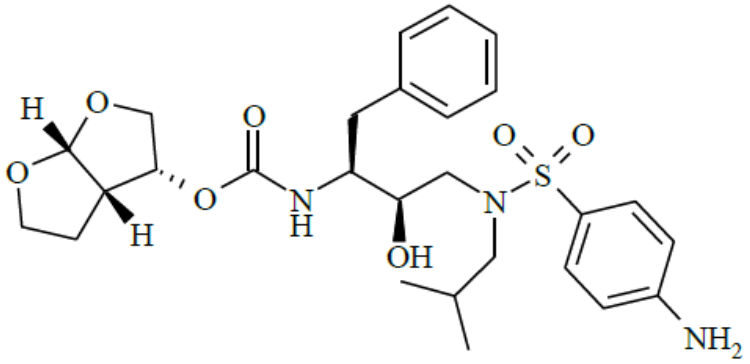

Figure 1: Darunavir active substance structure

The chemical structure of darunavir was elucidated by a combination of high resolution mass spectrometry, mass spectrometry, nuclear magnetic resonance spectroscopy (^{1}H NMR), infra-red spectroscopy (IR), UV spectroscopy, XRD, and identification by HPLC.

The active substance is a white to pale yellow colour slightly hygroscopic solid, freely soluble in dichloromethane, very slightly soluble in ethyl alcohol absolute and practically insoluble in water.

Darunavir exhibits stereoisomerism due to the presence of 5 chiral centres. These chiral centers originate from its starting materials. Enantiomeric purity is controlled routinely by chiral HPLC in the specifications.

Polymorphism has been observed in the active substance. The manufacturing process consistently produces the amorphous form which is identified by XRD.

Manufacture, characterisation and process controls

Detailed information on the manufacturing of the active substance has been provided in the restricted part of the ASMF and it was considered satisfactory.

The active substance is manufactured in one manufacturing site. It synthesized in 4 main stages using well-defined starting materials with acceptable specifications following by pulverization (based on customer requirement). During assessment, one of the starting materials was considered not to be acceptable and it was considered that it should be redefined further back in the synthesis. The applicant redefined the starting material which then, was considered acceptable both due to its less complex nature and also since the control strategy proposed to control was considered adequate.

Adequate in-process controls are applied during the synthesis. The specifications and control methods for intermediate products, starting materials and reagents have been presented and are acceptable. 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 commercial manufacturing process for the active substance was developed in parallel with the clinical development program.

Specification

The active substance specification includes tests for: appearance (visual), solubility (Ph. Eur), identification (IR, HPLC), water content (KF), sulfated ash (Ph. Eur), diastereomer content (HPLC), related substances (HPLC), assay (HPLC), residual solvents (GC), content of propanoic acid and acetic acid (HPLC), microbiological quality (Ph. Eur.), solid state form (X-Ray), particle size (laser diffraction), elemental impurities (Pb) and solid state form (XRPD).

Impurities present at higher than the qualification threshold according to ICH Q3A were qualified by toxicological and clinical studies and appropriate specifications have been set.

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 multiple batches of the active substance are provided. The results are within the specifications and consistent from batch to batch.

Stability

Stability data from multiple batches of the un-pulverized active substance from the proposed manufacturer stored in the intended commercial package for up to 18 months under long term conditions (25 ºC / 60% RH) and for up to 6 months under accelerated conditions (40 ºC / 75% RH) according to the ICH guidelines were provided.

Stability data from 3 pilot scale batches of the pulverized active substance from the proposed manufacturer stored in the intended commercial package for up to 6 months under long term conditions (25 ºC / 60% RH) and for up to 6 months under accelerated conditions (40 ºC / 75% RH) according to the ICH guidelines were provided.

The following parameters were tested: description, identification, water content, diastereomer content, related substances, and assay. The analytical methods used were the same as for release and were stability indicating.

Evaluation of the available stability data shows that active substance is stable under long term conditions; however the packaging material is unstable under accelerated conditions. Due to failure at 40 ± 2°C / 75 ± 5 % RH conditions, the sample at refrigerated condition, 5±3°C was tested at 3rd month and 6th month and data revealed that active substance is stable at refrigerated conditions.

Evaluation of the available stability data at refrigerated conditions showed that there is no change in the unknown and total impurities, and are below the acceptable limit as specified in the active

substance specification. No specific unknown impurity generation trend has been observed. Assay by HPLC is within the specification limit.

Photostability testing following the ICH guideline Q1B was performed on two batches. The sample was considered stable in the proposed commercial packing conditions.

Results on stress conditions (base hydrolysis (0.5N (NaOH), acid hydrolysis (1.0N HCl), oxidation (30% H_2O_2), thermal degradation (60^oC), and humidity (85±5%) were also provide on one batch. No significant variation in assay, related substances and diastereomer content were found.

The stability results indicate that the active substance manufactured by the proposed supplier is sufficiently stable. Based on available 18 months stability data at 25±2°C/60±5%RH and 6 months stability data at 2-8°C, 12 months retest period has been assigned for un-pulverized active substance. Based on available 6 months long term data at 2-8°C6 months retest period has been assigned for pulverizedactive substance. Store in a well closed containers at 2-8°C and pack under nitrogen atmosphere. The CHMP recommended that it should be ensured for commercial batches that the proposed storage condition (2-8°C and packing under nitrogen atmosphere and the reduced retest periods of 6 months) will be adhered for transport, storage and dispensing at the manufacturing stage.

2.2.3. Finished medicinal product

Description of the product and Pharmaceutical development

The finished product is manufactured as conventional immediate release film-coated tablets. The appearance of each of the strengths of finished product is:

- 400 mg: yellowish brown, oval, biconvex film-coated tablets, engraved with a mark S 1 on one side.

- 600 mg: orangish brown, oval, biconvex film-coated tablets, engraved with a mark S 2 on one side.

- 800 mg: brownish red, oval, biconvex film-coated tablets, engraved with a mark S 3 on one side.

The aim of the development was to develop a generic product of the reference medicinal product (Prezista) 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.

Darunavir is poorly soluble substance according to the BCS is a class II substance, therefore the effect of particle size was evaluated in vivo and in vitro conditions. It was confirmed with the experiments during product development that particle size of the active substance leads to adequate feasibility and good technological properties of the finished product. Darunavir is known to exhibit polymorphism. A number of different forms are known. They differ in terms of stability, physical properties, spectral data and methods of preparation. Amorphous form was used for the development of the finished product, whereas the reference product uses form A. The stability of the amorphous form in the final formulation was confirmed during development.

The purpose of the development was to choose the same or similar excipients (i.e. with the same functionality) for the finished product as they are incorporated in the reference medicinal product. However, a minor modification of qualitative composition comparing to the reference product has been made, i.e. different type of binder was chosen. The effect of this compositional variation had no effect on the product's chemical stability, which was also confirmed during the initial stage of the development. Moreover, the compatibility of the active substance with the proposed excipients was additionally verified through the stability. From the results of the stability studies, it was concluded that the active substance was compatible with excipients of the present formulation.

All excipients are well-known pharmaceutical ingredients and all excipients except silicified microcrystalline cellulose and ferric oxides are compliant with Ph. Eur. standards. Silicified microcrystalline cellulose complies with in-house specifications and ferric oxides meet the general requirements as described in Directive 2009/35/EC and Regulation EU 231/2012. 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. In relation to the paediatric population, the suitability of the excipients has been justified since they are almost all the same excipients (except hydroxypropylcellulose LF) as those in the reference medicinal product, and are present in other paediatric medications, approved within the European Union in the target age group and are to be administered via the same or comparable route of administration. All the excipients are also included in the EU food legislation. The suitability of the tablet in the paediatric population was addressed during development; all strengths are film coated with standard PVA based coating in order to prevent direct contact between tablet core and patient's oral cavity. Since PVA film coating is tasteless and odourless pharmaceutical ingredient, the tablet exhibits no taste, smell, or aftertaste when being administered. Moreover, applied film-coating gives smooth texture to the tablet's surface, which enables its easy swallowing.

The reference medicinal product is presented in 6 different tablet strengths (75 mg, 150 mg, 300 mg, 400 mg, 600 mg, and 800 mg). However, the generic medicinal product was developed as 400 mg, 600 mg, and 800 mg strengths only. The formulation was based on the development of the highest, 800 mg, strength. Afterwards, other two strengths, 400 mg and 600 mg, were prepared proportionally from the highest strength (same qualitative and quantitative composition of the compression mixture and proportionally reduced tablet weight). Furthermore, the objective of the development of the formulation was to ensure adequate chemical stability of the finished product, develop a robust formulation and an efficient, and a simple and reproducible manufacturing process.

The development of the QC dissolution method was guided by the recommendations of the relevant chapters of the European Pharmacopoeia and relevant sections of guideline CPMP/EWP/QWP/1401/98 Rev. 1/Corr**. In compliance with these guidelines, the basic criteria which governed the choice of the dissolution method (apparatus, medium, volume, stirring speed) were: the discriminatory power of the method, reflecting *in vivo* conditions, fulfilment of sink conditions and complete release of the active substance within the specified time. The dissolution testing was conducted using Ph. Eur. compliant equipment.

The dissolution profiles obtained with these batches were compared to the dissolution profile of the bioequivalence batch using the proposed QC dissolution method and demonstrated the discriminatory power of the dissolution method.

Bioequivalence study was performed showing bioequivalence between the generic medicinal product formulation and the reference medicinal product. The bioequivalence study was conducted with the highest strength of darunavir at 800 mg. The pharmacokinetics of darunavir is linear. 800, 600 and 400 mg strengths are all manufactured by the same manufacturing process, the qualitative composition between the strengths is the same and the composition of the strengths is quantitatively proportional. Therefore, studies on 600 and 400 mg strengths were waived.

Dissolution profile comparison between test products of different strengths was carried out using simple model independent method. According to guideline on the investigation of bioequivalence (CPMP/EWP/QWP/1401/98 Rev.1/ Corr**), the similarity should be justified by dissolution profiles, covering at least three time points, attained in three different dissolution media at pH range 1 - 6.8 and performed on 12 tablets. It was claimed that from the dissolution results presented and the fact that in all tested media Darunavir 600mg and 400mg showed similar dissolution behaviour with Darunavir 800mg, the requirements in regard to in vitro comparisons for biowaiver were fulfilled. No comparative dissolution of the 400mg and 600mg with the reference product were provided. In view of the bioequivalence guideline, the CHMP recommended to compare dissolution profiles of the first

three full production scale batches of each strength to be marketed with the bioequivalence study test batch. The results should be provided to the competent authorities if requested. The results will also be also provided if the dissolution profiles are not similar with a proposed action to be taken.

The primary packaging is HDPE bottle, child resistant tamper evident PP closure with a desiccant. The material complies with Ph.Eur. and EC requirements. The cap is compliant to ISO 8371 for chid resistant packaging. 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 finished product is manufactured by wet granulation. The manufacturing process consists of 7 main steps: sieving, granulating, drying/sieving, blending, tabletting, film-coating, and packaging. The process is considered to be a standard manufacturing process.

It was confirmed that all the batches/commercial batches of the finished product will use the pulverised active substance form. The CHMP recommended that if un-pulverised active substance form would be used, a variation should be submitted with supporting data (dissolution data, bioequivalence study, batch analysis, holding times, validation, stability, etc) to include the use of the unpulverised form of the active substance in the finished product.

Major steps of the manufacturing process have been validated by a number of studies. Considering the fact that there are no differences in the technological procedure, type of manufacturing equipment or in the composition of different strengths the process validation was carried out on six production batches altogether (two per strength). In addition, the suitability of the manufacturing process was additionally supported by the data of three smaller batches (one per strength). Therefore, the CHMP recommended that an additional small production scale batch per strength (100, 000 tablets) should be validated to confirm process suitability before placing to the market. In addition, manufacturing of the finished product is considered as standard and noncomplex (no steps with expected scale-up difficulties) technological procedure and thus the stated data should adequately confirm process suitability for the whole proposed batch size. Nevertheless, the CHMP recommended that the process of manufacturing of the finished product should be validated on three consecutive batches for each scale-up according to the process validation scheme.

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. The intermediates are defined and holding times and packaging materials where needed were adequately described and considered appropriate.

Product specification

The finished product release specifications include appropriate tests for this kind of dosage form: appearance (visual), identification (HPLC, DAD), uniformity of dosage units- mass variation (Ph. Eur.), water (Ph. Eur.), content of darunavir (HPLC), impurities (HPLC), dissolution (Ph. Eur.), microbiological quality (Ph. Eur.).

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 1 pilot and 2 commercial scale batches per 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 above release specifications, through traditional final product release testing.

Stability of the product

Stability data from 2 commercial and 1 pilot scale batches per strength of finished product stored for up to 12 months under long term conditions (25 ºC / 60% RH) and for up to 6 months under accelerated conditions (40 ºC / 75% RH) according to the ICH guidelines were provided. The batches of the medicinal product are identical to those proposed for marketing and were packed in a similar primary packaging than the one for marketing with a different child resistant tamper.

Samples were tested for appearance, identification, uniformity of dosage, water, content of darunavir, impurities, dissolution and microbiological quality. The analytical procedures used are stability indicating. All principal physical and chemical parameters were well within the proposed limits during the accelerated and long term storage conditions without showing any sign of degradation.

One batch per strength of the finished product, packed in in-bulk packaging (primary transparent low density polyethylene (LDPE) bag closed with a plastic clip and inserted into laminated Polyethylene terephthalate/Aluminum/ Polyethylene (PET/Al/PE) bag closed by sealing) were put on long-term (25±2 °C/ 60±5% RH) for 12 months and accelerated stability testing conditions (40±2 °C/ 75±5% RH) for 6 months. The same analytical methods are used in the stability testing as for finished product release testing. All the results of the stability testing comply with the release specifications.

The CHMP recommended to continue the long term studies through the proposed shelf life in accordance to the proposed stability protocol/study schedule, and to place additional production batches, to a total of at least three (for each strength i.e. three batches per strength) packed with the new child resistant tamper evident closure, on long term stability studies through the proposed shelf life and on accelerated studies for 6 months in accordance to the proposed stability protocol/study schedule.

In addition, a number of batches (400 mg and 800 mg) were exposed to light as defined in the ICH Guideline on Photostability Testing of New Drug Substances and Products. All results were within specifications however, an increase of water content was observed when tablets are exposed to light.

Data of in-use stability testing were presented. In-use stability testing after the first opening of container at the beginning of the shelf-life was carried out at 25±2°C/60±5%RH (on two batches of each strength) with the intention of established the period during which the film-coated tablets may be used after the first dose has been taken from the multidose plastic containers in accordance with the Note for Guidance on In-Use Stability Testing of Human Medicinal Products (CPMP/QWP/2934/99). Additionally in-use stability testing was performed on one production batch for each strength after 12 months at 25±2°C/60±5%RH for 1 month. No changes were observed during these times. As the in-use stability data has been given for three months in only two batches, the shelf-life after opening is 1 month. However, the CHMP recommended that one additional batch approaching the end of its shelf-life should be subjected to the in-use stability testing and when 3 months in use after 12 months at 25±2°C/60±5%RH stability results will be available, a variation should be submitted to extend the in-use shelf life to 3 months

Based on available stability data, the proposed shelf-life of 24 months and keep the bottle tightly closed in order to protect from moisture as stated in the SmPC (section 6.3) are acceptable.
The shelf-life after first opening is 1 month.

Adventitious agents

No excipients derived from animal or human origin have been used.

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.

At the time of the CHMP opinion, there were a number of minor unresolved quality issues having no impact on the Benefit/Risk ratio of the product.

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.

2.2.6. Recommendations for future quality development

In the context of the obligation of the MAHs to take due account of technical and scientific progress, the CHMP recommends the following points for investigation:

- It should be ensured for commercial batches that the proposed storage condition (2-8°C and packing under nitrogen atmosphere and the reduced retest periods of 6 months) will be adhered for transport, storage and dispensing at the manufacturing stage.
- To compare dissolution profiles of the first three full production scale batches of each strength to be marketed with the bioequivalence study test batch. The results should be provided to the competent authorities if requested. The results will also be also provided if the dissolution profiles are not similar with a proposed action to be taken.
- If un-pulverised active substance form would be used, a variation should be submitted with supporting data (dissolution data, bioequivalence study, batch analysis, holding times, validation, stability etc) to include the use of the unpulverised form of the active substance in the finished product.
- An additional small production scale batch per strength (100,000 tablets) should be validated to confirm process suitability before placing to the market. In addition, the process of manufacturing of the finished product will be validated on three consecutive batches for each scale-up according to the process validation scheme.
- To continue the long term studies through the proposed shelf life in accordance to the proposed stability protocol/study schedule, and to place additional production batches, to a total of at least three

(for each strength i.e. three batches per strength) packed with the new child resistant temper evident closure, on long term stability studies through the proposed shelf life and on accelerated studies for 6 months in accordance to the proposed stability protocol/study schedule.

- One additional batch approaching the end of its shelf-life should be subjected to the in-use stability testing and when 3 months in use after 12 months at 25±2°C/60±5%RH stability results will be available, a variation should be submitted to extend the in-use shelf life to 3 months

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. Ecotoxicity / environmental risk assessment

No Environmental Risk Assessment was submitted. This was justified by the applicant as the introduction of Darunavir KrKa d.d. manufactured by KRKA, d.d., Novo mesto is considered unlikely to result in any significant increase in the combined sales volumes for all darunavir containing products and the exposure of the environment to the active substance. Thus, the ERA is expected to be similar and not increased.

2.3.3. Discussion on non-clinical aspects

The submitted non clinical documentation is in line with requirements for applications under the generic medicinal product status. No further non-clinical studies are required. Also, since Darunavir Krka d.d. 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.

2.3.4. Conclusion on the non-clinical aspects

The CHMP considers that there are no objections to approval of Darunavir Krka d.d. from a non-clinical point of view.

2.4. Clinical aspects

2.4.1. Introduction

This is an application for film-coated tablets containing darunavir. To support the marketing authorisation application the applicant conducted one bioequivalence study with two-sequence, two-period cross-over design under fed conditions. This study was the pivotal study for the assessment.

For the clinical assessment the Guideline on the Investigation of Bioequivalence CPMP/EWP/QWP/1401/98) as well as the Guideline on Bioanalytical method validation (EMEA/CHMP/EWP/192217/09) are of particular relevance.

GCP

The Clinical trial was performed in accordance with GCP as claimed by the applicant.

The applicant has provided a statement to the effect that clinical trial conducted outside the community was carried out in accordance with the ethical standards of Directive 2001/20/EC.

Exemption

No request for a BCS biowaivers has been considered necessary or made by the applicant. However a biowaiver for the lower strengths (600 mg and 400 mg) has been applied for on the basis of data according to the Guideline on the Investigation of Bioequivalence, CPMP/EWP/QWP/1401/98 Rev. 1/ Corr **, point 4.1.6 Strength to be investigated. These data and corresponding assessment and discussion are fully presented in the Assessment Report. Furthermore the pharmacokinetics of darunavir in single doses may be assumed to be linear or dose independent as per EPAR Scientific Discussion for the innovator drug product Prezista.

Clinical studies

To support the application, the applicant has submitted one bioequivalence study.

Table 1. Tabular overview of clinical studies

Type of Study	Study Identifier	Location of Study Report	Objective of the Study	Study Design; Type of Control	Test Product(s); Dosage Regimen; Route of Administration	No. of Subjects	Healthy Subjects/ Diagnosis of Patients	Duration of Treatment	Study Status; Type of report
BE	16-495 KRS-P8-015	Section 5.3.1.2.	CROSSOVER COMPARATIVE BIOAVAILABILITY STUDY OF SINGLE DOSE DARUNAVIR 800 mg TABLETS IN HEALTHY MALE AND FEMALE VOLUNTEERS FED STATE	Open-label, single-dose, randomized, two-period, two-treatment, two-sequence, crossover, comparative bioavailability study 14 days wash-out period fed conditions	**Treatment A (test formulation)** Darunavir 800 mg film-coated tablets (B.No.: R42109) One film-coated tablet of the test formulation in one period / 800 mg of darunavir per tablet / Oral **Treatment B (reference formulation)** Prezista® (darunavir) 800 mg film-coated tablets (B.No.: FAZ0W00.A) One film-coated tablet of the test formulation in one period / 800 mg of darunavir per tablet / Oral	24	Healthy male and female subjects	One tablet of the test formulation in one period and one tablet of the reference formulation in the other period	Complete Full

2.4.2. Pharmacokinetics

Study 16-495: Crossover Comparative Bioavailability Study of Single Dose Darunavir 800 mg Tablets in Healthy Male and Female Volunteers/Fed State

Methods

Study design

The study was designed as single centre, randomized, single dose, laboratory-blinded, 2-period, 2-sequence, crossover study under fed conditions. The composition of the meal is specified in the Table from the Applicant's BE report:

Table 2. Composition of the standardised High-fat, high-calorie meal

Ingredients	Amount (g)	Energy (kcal)	Protein (kcal)	Fat (kcal)	Carbohydrate (kcal)
240 mL of whole milk	29	156	36	72	48
2 large eggs	24	146	48	90	8
4 ounces of hash brown potatoes/2 patties	52	288	8	144	136
2 slices of toast	46	194	32	18	144
2 x 4.5 g of butter	7	63	0	63	0
2 strips of bacon	21	164	20	144	0
TOTAL	179	1011	144	531	336
PERCENTAGE	--	--	14.2%	52.5%	33.2%

This meal was composed of approximately 36 g of protein (144 calories), 84 g of carbohydrate (336 calories) and 59 g of fat (531 calories) for a total of 1011 calories.

Twenty four (24) healthy male subjects were included in this study and 22 subjects completed both treatment periods. Each subject received a single dose of both Test and Reference products, according with the randomization scheme.

Test and reference products

Test product: Darunavir 800 mg film-coated tablets, batch nº R42109, exp. date September 2016.

Reference product: Prezista (darunavir) 800 mg film-coated tablets, batch nº FAZ0W00.A, exp. date December 2016 (corresponding to one tablet).

Co-administration: Single 100 mg dose of ritonavir was administered once daily (every 24 hours) for a total of 5 consecutive doses per study period as follows:

- Ritonavir was administered following a standard meal approximately 48 hours (Days 1 and 15) and 24 hours (Days 2 and 16) prior to as well as approximately 24 hours (Days 4 and 18) and 48 hours (Days 5 and 19) after each darunavir administration.

- In addition, ritonavir was co-administered with each darunavir administration following a high-fat, high-calorie breakfast (Days 3 and 17).

Population studied

Twenty four (24) healthy male subjects were included in this study and 22 subjects completed both treatment periods.

Sample size calculation was reviewed according to usual standards as follows:

Based on sponsor's data, the intra-subject variation following a single dose of darunavir appears to be about 12% for Cmax and about 15% for AUC0-T. Statistically, given that the expected Test to Reference ratio of geometric LS means was to fall within 95 and 105% and taking into account the possibility of drop-outs, it was estimated that the number of subjects to meet the 80 to 125% bioequivalence range with a statistical a priori power of at least 80% was about 24.

The number of subjects, including provision for dropouts, is the important figure and it is stated: 24

The level of significance is that the 90% CI should be within the 80 to 125% bioequivalence range as follows:

The ratio of geometric LSmeans with corresponding 90% confidence interval calculated from the exponential of the difference between the Test and Reference for the ln-transformed parameters Cmax and AUC0-T should all be within the 80.00 to 125.00% bioequivalence range.

Analytical methods

The applicant provided a full bioanalytical report, including, besides the validation report, the results for in-study analysis covering: carryover, deviations, calibration standard concentrations and standard curve parameters, quality control, sample analyses, study sample concentrations, repeat analyses and incurred sample reproducibility.

The validation report included values for lower limit of quantification, between-run accuracy and precision, within-run accuracy and precision, recovery of analyte and internal standard, as well as specificity and selectivity of the HPLC method using MS/MS detection.

The results are in compliance with the Guideline on Bioanalytical method validation (EMEA/CHMP/EWP/192217/09).

The stability of the analyte in the matrix as well as of the reference standard in the different steps of the analytical procedure and storage conditions is adequate for the purpose of the study and complies with the requirements in Guideline on Bioanalytical method validation (EMEA/CHMP/EWP/192217/09).

Pharmacokinetic variables

The main absorption and disposition parameters were calculated using a non-compartmental approach with a log-linear terminal phase assumption. The trapezoidal rule was used to estimate area under the curve. The terminal phase estimation was based on maximizing the coefficient of determination. The pharmacokinetic parameters of this trial were Cmax, Tmax, AUC0-T, AUC0-∞, residual area, λZ and Thalf.

Statistical methods

The statistical analysis was based on a parametric ANOVA model of the pharmacokinetic parameters; the two-sided 90% confidence interval of the ratio of geometric means for the Cmax and AUC0-T was based on ln-transformed data; Tmax was based on a non-parametric approach.

The ratio of geometric LS means with corresponding 90% confidence interval calculated from the exponential of the difference between the Test and Reference product for the ln-transformed parameters Cmax and AUC0-T must be all within the 80.00 to 125.00% bioequivalence range.

The statistical methods employed are in compliance with the Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98)

In addition, the applicant specified the testing approach applied in the study.

Results

The applicant presented a full report on the results of the study, including darunavir concentrations for each sampling time, phase and subjects. Tables and figures were included.

Moreover, from the individual pharmacokinetic parameters it can be concluded that profiles were well characterized.

Table 3. Summary of the Statistical Analysis of Darunavir

PARAMETER	INTRA-SUBJECT C.V. (%)	GEOMETRIC LSMEANS[a]		RATIO (%)	90% CONFIDENCE LIMITS (%)	
		TEST (n=22)	REFERENCE (n=22)		LOWER	UPPER
C_{max}	12.9	9453.2	9662.9	97.83	91.5[illegible]	104.57
AUC_{0-T}	9.2	163650.0	162443.0	100.74	[illegible].02	105.69

[a] units are ng/mL for C_{max} and ng·h/mL for AUC_{0-T}

The results are presented as median and range for test and reference respectively.

Tmax (hours): 4.50 (1.33-8.00) 3.67 (1.33-8.00)

Safety data

A total of 24 subjects entered the study, 23 (96%) of which received the Test (Darunavir) and the Reference (Prezista); all 24 subjects received at least one dose of the concomitant Ritonavir medication (Norvir). Four additional subjects only received 2 consecutive doses of the concomitant ritonavir medication. No serious adverse events (SAE) and no deaths were reported for any of the subjects enrolled in this study. None of the subjects who received the investigational products was withdrawn by the investigator for safety reasons. A total of 19 AEs were reported by 11 (46%) of the 24 subjects who participated in this study. Of these AEs, 7 were experienced following the administration of ritonavir, 8 occurred after administration of the Test and 4 occurred after administration of the Reference. Six AEs (32%) were considered drug-related.

Overall, the drugs tested were generally safe and well tolerated by the subjects (male and female) included in this study and no new safety concerns were raised during the conduct of the study.

Conclusions

Based on the presented bioequivalence study, Darunavir 800 mg film-coated tablets manufactured by KrKa d.d. Novo mesto, is considered bioequivalent with PREZISTA 800 mg film-coated tablets.

The results of study No KRS-P8-015 with 800 mg formulation can be extrapolated to other strengths 600 mg and 400 mg, according to conditions in the relevant Guidelines.

2.4.3. Pharmacodynamics

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

application.

2.4.4. Post marketing experience

No post-marketing data are available. The medicinal product has not been marketed in any country.

2.4.5. Discussion on clinical aspects

The applicant has presented one bioequivalence study using the 800mg presentation. The results conclude that the test product is bioequivalent to the chosen reference product.

As for the two other strengths (600 mg and 400 mg) applied for, a biowaiver can be granted based on the compliance with the general requirements for a waiver for additional strength(s) as per Guideline on the Investigation of Bioequivalence, CPMP/EWP/QWP/1401/98 Rev. 1/ Corr **, point 4.1.6 Strength to be investigated.

2.4.6. Conclusions on clinical aspects

Based on the presented bioequivalence study Darunavir 800mg film coated tablets of KrKa d.d. Novo mesto, Slovenia, is considered bioequivalent with Prezista (Darunavir) 800mg film coated tablets manufactured by Janssen-Cilag SpA Italy.

The results of study 16-495 with the 800mg film- coated tablet formulation can be extrapolated to Darunavir 400mg and 600 mg (bio waiver criteria are fulfilled).

2.5. Risk management plan

Safety concerns

Important identified risks:	Severe Skin Reactions
	Hepatotoxicity
	Hyperglycaemia
	Lipid Abnormalities
	Immune Reconstitution Inflammatory Syndrome
	Development of Drug Resistance
	Overdose due to Medication Error
	Drug-Drug Interactions
Important potential risks:	Coronary Artery Events
	Growth Abnormalities in the Paediatric Population
	Off-Label Use of DRV/COBI in the Paediatric Population and in ARV treatment-experienced patients with HIV-1 RNA >100,000 copies/mL
Missing information:	Older People (65 years and above)
	Pregnant and breast-feeding women
	Subjects with severe hepatic impairment (Child-Pugh C)
	Subjects with renal impairment
Missing information – DRV/rtv:	Long-term safety data in children 3 to <6 years of age
Missing information – DRV/COBI:	Children <18 years of age
	Long-term safety of DRV/COBI in adults
	Subjects co-infected with HIV and HBV and/or HCV

Pharmacovigilance plan

There are no additional PhV activities on-going or planned. However, pregnancy reports will be actively followed-up using Pregnancy Report Forms.

Risk minimisation measures

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Important identified risks:		
Severe skin reactions as Stevens-Johnson sydrome (SJS), Toxic epidermal necrolysis (TEN), Acute generalised exanthematous pustulosis & Drug reaction with eosinophilia and systemic symptoms (DRESS)	Content in SPC Section: Warning in section 4.4 Listed in section 4.8 Prescription only medicine.	None
Hepatotoxicity	Content in SPC Section: Warning in section 4.2 Contraindication in section 4.3 Warning in section 4.4 Listed in section 4.8 Wording in section 5.2 Prescription only medicine.	None
Hyperglycaemia	Content in SPC Section: Warning in section 4.4 Listed in section 4.8 Prescription only medicine.	None
Lipid Abnormalities	Content in SPC Section: Warning in section 4.4 Listed in section 4.8 Prescription only medicine.	None
Immune Reconstitution Inflammatory Syndrome	Content in SPC Section: Warning in section 4.4 Listed in section 4.8 Prescription only medicine.	None
Development of Drug Resistance	Content in SPC Section: Wording in section 4.1 Contraindication in section 4.3 Advice in section 4.4 Warning in section 4.5 Wording in section 5.1 Prescription only medicine.	None
Overdose due to Medication Error	Content in SPC Section: Advice/posology in section 4.2 Prescription only medicine.	None
Drug-Drug Interactions	Content in SPC Section: List of contraindicated drugs in section 4.3 Warning in section 4.4 Warning in section 4.5 Prescription only medicine.	None
Important potential risks:		
Coronary Artery Events	Content in SPC Section: Listed in section 4.8 Prescription only medicine.	None
Growth Abnormalities in the Paediatric Population	No risk minimisation activities in addition to prescription only are proposed. Should the PhV activities uncover additional data, another risk minimisation activities may be proposed if necessary. Prescription only medicine.	None
Off-Label Use of DRV/COBI in the Paediatric Population and in ARV treatment-experienced patients with HIV-1 RNA >100,000 copies/mL	Content in SPC Section: Warning in section 4.2 Warning in section 4.4 Prescription only medicine.	None
Missing information:		
Older People (65 years and above)	Content in SPC Section:	None

	Warning in section 4.2 Warning in section 4.4 Wording in section 5.2 Prescription only medicine.	
Pregnant and breast-feeding women	Content in SPC Section: Information in section 4.2 Warning in section 4.4 Wording in section 4.6 Prescription only medicine.	None
Subjects with severe hepatic impairment (Child-Pugh C)	Content in SPC Section: Information in section 4.2 Contraindication in section 4.3 Warning in section 4.4 Wording in section 5.2 Prescription only medicine.	None
Subjects with renal impairment	Content in SPC Section: Wording in section 4.2 Warning in section 4.4 Prescription only medicine.	None
Missing information - DRV/rtv:		
Long term safety in children 3 to <6 years of age	Content in SPC Section: Wording in section 4.8, subsection Paediatric population Wording in section 5.1, subsection Clinical results Prescription only medicine	None
Missing information - DRV/COBI:		
Children <18 years of age	Content in SPC Section: Information in section 4.2 Prescription only medicine.	None
Long-term safety of DRV/COBI in adults	Content in SPC Section: Warning in section 4.4 List of ADRs in section 4.8 Prescription only medicine.	None
Subjects coinfected with HIV and HBV and/or HCV	Content in SPC Section: Warning in section 4.4 Warning in section 4.5 Prescription only medicine.	None

Conclusion

The CHMP and PRAC considered that the risk management plan version 1.3 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.

Periodic Safety Update Reports submission requirements

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.

2.7. Product information

During the Marketing Application procedure, the applicant agreed to fully mirror the indications as granted for Prezista, allowing Darunavir KrKa d.d. to be co-administered either with ritonavir (for all applied dose strengths) or cobicistat pharmaco-enhancer (for 400mg /800mg dose strengths):

400 mg and 800 mg

"Darunavir Krka d.d., co-administered with low dose ritonavir is indicated in combination with other antiretroviral medicinal products for the treatment of patients with human immunodeficiency virus (HIV-1) infection."

Darunavir Krka d.d , co-administered with cobicistat is indicated in combination with other antiretroviral medicinal products for the treatment of human immunodeficiency virus (HIV-1) infection in adult patients (see section 4.2)."

600 mg

"Darunavir Krka d.d., co-administered with low dose ritonavir is indicated in combination with other antiretroviral medicinal products for the treatment of patients with human immunodeficiency virus (HIV-1) infection."

2.7.1. User consultation

The results of the user consultation with target patient groups on the package leaflet for 400mg /800 mg film-coated tablets 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.

No full user consultation with target patient groups on the package leaflet for 600mg film-coated tablets has been performed on the basis of a bridging report making reference to Darunavir Krka 400mg /800mg film-coated tablets. The bridging report submitted by the applicant has been found acceptable.

3. Benefit-risk balance

This application concerns a generic version of darunavir film-coated tablets formulation.
The reference product Prezista, co-administered with low dose ritonavir, is indicated in combination with other antiretroviral medicinal products for the treatment of patients with human immunodeficiency virus (HIV-1) infection. Prezista, co-administered with cobicistat, is indicated in combination with other antiretroviral medicinal products for the treatment of human immunodeficiency virus (HIV-1) infection in adult patients.

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 studies conducted with 800 mg film-coated tablet formulation, forms the pivotal basis, with a randomized single-dose, two-treatment, two-sequence, two-period crossover design (concomitant medication : ritonavir 100mg OD for 5 days in all subjects). 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 and "wash-out" period were adequate. The analytical method was validated. Pharmacokinetic and statistical methods applied were adequate.

The test formulation of Darunavir film-coated Tablet 800 mg manufactured by krKa d.d. Novo mesto, met the protocol-defined criteria for bioequivalence when compared with the [reference product]. 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, 80.00 to 125.00%]. Bioequivalence of the two formulations was demonstrated.

As for the two other strengths (600 mg and 400 mg) applied for, a biowaiver can be granted based on the compliance with the general requirements for a waiver for additional strength(s) as per Guideline on the Investigation of Bioequivalence, CPMP/EWP/QWP/1401/98 Rev. 1/ Corr **, point 4.1.6 Strength to be investigated.

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 Darunavir Krka d.d. is favourable in the following indication:

<u>400 mg and 800 mg Film-coated Tablet formulation</u>

Darunavir Krka d.d., co-administered with low dose ritonavir is indicated in combination with other antiretroviral medicinal products for the treatment of patients with human immunodeficiency virus (HIV-1) infection.

Darunavir Krka d.d., co-administered with cobicistat is indicated in combination with other antiretroviral medicinal products for the treatment of patients with human immunodeficiency virus (HIV-1) infection in adult patients (see section 4.2).

Darunavir Krka d.d. 400 mg and 800 mg tablets may be used to provide suitable dose regimens for the treatment of HIV-1 infection in adult and paediatric patients from the age of 3 years and at least 40 kg body weight who are:

- antiretroviral therapy (ART)-naïve (see section 4.2).

- ART-experienced with no darunavir resistance associated mutations (DRV-RAMs) and who have plasma HIV-1 RNA < 100,000 copies/ml and CD4+ cell count ≥ 100 cells x 10^6/l. In deciding to initiate treatment with darunavir in such ART-experienced patients, genotypic testing should guide the use of darunavir (see sections 4.2, 4.3, 4.4 and 5.1).

<u>600 mg Film-coated Tablet formulation</u>

Darunavir Krka d.d., co-administered with low dose ritonavir is indicated in combination with other antiretroviral medicinal products for the treatment of patients with human immunodeficiency virus (HIV-1) infection.

Darunavir Krka d.d. 600 mg tablets may be used to provide suitable dose regimens (see section 4.2):

- For the treatment of HIV-1 infection in antiretroviral treatment (ART)-experienced adult patients, including those that have been highly pre-treated.
- For the treatment of HIV-1 infection in paediatric patients from the age of 3 years and at least 15 kg body weight.

In deciding to initiate treatment with darunavir co-administered with low dose ritonavir, careful consideration should be given to the treatment history of the individual patient and the patterns of mutations associated with different agents. Genotypic or phenotypic testing (when available) and treatment history should guide the use of darunavir.

The CHMP 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).

Other 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.