CBG MEB

Public Assessment Report

Scientific discussion

Ciastad 20 mg film-coated tablets

(tadalafil)

NL/H/3927/001/DC

Date: 13 February 2018

This module reflects the scientific discussion for the approval of Ciastad 20 mg film-coated tablets. The procedure was finalised on 6 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
RMS	Reference Member State
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 Ciastad 20 mg film-coated tablets from Stada Arzneimittel AG.

The product is indicated in adults for the treatment of pulmonary arterial hypertension (PAH) classified as WHO functional class II and III, to improve exercise capacity.
Efficacy has been shown in idiopathic PAH (IPAH) and in PAH related to collagen vascular disease.

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 product Adcirca 20 mg, film-coated tablets which has been registered in the EEA through centralised procedure EMEA/H/C/001021 by Eli Lilly Nederland B.V. since 1 October 2008.

The first marketing authorisation for Tadalafil in the European Union was granted on 12 November 2002 via the centralised procedure for the treatment of erectile dysfunction in adult males; the authorisation was granted under the brand name Cialis film-coated tablets by Eli Lilly Nederland B.V. On 1 October 2008, a new centralised marketing authorisation was granted, under the brand name Tadalafil Lilly 20 mg film-coated tablets, as an informed consent application of Cialis film-coated tablets. Tadalafil Lilly 20 mg film-coated tablets was then renamed to Adcirca film-coated tablets (in 2009) and also a variation was submitted for changing the therapeutic indication of Adcirca from erectile dysfunction to the treatment of pulmonary arterial hypertension (PAH).

The concerned member state (CMS) involved in this procedure was Sweden.

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

II. QUALITY ASPECTS

II.1 Introduction

Ciastad 20 mg is a ochre to yellow, caplet shaped, biconvex, film-coated tablet, debossed with “T 20” on one side and plain on the other. Each tablet contains 20 mg Tadalafil.

The film-coated tablets are packed in PVC/PVdC/Aluminium blisters.

The excipients are:
Tablet core – anhydrous lactose, croscarmellose sodium, sodium laurilsulfate, hydroxypropylcellulose, polysorbate 80 and magnesium stearate
Tablet coating – hypromellose (E464), lactose monohydrate, titanium dioxide (E171), triacetin, talc (E553b) and yellow iron oxide (E172).

II.2 Drug Substance

The active substance is tadalafil, an established active substance described in the European Pharmacopoeia (Ph.Eur.). Tadalafil is a white or almost white powder. It is practically insoluble in water, freely soluble in dimethyl sulfoxide and slightly soluble in methylene chloride. Tadalafil can exist in different crystalline forms and an amorphous form and exhibits polymorphism. The manufacturer consistently produces the crystalline form-1.

The CEP procedure is used for the active substance. Under the official Certification Procedures of the EDQM of the Council of Europe, manufacturers or suppliers of substances for pharmaceutical use can apply for a certificate of suitability concerning the control of the chemical purity and microbiological quality of their substance according to the corresponding specific monograph, or the evaluation of reduction of Transmissible Spongiform Encephalopathy (TSE) risk, according to the general

monograph, or both. This procedure is meant to ensure that the quality of substances is guaranteed and that these substances comply with the Ph.Eur.

Manufacturing process
A CEP has been submitted; therefore no details on the manufacturing process have been included.

Quality control of drug substance
The active substance specification is considered adequate to control the quality. It meets the requirements of the monograph in the Ph.Eur. and additional requirements of the CEP, with an additional test for particle size. Batch analytical data demonstrating compliance with this specification have been provided for three batches.

Stability of drug substance
The active substance is stable for 60 months when stored under the stated conditions. Assessment thereof was part of granting the CEP and has been granted by the EDQM.

II.3 Medicinal Product

Pharmaceutical development
The product is an established pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines. The choice of excipients is justified and their functions explained. The main development studies were the characterisation of the reference product, optimisation of the excipient levels in the formulation and the performance of comparative dissolution studies. The choices of the packaging and manufacturing are justified. Two bioequivalence studies, under fasted and fed conditions, have been performed. The dissolution studies showed similarity in dissolution between the test product and the reference product.

Manufacturing process
The main steps of the manufacturing process are dry mixing, wet mixing/granulation, drying, sizing, blending, lubrication, 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 three pilot scaled batches. The product is manufactured using conventional manufacturing techniques. Process validation for full scaled batches will be performed post authorisation.

Control of excipients
All excipients comply with their Ph.Eur. monographs except the film-coating material, which is controlled according to an in-house specification. The 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 appearance, identification, water content, average weight, disintegration, dissolution, uniformity of dosage units, assay, related substances, residual acetone and microbiological quality. Except for water content and total impurities, the release and shelf-life requirements are identical. Limits in the specification have been justified and are considered appropriate for adequate quality control of the product.
Satisfactory validation data for the analytical methods have been provided. Batch analytical data from three pilot scale batches from the proposed production site have been provided, demonstrating compliance with the specification.

Stability of drug product
Stability data on the product have been provided for three pilot scaled batches stored at 25°C/60% RH (24 months) and 40°C/75% RH (6 months). The conditions used in the stability studies are according to the ICH stability guideline. The batches were stored in the proposed packaging. Except for a slight increase in water content at both storage conditions, the stability data showed no clear trends or changes at both storage conditions. Results of a formal photostability study showed that the drug product was not sensitive to light exposure when directly exposed. Based on the presented stability data, the proposed shelf-life of 36 months without any special storage requirements is justified.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies
Anhydrous lactose and lactose monohydrate are of animal origin. The milk used for the production of these excipients has been sourced form healthy cows in the same conditions as milk collected for human consumption. The lactose has been prepared without the use of other ruminant material than calf rennet according to the description as published in Public Statement EMEA/CPMP/571/02 of 27 February 2002. The BSE risk is therefore negligible

II.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the member states consider that Ciastad 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 Ciastad 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 Adcirca 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

Tadalafil 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 two bioequivalence studies, which are discussed below.

IV.2 Pharmacokinetics

Bioequivalence studies
In total the MAH conducted two bioequivalence studies in which the pharmacokinetic profile of the test product Tadalafil CF (Stada Arzneimittel AG., Germany) is compared with the pharmacokinetic profile of the reference product Cialis (Eli Lilly, UK):

- Single dose bioequivalence study with the 20 mg tablet under fasting conditions.
- Single dose bioequivalence study with the 20 mg tablet under fed conditions.

Biowaiver
The MAH claims a biowaiver of the reference product which was used in the bioequivalence study (Cialis) with Adcirca (20 mg tadalafil tablet). The claimed biowaiver versus the Adcirca reference

product is acceptable based on bioequivalence versus the Cialis 20 mg film coated EU reference product, similarity in quality between Adcirca and Cialis 20 mg film-coated tablets and similarity in dissolution profiles at three different pH covering a range of 1.2 to 6.8 and QC medium between the generic and Adcirca and Cialis reference products (see Quality assessment report). In fact, Adcirca and Cialis are the same product and as a consequence, quality, safety and efficacy of Adcirca are identical to the up to date quality, safety and efficacy profile of Cialis. (http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Public_assessment_report/human/001021/WC500032788.pdf)

The tadalafil product specific Bioequivalence Guidance states that the reference product has specific formulation characteristics and thus that both fasted and fed studies should be performed. As such, the submission of bioequivalence studies under fasting and fed conditions is in accordance with these guidelines.

The choice of the reference product
The choice of the reference product from the UK in the bioequivalence studies has been justified.

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.

Single dose bioequivalence study with the 20 mg tablet under fasting conditions
Design
A open-label, balanced, randomised, single-dose, two-treatment, two-sequence, two-period, crossover bioequivalence study was carried out under fasted conditions in 38 healthy male subjects, aged 19-43 years. Each subject received a single dose (20 mg) of one of the 2 tadalafil formulations. The tablet was orally administered with 240 ml water after an overnight fast. There were 2 dosing periods, separated by a washout period of 21 days.

Blood samples were collected pre-dose and at 0.33, 0.67, 1, 1.33, 1.67, 2, 2.33, 2.67, 3, 3.33, 3.67, 4, 4.5, 5, 6, 8, 10, 12, 16, 24, 36, 48 and 72 hours after administration of the products.

Results
One subject was withdrawn due to an adverse event (vomiting) in period I. Therefore, 37 subjects were eligible for pharmacokinetic analysis.

Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of 20 mg tadalafil under fasted conditions.

Treatment N=37	AUC_{0-72} ng.h/ml	C_{max} ng/ml	t_{max} h	$t_{1/2}$ h
Test	11584 ± 3979	358 ± 91	3.0 (0.67 – 24.0)	35 ± 19
Reference	10848 ± 3122	391 ± 104	2.67 (0.67 – 4.5)	35 ± 19
***Ratio (90% CI)**	1.06 (0.96 – 1.17)	0.92 (0.83 – 1.01)	--	--
CV (%)	22.4	25.6	--	--

AUC_{0-72} area under the plasma concentration-time curve from time zero to 72 hours
C_{max} maximum plasma concentration
t_{max} time for maximum concentration
$t_{1/2}$ half-life
CV coefficient of variation

**ln-transformed values*

Eight subjects did not report for the 72 hour ambulatory sample in period I and two subjects did not report for the 72 hour ambulatory sample in period II. For these subjects, the primary pharmacokinetic parameter AUC_{0-72h} could not be estimated precisely due to the missed 72 hour blood draw. These subjects were identified before bio-analysis and their data was excluded from the statistical analysis of AUC_{0-72h}. However, these subjects were included in the statistical calculations of C_{max}. This is considered acceptable.

Bioequivalence study II – Tadalafil 20 mg, single dose, fed conditions

Design

A single-dose, randomised, two-period, two-treatment, two-sequence, crossover bioequivalence study was carried out under fed conditions in 38 healthy male subjects, aged 19-42 years. Each subject received a single dose (20 mg) of one of the 2 tadalafil formulations. The tablet was orally administered with 240 ml water 30 minutes after start of intake of a high fat, high caloric breakfast. There were 2 dosing periods, separated by a washout period of 21 days.

Blood samples were collected pre-dose and at 0.33, 0.67, 1, 1.33, 1.67, 2, 2.33, 2.67, 3, 3.33, 3.67, 4, 4.5, 5, 6, 8, 10, 12, 16, 24, 36, 48 and 72 hours after administration of the products.

The design of the study is acceptable.

Results

One subject was withdrawn due to an adverse event (vomiting) in period I. Two subjects did not report for period II. Therefore 35 subjects were eligible for pharmacokinetic analysis.

Table 2. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of 20 mg tadalafil under fed conditions.

Treatment N=35	AUC_{0-72} ng.h/ml	C_{max} ng/ml	t_{max} h	$t_{1/2}$ h
Test	11914 ± 2968	448 ± 102	4.0 (1.67 – 5.0)	28 ± 13
Reference	12232 ± 3384	457 ± 86	3.67 (1.67 – 8.0)	29 ± 13
***Ratio (90% CI)**	0.98 (0.91 – 1.06)	0.97 (0.92 – 1.04)	--	--
CV (%)	15.6	15.5	--	--

AUC_{0-72} area under the plasma concentration-time curve from time zero to 72 hours
C_{max} maximum plasma concentration
t_{max} time for maximum concentration
$t_{1/2}$ half-life
CV coefficient of variation

**ln-transformed values*

Nine subjects did not report for the 72 hour ambulatory sample in period I. For these subjects, the primary pharmacokinetic parameter AUC_{0-72h} could not be estimated precisely due to the missed 72 hour blood draw. These subjects were identified before bio-analysis and their data was excluded from the statistical analysis of AUC_{0-72h}. However, these subjects were included in the statistical calculations of C_{max}. This is considered acceptable.

Conclusion on bioequivalence study

The 90% confidence intervals calculated for AUC_{0-72} and C_{max} are within the bioequivalence acceptance range of 0.80 – 1.25. Based on the submitted bioequivalence studies Ciastad is considered bioequivalent with Adcirca.

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 Ciastad.

Summary table of safety concerns as approved in RMP:

Important identified risks	• Priapism • hypotension/increased hypotensive effect
Important potential risks	• Non-arteritic anterior ischaemic optic neuropathy (NAION) • Sudden hearing loss • Increased uterine bleeding (menorrhagia/vaginal haemorrhage)
Missing information	• Characterisation of adverse events in elderly patients (≥65 years)

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 Adcirca. 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 has been evaluated via a user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC. The test consisted of a pilot test, followed by two rounds with 15 questions addressing the key safety issues and presentation of information. The questions covered the following areas sufficiently: traceability, comprehensibility and applicability. The results 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.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Ciastad 20 mg film-coated tablets has a proven chemical-pharmaceutical quality and is a generic form of Adcirca 20 mg, film-coated tablets. Adcirca 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 Ciastad with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 6 September 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/3927/IB/001/G	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	Yes	04-01-2018	Approved	-