CBG MEB

Public Assessment Report

Scientific discussion

Darunavir CF 75 mg, 150 mg, 300 mg, 400 mg, 600 mg and 800 mg, film-coated tablets

(darunavir)

NL/H/3609/001-006/DC

Date: 16 November 2017

This module reflects the scientific discussion for the approval of Darunavir CF 75 mg, 150 mg, 300 mg, 400 mg, 600 mg and 800 mg, film-coated tablets. The procedure was finalised on 15 February 2017. 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
ICH	International Conference of Harmonisation
MAH	Marketing Authorisation Holder
Ph.Eur.	European Pharmacopoeia
PL	Package Leaflet
RH	Relative Humidity
RMP	Risk Management Plan
SmPC	Summary of Product Characteristics
TSE	Transmissible Spongiform Encephalopathy

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for Darunavir CF 75 mg, 150 mg, 300 mg, 400 mg, 600 mg and 800 mg, film-coated tablets, from Centrafarm B.V.

The product, 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 CF 75 mg, 150 mg, 300 mg and 600 mg film-coated tablets
These strengths may be used to provide suitable dose regimens:

- 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 these strengths 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 these products.

Darunavir CF 400 mg and 800 mg, film-coated tablets
These strengths, co-administered with cobicistat are indicated in combination with other antiretroviral medicinal products for the treatment of human immunodeficiency virus (HIV-1) infection in adult patients.

The film-coated 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.
- 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 these strengths in such ART-experienced patients, genotypic testing should guide the use of these products.

A comprehensive description of the indications and posology is given in the SmPC.

This decentralised procedure concerns a generic application claiming essential similarity with the innovator product Prezista 800 mg, film-coated tablets which has been registered in EEA by Janssen-Cilag International NV since 12 February 2007 through a centralised procedure.

The concerned member states (CMS) involved in this procedure were Austria (only 800 mg), Belgium, Germany, Denmark (only 400 mg, 600 mg and 800 mg), Finland (only 400 mg, 600 mg and 800 mg), France (only 400 mg, 600 mg and 800 mg), Ireland(only 400 mg, 600 mg and 800 mg), Italy (only 400 mg, 600 mg and 800 mg), Luxembourg, Poland (only 400 mg, 600 mg and 800 mg) and Sweden (only 400 mg, 600 mg and 800 mg).

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

II. QUALITY ASPECTS

II.1 Introduction

- Darunavir CF 75 mg is a white, caplet shaped film-coated tablet, debossed with ‘75’ on one side and plain on the other side. Each film-coated tablet contains 75 mg darunavir.

- Darunavir CF 150 mg is a white, oval shaped film-coated tablet, debossed with '150' on one side and plain on the other side. Each film-coated tablet contains 150 mg darunavir.
- Darunavir CF 300 mg is an orange, oval shaped film-coated tablet, debossed with '300' on one side and plain on the other side. Each film-coated tablet contains 300 mg darunavir.
- Darunavir CF 400 mg is a light orange, oval shaped film-coated tablet, debossed with '400' on one side and plain on the other side. Each film-coated tablet contains 400 mg darunavir
- Darunavir CF 600 mg is an orange, oval shaped film-coated tablet, debossed with '600' on one side and plain on the other side. Each film-coated tablet contains 600 mg darunavir
- Darunavir CF 800 mg is a dark red, oval shaped film-coated tablet, debossed with '800' on one side and plain on the other side. Each film-coated tablet contains 800 mg darunavir.

The strengths are dose proportional.

The film-coated tablets are packed in HDPE bottles stoppered with a polypropylene, child resistant closure or Aluminium-PVC/PE/PVDC perforated blisters.

The excipients are:
Tablet core – microcrystalline cellulose (E460), crospovidone Type A (E1202), colloidal anhydrous silica (E551) and magnesium stearate (E470b)
Tablet coating – poly (vinyl alcohol) (E1203), titanium dioxide (E171), macrogol 3350 (E1521) and talc (E553b). In addition, the 300 mg, 400 mg and 600 strengths contain sunset yellow FCF (E110) and the 800 mg strength contains iron oxide red (E172).

II.2 Drug Substance

The active substance is darunavir, an established active substance, not described in any Pharmacopoeia. It is a white to off-white powder which soluble in dichloromethane, sparingly soluble in methanol, and insoluble in water. A total of 5 chiral centers are present and one single enantiomer is consistently produced. The polymorphic form of this active substance is amorphous.

The Active Substance Master File (ASMF) procedure is used for the active substance. The main objective of the ASMF procedure, commonly known as the European Drug Master File (EDMF) procedure, is to allow valuable confidential intellectual property or 'know-how' of the manufacturer of the active substance (ASM) to be protected, while at the same time allowing the applicant or marketing authorisation holder (MAH) to take full responsibility for the medicinal product, the quality and quality control of the active substance. Competent Authorities/EMA thus have access to the complete information that is necessary to evaluate the suitability of the use of the active substance in the medicinal product.

Manufacturing process
The manufacturing process consists of 7 synthetic steps. No class 1 solvents or heavy metals are used in this process. The active substance has been adequately characterised and acceptable specifications have been adopted for the starting materials, solvents and reagents.

Quality control of drug substance
The active substance specification has been established in-house by the MAH and is identical to the specification of the ASMF-holder. The specification is considered adequate to control the quality. Batch analytical data demonstrating compliance with this specification have been provided for 6 batches.

Stability of drug substance
Stability data on the active substance(s) have been provided for 6 batches stored at 25°C/60% RH (3 months) and 40°C/75% RH (3 months) which was insufficient to grant a retest period. The active substance is therefore fully tested to ensure compliance with its specification immediately prior to its use in manufacture of the product.

II.3 Medicinal Product

Pharmaceutical development
The development of the product has been described, the choice of excipients is justified and their functions explained. The choices of the packaging and manufacturing process are justified.
The main development studies were formulation trials and comparative dissolution studies with the innovator product. A bioequivalence study has been performed for the 800 mg product strength versus the reference product. For the additional strengths a biowaiver has been justified based on comparative dissolution studies. The drug product batch that was used in the bioequivalence study is representative for the finalised formulation and composition. The pharmaceutical development of the product has been adequately performed.

Manufacturing process
The manufacturing process consists of mixing, lubrication, dry granulation, compression and film-coating. The manufacturing process has been adequately validated according to relevant European guidelines. Process validation data on the product has been presented for 3 commercial scale batches per strength. The product is manufactured using conventional manufacturing techniques.

Control of excipients
The excipients comply with the requirements of their respective Ph. Eur. Monographs These specifications are acceptable.

Quality control of drug product
The finished product specifications are adequate to control the relevant parameters for the dosage form. The specification includes tests for description, identification, dimensions, water, assay, related substances, uniformity of dosage units (mass variation), uniformity of mass, dissolution, and microbiological quality. Limits in the specification have been justified and are considered appropriate for adequate quality control of the product. Except for water content and related substances, the release and shelf-life requirements are identical. The specification is acceptable. The analytical methods have been adequately described and validated. Batch analytical data 3 commercial scale batches per strength from the proposed production site have been provided, demonstrating compliance with the specification.

Stability of drug product
Stability data on the product has been provided on at least three commercial scaled batches per strength packed in HDPE bottles that were stored at 25°C/60% RH (up to 18 months) and 40°C/75% RH (up to 6 months). The conditions used in the stability studies are according to the ICH stability guideline. Based on the available stability data, the claimed shelf-life of 30 months without any special storage restriction for tablets packed in HDPE bottles is justified. Stability data have been provided demonstrating that the product remains stable for 6 months following first opening of the container when stored below 25°C.

Specific measures for the prevention of the transmission of animal spongiform encephalopathies
Magnesium stearate is the only substance of animal origin. The applied manufacturing process for magnesium stearate is sufficiently rigid, so the use of this excipient will not pose a risk of transmitting TSE.

II.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the member states consider that Darunavir CF has a proven chemical-pharmaceutical quality. Sufficient controls have been laid down for the active substance and finished product. No post-approval commitments were made.

III. NON-CLINICAL ASPECTS

III.1 Ecotoxicity/environmental risk assessment (ERA)

Since Darunavir CF 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.2 Discussion on the non-clinical aspects

This product is a generic formulation of Prezista which is available on the European market. Reference is made to the preclinical data obtained with the innovator product. 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. Therefore, the member states agreed that no further non-clinical studies are required.

IV. CLINICAL ASPECTS

IV.1 Introduction

Darunavir is a well-known active substance with established efficacy and tolerability.
A clinical overview has been provided, which is based on scientific literature. The overview justifies why there is no need to generate additional clinical data. Therefore, the member states agreed that no further clinical studies are required.

For this generic application, the MAH has submitted a bioequivalence study, which is discussed below.

IV.2 Pharmacokinetics

The MAH conducted a bioequivalence study in which the pharmacokinetic profile of the test product Darunavir CF 800 mg, film-coated tablets (Centrafarm B.V., NL) is compared with the pharmacokinetic profile of the reference product Prezista (Janssen-Cilag International NV, Belgium). In this study darunavir was administered with 100 mg ritonavir.

The choice of the reference product in the bioequivalence studies is accepted, as Prezista has been registered through a centralised procedure. The formula and preparation of the bioequivalence batch is identical to the formula proposed for marketing.

Biowaiver
With respect to the above presented conditions, it can be concluded that:

- All strengths of the test product are manufactured with the same manufacturing process followed.
- The qualitative composition of the strengths is the same and their composition is quantitatively proportional.
- Appropriate in vitro dissolution has confirmed the adequacy of waiving additional in vivo bioequivalence testing.

Dissolution data of the additional strengths versus the 800 mg strength showed that in some cases the obtained dissolution profiles were found to be not similar. In accordance with the Guideline on the investigation of bioequivalence (CPMP/EWP/QWP/1401/98 Rev. 1/ Corr **), at pH values where sink conditions may not be achievable for all strengths in vitro dissolution may differ between strengths. Comparison with the respective strength of the reference medicinal product has confirmed that this finding is drug substance rather than formulation related. However dissolution data with the respective strength of the reference have been provided for the 75, 150 and 400 mg tablets, but not for the 300 mg tablet

As the reference Prezista 300 mg tablets were not available on the market, the MAH used 2 x 150 mg Prezista tablets instead. Considering the dose proportionality in formulations, comparable dissolution shown for the 150 mg Test tablet vs. the 150 mg Prezista tablet and the comparable dissolution shown for the 300 mg Test tablet vs. 2 x 150 mg Prezista tablets, this is considered acceptable.

Bioequivalence study

Design

A single-dose, randomised, two-period, two-treatment, two-sequence, crossover bioequivalence study was carried out under fed conditions in 42 healthy male subjects, aged 19-44 years. Each subject received a single dose (800 mg) of one of the 2 darunavir formulations. In addition, the subjects received 100 mg ritonavir each period. The tablet was orally administered with 240 ml water 30 minutes after a high-fat, high-calorie breakfast (consisting of milk, chana chat, bread with butter, egg fry and tomato ketchup). There were 2 dosing periods, separated by a washout period of 9 days.

Blood samples were collected at pre-dose and at 0.33, 0.67, 1.00, 1.33, 1.67, 2.00, 2.33, 2.67, 3.00, 3.33, 3.67, 4.00, 4.33, 4.67, 5.00, 6.00, 8.00, 10.00, 12.00, 16.00, 24.00, 36.00, 48.00 and 72.00 hours after administration of the products.

The design of the study is acceptable. A single dose, crossover study under fed conditions to assess bioequivalence is considered adequate. According to the SmPC, the tablets should be taken with food. As such, the fed conditions applied in the study are considered adequate. Darunavir was administered with ritonavir, which is also in accordance with the SmPC. This is acceptable.

Analytical/statistical methods

The analytical method has been adequately validated and is considered acceptable for analysis of the plasma samples. The methods used in this study for the pharmacokinetic calculations and statistical evaluation are considered acceptable.

Results

One subject was withdrawn from the study due to adverse events. Therefore, 41 subjects completed the study and were eligible for pharmacokinetic analysis.

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

Treatment N=41	**AUC_{0-t}** µg.h/ml	**$AUC_{0-\infty}$** µg.h/ml	**C_{max}** µg/ml	**t_{max}** h	**$t_{1/2}$** h
Test	108 ± 34	119 ± 36	8.1 ± 1.7	4.33 (1.33 – 8.0)	11.5 ± 5.2
Reference	116 ± 38	124 ± 38	9.2 ± 1.8	4.33 (2.0 – 6.0)	9.3 ± 3.0
***Ratio (90% CI)**	0.94 (0.88 – 0.99)		0.88 (0.85 – 0.92)		
CV (%)	15.3		10.6		

$AUC_{0-\infty}$ area under the plasma concentration-time curve from time zero to infinity
AUC_{0-t} area under the plasma concentration-time curve from time zero to t hours
C_{max} maximum plasma concentration
t_{max} time for maximum concentration
$t_{1/2}$ half-life
CV coefficient of variation

**ln-transformed values*

Conclusion on bioequivalence study
The 90% confidence intervals calculated for AUC_{0-t} and C_{max} are within the bioequivalence acceptance range of 0.80 – 1.25. Based on the submitted bioequivalence study Darunavir CF 800 mg, film-coated tablets is considered bioequivalent with Prezista 800 mg, film-coated tablets.

The MEB has been assured that the bioequivalence study has been conducted in accordance with acceptable standards of Good Clinical Practice (GCP, see Directive 2005/28/EC) and Good Laboratory Practice (GLP, see Directives 2004/9/EC and 2004/10/EC).

The results of the study with 800 mg formulation can be extrapolated to other strengths 75 mg, 150 mg, 300 mg, 400 mg and 600 mg according to conditions in Guideline on the Investigation of Bioequivalence CPMP/EWP/QWP/1401/98 Rev. 1/Corr*, section 4.1.6.

IV.3 Risk Management Plan

The MAH has submitted a risk management plan, in accordance with the requirements of Directive 2001/83/EC as amended, describing the pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to Darunavir CF.

- Summary table of safety concerns as approved in RMP

Important identified risks	- Severe skin reactions - Hepatotoxicity - Hyperglycaemia - Lipid abnormalities - Pancreatitis - Fat redistribution - Immune Reconstitution Inflammatory Syndrome - Development of drug resistance - Overdose due to medication error - Drug-drug interactions
Important potential risks	- Coronary artery events - Cardiac conduction abnormalities - Convulsions - Growth abnormalities in the paediatric population - Off-label use of darunavir/cobicistat in the paediatric population and in Acquired Immune Deficiency syndrome -related virus treatment-experienced patients with HIV-1 ribonucleic acid>100.000 copies/ml - Renal toxicity of darunavir/cobicistat
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 **Darunavir/ritonavir** - Long-term safety data in children from 3 to 17 years of age **Darnunavir/cobicistat** - Long-term safety in adults - Children <18 years of age - Subects coinfected with HIV and Hepatitis B Virus and/or Hepatitis C Virus

The member states agreed that routine pharmacovigilance activities and routine risk minimisation measures are sufficient for the risks and areas of missing information.

IV.4 Discussion on the clinical aspects

For this authorisation, reference is made to the clinical studies and experience with the innovator product Prezista. No new clinical studies were conducted. The MAH demonstrated through a bioequivalence study that the pharmacokinetic profile of the product is similar to the pharmacokinetic profile of this reference product. Risk management is adequately addressed. This generic medicinal product can be used instead of the reference product.

V. USER CONSULTATION

The package leaflet (PL) for Darunavir 75 mg, 150 mg, 300 mg, 400 mg, 600 mg and 800 mg, film-coated tablets is predominantly identical in content to the currently approved and successfully user tested PL for the originator product Prezista. Minor differences in PL content relate to Quality Review of Documents (QRD) changes only, which is acceptable as it does not affect the readability. Other differences due to a different company house style have been subject to a successful user test for many other products, including for example EMEA/H/C/1181-1183, AT/H/0350/DC, DE/H/1354-1356, DK/H/300/01-02/II/18, SE/357,359,361/01-04/R01 and UK/H/2385-2387/001-004. These user tests confirm that the house style does not affect readability of the leaflet. Therefore, the PL does not need additional testing and bridging and is acceptable.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Darunavir CF 75 mg, 150 mg, 300 mg, 400 mg, 600 mg and 800 mg, film-coated tablets have a proven chemical-pharmaceutical quality and are generic forms of Prezista 75 mg, 150 mg, 300 mg, 400 mg, 600 mg and 800 mg, film-coated tablets. Prezista is a well-known medicinal product with an established favourable efficacy and safety profile.

Bioequivalence has been shown to be in compliance with the requirements of European guidance documents.

The Board followed the advice of the assessors.

There was no discussion in the CMD(h). Agreement between member states was reached during a written procedure. The member states, on the basis of the data submitted, considered that essential similarity has been demonstrated for Darunavir with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 15 February 2017.

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
NL/H/3609/IB/001/G	– Change in the name and/or address of: a manufacturer (including where relevant quality control testing sites); or an ASMF holder; or a supplier of the active substance, starting material, reagent or intermediate used in the manufacture of the active substance (where specified in the technical dossier) where no Ph. Eur. Certificate of Suitability is part of the approved dossier; or a manufacturer of a novel excipient (where specified in the technical dossier) – Other variation; An alternative manufacturer has been incorporated in addition to the existing manufacturer – Other variation; Change in the re-test period: including 6 months stability data for the active substance	-	23-06-2017	Approved	-
NL/H/3609/1-6/IA/002	Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the risk management plan;	-	14-09-2017	Approved	-
NL/H/3609/1-6/IB/003	Change(s) in the Summary of Product Characteristics, Labelling or Package Leaflet of a generic/hybrid/biosimilar medicinal products following assessment of the same change for the reference product;	SmPC, PL, Packaging	02-10-2017	Approved	-