CBG MEB

Public Assessment Report

Scientific discussion

Darunavir Teva 800 mg, film-coated tablets

(darunavir)

NL/H/3815/001/DC

Date: 20 March 2018

This module reflects the scientific discussion for the approval of Darunavir Teva 800 mg, film-coated tablets. The procedure was finalised on 13 September 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 Teva 800 mg, film-coated tablets, from Teva 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.

The product co-administered with cobicistat is indicated in combination with other antiretroviral medicinal products for the treatment of human 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 Darunavir Teva in such ART-experienced patients, genotypic testing should guide the use of this product.

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 centralised procedure (EU/1/06/380/007-008).

The concerned member states (CMS) involved in this procedure were: Austria, Czech Republic, Germany, Denmark, Estonia, Spain, France, Croatia, Italy, Poland, Portugal, Romania, Sweden, Slovenia and the United Kingdom.

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

II. QUALITY ASPECTS

II.1 Introduction

Darunavir Teva 800 mg is a red, oval shaped film-coated tablet, scored on one side and debossed with “800” on the other side. Each film-coated tablet contains 800 mg darunavir. The score line is only to facilitate breaking for ease of swallowing.

The film-coated tablets are packed in HDPE bottles stoppered with a polypropylene, child resistant closure.

The excipients are:
Tablet core – microcrystalline cellulose (E460), colloidal anhydrous silica (E551), copovidone, crospovidone (E1202), and magnesium stearate (E470b)
Tablet coating – poly (vinyl alcohol), partially hydrolysed macrogol, talc (E553b) and iron oxide red (E172)

II.2 Drug Substance

The active substance is darunavir, an established active substance, not described in the European Pharmacopoeia. It is a white to light brown powder which is freely soluble in acetone, sparingly soluble ethyl acetate and practically insoluble in water. Darunavir is slightly hygroscopic and has five chiral centres. 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 is divided into three parts, consisting of eleven steps in total (including purification steps). 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 adopted by the MAH of the ASMF-holder, with an additional limit for particle size. The specification is considered adequate to control the quality Descriptions of all analytical procedures have been provided and the analytical methods have been adequately validated. Batch analytical data demonstrating compliance with this specification have been provided for 3 batches.

Stability of drug substance
No data have been provided by the MAH on the stability of the drug substance. The MAH has confirmed that the same re-test period and storage conditions as are defined in the ASMF will be used. This is acceptable.

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 manufacturing process (direct compression vs. dry granulation), filler amount, binder type and amount, glidant amount, disintegrant amount, lubricant amount and sieving size were the main topics evaluated during pharmaceutical development. In addition, several parameters with regard to dissolution were evaluated. A bioequivalence study has been performed for the 800 mg product strength versus the 800 mg reference product. The provided dissolution profiles of the test and the reference product batches at three different pH values were not similar. However, bioequivalence has been demonstrated in the clinical studies. The pharmaceutical development of the product has been adequately performed.

Manufacturing process
The manufacturing process is divided into six main steps, which consists of preparation of initial blend, granulation and milling, final blend, compression, coating and packaging. The process is considered to be a standard manufacturing process. Process validation of the drug product has been presented on 2 pilot scale batches. The MAH has committed that process validation will be performed on the first three commercial scale batches (with the maximum batch size).

Control of excipients
With the exception of the Opadry film-coating, all excipients comply with their respective Ph. Eur. monograph. For the Opadry film-coating, an in-house specification is included. The MAH has determined critical functional-related characteristics for the excipients anhydrous calcium hydrogen phosphate, colloidal anhydrous silica, copovidone, crospovidone, magnesium stearate and microcrystalline cellulose. The functional-related characteristics have been included in the respective excipient specifications.

Quality control of drug product
The finished product specifications are adequate to control the relevant parameters for the dosage form. The specification includes tests description and appearance, identification, dissolution, uniformity of dosage units, assay, impurities and degradation products, water content, microbiological quality and uniformity of mass for subdivided tablets. Limits in the specification have been justified and are

considered appropriate for adequate quality control of the product. Except for 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 from 2 pilot scaled batches 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 2 batches for the 800 mg strength that were stored at 25°C/60% RH (18 months), 30°C/35% RH (12 months) and 40°C/75% RH (6 months). The conditions used in the stability studies are according to the ICH stability guideline. No clear trends or changes were observed in any of the tested parameters. In addition, photostability studies indicate that the product is not sensitive to light. Based on the available stability data, the claimed shelf-life of 24 months without any special storage restriction for tablets packed in HDPE bottles and 24 months when stored below 30°C is justified.

Specific measures for the prevention of the transmission of animal spongiform encephalopathies
There are no substances of ruminant animal origin present in the product nor have any been used in the manufacturing of this product, so a theoretical risk of transmitting TSE can be excluded.

II.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the member states consider that Darunavir Teva 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 Teva 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 Teva 800 mg, film-coated tablets (Teva 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.

Bioequivalence study

Design

A single-dose, randomised, two-period, two-treatment, two-sequence, crossover bioequivalence study was carried out under fed conditions in 56 healthy male subjects, aged 21-44 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, vegetable cutlets and tomato chutney). There were 2 dosing periods, separated by a washout period of 9 days.

Blood samples were collected at pre-dose and at 0.5, 1.0, 1.5, 2.0, 2.50, 3.0, 3.33, 3.67, 4.0, 4.33, 4.67, 5.0, 5.5, 6.0, 8.0, 10.0, 12.0, 18.0, 24.0, 36.0, 48.0, and 72.0 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 withdrew consent and five subjects were withdrawn from the study due to adverse events. Therefore, 50 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=50	**AUC_{0-t}** µg.h/ml	**$AUC_{0-\infty}$** µg.h/ml	**C_{max}** µg/ml	**t_{max}** h	**$t_{1/2}$** h
Test	138 ± 47	142 ± 47	11.3 ± 2.5	4.33 (2.0 – 6.0)	9.3 ± 3.0
Reference	122 ± 49	125 ± 49	9.9 ± 2.8	4.33 (2.0 – 8.0)	8.7 ± 2.5
***Ratio (90% CI)**	1.16 (1.09 – 1.23)	--	1.16 (1.11 – 1.21)	--	--
CV (%)	17.8	--	13.6	--	--

$AUC_{0-\infty}$	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 Teva 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).

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 Teva.

- Summary table of safety concerns as approved in RMP

Important identified risks	- Severe skin reactions - Hepatotoxicity - Hyperglycaemia - Lipid abnormalities - Pancreatitis - 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	- Elderly (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

A user consultation with target patient groups on the package leaflet (PL) has been performed on the basis of a bridging report making reference to Darunavir Teva 400 mg, film-coated tablets (DE/H/4338/003). The PL is justified to be supported by the user test conducted on the PL for Darunavir Teva 400 mg, film-coated tablets for the following reasons. The products:

- have identical indications and active ingredient;
- have the same pharmaceutical form;
- have closely similar key issues for safe use and target population of potential users;
- have the same complexity of the message and language;
- have similar text, identical writing style and the text used is identical wherever possible;
- have identical mock up formats;

Overall, the bridging report submitted by the MAH has been found acceptable

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Darunavir Teva 800 mg, film-coated tablets have a proven chemical-pharmaceutical quality and are generic forms of Prezista 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

Scope	Procedure number	Type of modification	Date of start of the procedure	Date of end of the procedure	Approval/ non approval	Assessment report attached