COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Darunavir Laurus 400 mg, 600 mg and 800 mg film-coated tablets (darunavir)

NL/H/5642/001-003/DC

Date: 28 February 2023

This module reflects the scientific discussion for the approval of Darunavir Laurus 400 mg, 600 mg and 800 mg film-coated tablets. The procedure was finalised on 9 May 2019 in Germany (DE/H/5597/001-003/DC). After a transfer on 28 June 2022, the current RMS is the Netherlands. For information on changes after this date please refer to the 'steps taken after finalisation' at the end of this PAR.

List of abbreviations

ASMF	Active Substance Master File
CEP	Certificate of Suitability to the monographs of the European Pharmacopoeia
CHMP	Committee for Medicinal Products for Human Use
CMD(h)	Coordination group for Mutual recognition and Decentralised procedure for human medicinal products
CMS	Concerned Member State
EDMF	European Drug Master File
EDQM	European Directorate for the Quality of Medicines
EEA	European Economic Area
ERA	Environmental Risk Assessment
EMA	European Medicines Agency
ICH	International Conference of Harmonisation
MAH	Marketing Authorisation Holder
Ph.Eur.	European Pharmacopoeia
PL	Package Leaflet
RH	Relative Humidity
RMP	Risk Management Plan
RMS	Reference Member State
SmPC	Summary of Product Characteristics
TSE	Transmissible Spongiform Encephalopathy

INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for Darunavir Laurus 400 mg, 600 mg and 800 mg film-coated tablets, from Laurus Generics GmbH.

Darunavir is used together with low-dose ritonavir and other antiviral medicines to treat adults and children from the age of 3 years 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). Darunavir is an inhibitor of the dimerisation and of the catalytic activity of the HIV-1 protease (KD of 4.5 x 10-12 M). It selectively inhibits the cleavage of HIV encoded Gag-Pol polyproteins in virus infected cells, thereby preventing the formation of mature infectious virus particles. Darunavir exhibits activity against laboratory strains and clinical isolates of HIV-1 and laboratory strains of HIV-2 in acutely infected T-cell lines, human peripheral blood mononuclear cells and human monocytes/macrophages with median EC_{50} values ranging from 1.2 to 8.5 nM (0.7 to 5.0 ng/ml). Darunavir demonstrates antiviral activity in vitro against a broad panel of HIV-1 group M (A, B, C, D, E, F, G) and group O primary isolates with EC_{50} values ranging from < 0.1 to 4.3 nM. These EC_{50} values are well below the 50% cellular toxicity concentration range of 87 µM to > 100 µM.

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

This decentralised procedure concerns a generic application claiming essential similarity with the innovator product Prezista film-coated tablets (EMEA/H/C/000707) which has been registered in the EMEA by Janssen-Cilag International NV since 12 February 2007 (original product). In the Netherlands, Prezista has been registered since 19 January 2009 (400 mg), 29 January 2009 (600 mg) and 15 January 2013 (800 mg) by the procedure EU/1/06/380. The drug products for which marketing authorisation is applied for, contain the amorphous form of darunavir whereas the reference product Prezista contains the ethanolate salt of darunavir. This is not expected to affect the efficacy and safety as the tested product (800 mg film-coated tablet) exhibited an equivalent rate and extent of absorption compared to the reference product (see IV, Clinical Aspects).

The concerned member states (CMS) involved in this procedure were France, Spain, the Netherlands and the United Kingdom.

The marketing authorisation has been granted pursuant to Article 10(1) of Directive 2001/83/EC.

General comments on compliance with GMP, GLP, GCP and agreed ethical principles GMP

The RMS has been assured that acceptable standards of GMP are in place for these product types at all sites responsible for the manufacture and assembly of this product. For manufacturing sites within the Community, the RMS has accepted copies of current

manufacturer authorisations issued by inspection services of the competent authorities as certification that acceptable standards of GMP are in place at those sites. GMP active substance: Regarding the statement on GMP for the active substance and intermediate manufacturers a QP declaration is provided from the manufacturer responsible for batch release situated in the EU. GCP: A statement on the application of appropriate GCP standards in the submitted studies has been provided. The clinical site was inspected several times. The deviations observed and the comments made during the inspections do not question the acceptability of the study data within the scope of a marketing authorisation request and do not affect data integrity/quality with respect to the approval decision.

I. QUALITY ASPECTS

I.1 Introduction

Darunavir Laurus are film-coated tablets containing 400, 600 or 800 mg Darunavir packaged in blister materials and HDPE bottles with child resistant polypropylene screw caps with desiccant.

I.2 Drug Substance

The drug product contains Darunavir free base in amorphous form. Darunavir is not described in the Ph. Eur. or any other official European pharmacopeia.

Manufacturing process

The ASMF procedure is followed for the drug substance. The route of synthesis, detailed descriptions of the manufacturing process and flow diagrams have been provided. Information on the stereochemistry of Darunavir, carry-over of the reagents, intermediates, impurities, residual solvents and catalysts used in the manufacturing process, and genotoxic impurities have been provided.

Quality control of drug substance

The specifications for the drug substance for the ASMF holder and the drug product manufacturer are acceptable. The analytical methods have been adequately described in the dossier. Validation data for all in-house methods have been provided. The methods are suitable for their intended use. Batch analysis data for several batches tested at the drug substance supplier and drug product manufacturer have been provided. All results comply with the specifications. For each specification attribute a justification has been provided which is accepted.

Stability of drug substance

Darunavir is packed in the primary pack (transparent low density polyethylene bag) filled with nitrogen and strip sealed followed by another transparent low density polyethylene (LDPE) bag filled with nitrogen containing 1.0 g silica gel bags and strip sealed. Secondary pack is triple laminated sunlight barrier bag (TLSB) and heat sealed and finally kept in high density

polyethylene (HDPE) container in PAPP (polyester/ aluminium/ polyester/ polyethylene) bags enclosed in a carton canister.

Stability studies under ICH conditions and forced decomposition studies have been conducted. Stability data for pulverised and un-pulverised drug substance have been provided. Data for up to 18 months under the long term conditions are available for the un-pulverised drug substance. The pulverized drug substance batches were found to be unstable at 25°C and tend to convert to crystalline form over time. Therefore, a re-test period of 6 months has been proposed for the pulverised batches, which is accepted. The proposed storage conditions "Store in a well closed container at 2-8°C packed under nitrogen atmosphere" are acceptable.

I.3 Medicinal Product

Manufacturing process

The manufacturing process including in-process controls and controls of critical steps are described in detail. Satisfactorily process validation data for three production batches for each of the strengths are given.

Quality control of drug product

The proposed release and shelf life specifications contain the quality relevant characteristics required for this pharmaceutical form. All test procedures are adequate described. Satisfactory validation data in accordance with ICH validation guideline are provided. Batch analysis results of four production batches for each of the strengths are presented which show compliance with the set specifications.

Stability of drug product

ICH stability studies performed for each of the strengths stored in HDPE containers and blisters over 18 months at long-term and 6 months at accelerated conditions support the proposed shelf life of 30 months if stored in the original package in order to protect from moisture.

II. NON-CLINICAL ASPECTS

A bioequivalence study was performed comparing the 800 mg drug product and the originator product Prezista 800 mg film-coated tablets. Similar dissolution profiles of the 800 mg biobatch of the proposed product and the 400 and 600 mg strengths at three different pH values and the QC method are given. The requirements concerning in-vitro comparison for strengths biowaiver according to the EU guideline CPMP/EWP/QWP/1401/98 Rev. 1/Corr are fulfilled for the 400 and 600 mg strengths.

There are no objections to approval of Darunavir Laurus 400 mg, 600 mg and 800 mg film-coated tablets from a non-clinical point of view.

II.1 Ecotoxicity/environmental risk assessment (ERA)

Since Darunavir is intended for generic substitution, this will not lead to an increased exposure to the environment. An environmental risk assessment is therefore not deemed necessary.

III. CLINICAL ASPECTS

III.1 Introduction

To support this application, the applicant has submitted a bioequivalence study comparing the rate and extent of absorption of the generic darunavir 800 mg tablets with the reference product Prezista (Darunavir) 800 mg film-coated tablets marketed by Janssen-Cilag International NV after single dose administration under fed conditions. The requirement for bioequivalence studies for the additional strengths can be waived as darunavir exhibits linear pharmacokinetics over the range of 400-1200 mg and provided that all the general biowaiver criteria listed in the section 4.1.6 of the "Guideline on the Investigation of Bioequivalence" are met. Relevant for the assessment is the Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev 1/Corr) and the Guideline on Bioanalytical method validation (EMEA/CHMP/EWP/192217/2009 Rev.1 Corr). Both guidelines were followed. The clinical overview on the clinical pharmacology, efficacy and safety of darunavir refers to 45 publications up to the year 2018. The clinical overview is adequate.

III.2 Pharmacokinetics

Biowaiver

A bioequivalence study was performed comparing the 800 mg drug product and the originator product Prezista 800 mg film-coated tablets. Similar dissolution profiles of the 800 mg biobatch of the proposed product and the 400 and 600 mg strengths at three different pH values and the QC method are given. The requirements concerning in-vitro comparison for strengths biowaiver according to the EU guideline CPMP/EWP/QWP/1401/98 Rev. 1/Corr are fulfilled for the 400 and 600 mg strengths.

Bioequivalence studies

Design

To support this application, the applicant has submitted one single dose bioequivalence study under fed conditions (Code: 16-VIN-0521). The study was designed as an open label, balanced, randomized, single-dose, two treatment, two-sequence, two-period, crossover oral bioequivalence study in healthy, adult male and female subjects. The study objective was to compare the rate and extent of absorption of Darunavir 800 mg tablets (Test) and Prezista (darunavir) 800 mg film-coated tablets (Reference) co-administered with ritonavir under fed condition as well as to monitor the safety of the subjects. 48 subjects were included of which 40 completed the study. Selected reference and test product (source, batch size, expiry date) as well as statistical methods were appropriate. The bioanalytical method was sufficiently validated and documented.

Results

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

Treatment N=21	AUC_{0-t} (µg.h/mL)	$AUC_{0-\infty}$ (µg.h/mL)	C_{max} (µg/mL)	t_{max} (h)
Test	119.184 (± 45.5823)	123.405 (± 47.3813)	8.500 (± 1.6524)	4.330 (1.67 - 5.50)
Reference	119.665 (± 39.8074)	122.730 (± 41.0779)	8.919 (± 1.6192)	4.000 (1.33 - 6.00)
***Ratio (90% CI)**	98.97 (91.35 - 107.22)	--	95.28 (90.07 - 100.79)	--

AUC_{0-t} Area under the plasma concentration curve from administration to last observed concentration at time t. AUC_{0-72h} can be reported instead of AUC_{0-t}, in studies with sampling period of 72 h, and where the concentration at 72 h is quantifiable. Only for immediate release products.
$AUC_{0-\infty}$ Area under the plasma concentration curve extrapolated to infinite time. $AUC_{0-\infty}$ does not need to be reported when AUC_{0-72h} is reported instead of AUC_{0-t}.
C_{max} Maximum plasma concentration.
t_{max} Time until C_{max} is reached.

**In-transformed values*

Biowaiver

According to the Guideline on the investigation of bioequivalence (CPMP/EWP/QWP/1401/98 Rev. 1/Corr**) the following biowaiver criteria are fulfilled: All strengths are manufactured by the same process. The compositions of the different strengths are qualitatively the same and quantitatively proportional. The f_2 values are between 50 and 100, suggesting that the dissolution profiles of the three strengths are similar. Additionally, the pharmacokinetics of darunavir is linear after single dose administration over the 400 – 1200 mg dose range, when given with 100 mg ritonavir (as stated in the EPAR Scientific discussion of the innovator product Prezista) and the bioequivalence study was conducted at the highest strength, i.e. 800 mg tablets, for which the marketing authorisation is applied for.

Conclusion on bioequivalence study:

In conclusion, Darunavir 800 mg tablets are considered bioequivalent with Prezista 800 mg film-coated tablets.

III.3 Clinical safety

No specific safety concerns were raised from the single bioequivalence study.

III.4 Summary Pharmacovigilance system

The applicant has submitted a signed Summary of the applicant's and/or proposed Future MAH's Pharmacovigilance System. Provided that the Pharmacovigilance System Master File fully complies with the new legal requirements as set out in the Commission Implementing Regulation and as detailed in the GVP module, the RMS considers the Summary acceptable.

III.5 Risk Management Plan

The applicant has submitted a risk management plan in accordance with the requirements of Directive 2001/83/EC as amended, describing the pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to the medicinal product(s) applied for authorisation.

Safety specification

According to the Applicant the safety specification is in full accordance with the current safety specification agreed and published for a similar product which is acceptable:

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

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 • Off-label use of darunavir/cobicistat in the paediatric population and in antiretroviral (ARV) treatment-experienced patients with HIV-1 RNA > 100000 copies/mL.
Missing information	**Darunavir/ritonavir and Darunavir/cobicistat** • Elderly (65 years and above) • Subjects with severe hepatic impairment (Child-Pugh C) • Subjects with renal impairment **Darunavir/ritonavir** • Long-term safety data in children from 3 to < 6 years of age **Darunavir/cobicistat** • Children < 18 years of age • Long-term safety in adults • Subjects co-infected with HIV and Hepatitis B virus and/or Hepatitis C virus

Pharmacovigilance Plan

Routine pharmacovigilance is suggested and no additional pharmacovigilance activities are proposed by the applicant, which is endorsed. It should be noted that for the further evaluation of some of the safety concerns additional pharmacovigilance measures are in place for the Originator product. Additionally, a specific follow-up questionnaire on dose regimen

has been established for the Originator RMP and the applicant. The future MAH should ensure that appropriate follow-up on adverse reaction cases regarding the strengths of tablets, number of tablet(s) per intake, dosage frequency per day as well as potential, intake of concomitant ritonavir including dosing details are retrieved, where necessary.

Risk minimisation measures

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

Summary of the RMP

The submitted Risk Management Plan is acceptable. 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 RMS;
- 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.

If the dates for submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time, but via different procedures.

Periodic Safety Update Report (PSUR)

Use the below statement in case a substance is listed in the published EURD list. With regard to PSUR submission, the MAH should take the following into account:

- PSURs shall be submitted in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal. Marketing authorisation holders shall continuously check the European medicines web-portal for the DLP and frequency of submission of the next PSUR.
- For medicinal products authorized under the legal basis of Article 10(1) or Article 10a of Directive 2001/83/EC, no routine PSURs need to be submitted, unless otherwise specified in the EURD list.
- In case the active substance will be removed in the future from the EURD list because the MAs have been withdrawn in all but one MS, the MAH shall contact that MS and propose DLP and frequency for further PSUR submissions together with a justification.

IV. USER CONSULTATION

No User Testing has been submitted. The applicant has submitted a Bridging Report. The applicant has submitted 2 bridging requests. Parent and daughter leaflet are both generic medicinal products containing the active substance darunavir. Comparative documents for

the texts are provided by the applicant. The identified differences do not affect the usability of the leaflet as the information is well structured and written in a user friendly style. Patient friendly and comprehensible style is used in all leaflets. Based on the bridging evaluation it can be concluded that the text for the proposed daughter leaflets Darunavir 400 mg, 600 mg and 800 mg film-coated tablets are compliant with article 59(3) of Council Directive 2001/83EC (Consultation with Target Patient Groups).

V. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Pharmacokinetic results indicate bioequivalence between Darunavir 800 mg tablets and Prezista 800 mg film-coated tablets. Overall, approval can be recommended from the quality, non-clinical and clinical point of view.

The application is approved. For intermediate amendments see current product information.

STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

Procedure number*	Scope	Product Information affected	Date of end of procedure	Approval/ non approval	Summary/ Justification for refuse
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