COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Tadalafil AOP 20 mg film-coated tablets

(tadalafil)

NL/H/4322/001/DC

Date: 2 April 2019

This module reflects the scientific discussion for the approval of Tadalafil AOP 20 mg film-coated tablets. The procedure was finalised at 29 January 2019. For information on changes after this date please refer to the 'steps taken after finalisation' at the end of this PAR.

List of abbreviations

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
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 Tadalafil AOP 20 mg film-coated tablets from AOP Orphan Pharmaceuticals 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 (see SmPC section 5.1).

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 innovator product Adcirca film-coated tablets (EU/1/08/476) which is centrally registered 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 authorization was granted under the brand name Cialis film-coated tablets by Eli Lilly Nederland B.V. On 1st October 2008, a new centralized marketing authorization 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 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 states (CMS) involved in this procedure were Austria, Czech Republic, Germany, Denmark, Estonia, Finland, Croatia, Hungary, Latvia, Lithuania, Norway, Poland, Romania, Sweden, Slovenia, and Slovakia.

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

Similarity assessment
Having considered the arguments presented by the Marketing Authorisation Holder (MAH) and with reference to Article 8 of Regulation (EC) No 141/2000, Tadalafil AOP is considered not similar (as defined in Article 3 of Commission Regulation (EC) No. 847/2000) to Volibris (ambrisentan), Adempas (riocigaut), and Opsumit (macitentan).
Therefore, with reference to Article 8 of Regulation (EC) No. 141/2000, the existence of any market exclusivity for Volibris, Adempas, and Opsumit in the treatment of PAH, does not prevent the granting of the marketing authorisation of Tadalafil AOP.

II. QUALITY ASPECTS

II.1 Introduction

Tadalafil AOP is a yellow coloured, caplet shaped, biconvex, film-coated tablet, debossed with "T 20" on one side and plain on the other.

And contains as active substance 20 mg of tadalafil.

The film-coated tablets are packed in PVC/PVDC/Aluminum blisters.

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

II.2 Drug Substance

The active substance is tadalafil, an established active substance described in the European Pharmacopoeia (Ph.Eur.). The active substance is practically insoluble in water. Tadalafil shows polymorphism, the form used in the drug product is 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 and meets the requirements of the monograph in the Ph.Eur. 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, optimization of the excipient levels in the formulation and the performance of comparative *in vitro* dissolution studies complementary to the *in vivo* bioequivalence studies. The choices of the packaging and manufacturing are justified. The 20 mg batches used in the two bioequivalence studies were manufactured according to the finalised formulation and manufacturing process. The pharmaceutical development of the product has been adequately performed.

Manufacturing process

The product is manufactured using conventional manufacturing techniques. The main steps of the manufacturing process are dry, 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.

Control of excipients

The excipients comply with their Ph.Eur. monographs or in-house specification (film-coating material). 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 appearance, identification, water content, average weight, disintegration, dissolution, uniformity of dosage units, assay, related substances, residual acetone and microbiological quality. 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 has been provided on three pilot scale batches stored at 25°C/60% RH (36 months) and 40°C/75% RH (6 months). The conditions used in the stability studies are according to the ICH stability guideline. All parameters remained within the set limits. Results of a formal photostability study showed that the drug product was not sensitive to light exposure when directly exposed. On basis of the data submitted, a shelf-life of 36 months without any special storage requirements is granted.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies

Anhydrous lactose and lactose monohydrate (as a component of the coating agents) are the only materials of animal origin included in the drug product. 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 Tadalafil AOP 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 Tadalafil AOP 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

The MAH conducted two bioequivalence studies in which the pharmacokinetic profile of the test product Tadalafil AOP 20 mg film-coated tablets (MAH, country) is compared with the pharmacokinetic profile of the reference product Cialis 20 mg film-coated tablets (Eli Lilly, United Kingdom).

The choice of the reference product in the bioequivalence studies has been justified. The formula and preparation of the bioequivalence batch is identical to the formula proposed for marketing.

Biowaiver

This application concerns only one strength, so a biowaiver for additional strengths is not applicable. However the MAH claims a biowaiver of the reference product Cialis with Adcirca (20 mg tadalafil tablet). The clamed 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). Also 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.

Bioequivalence studies

Analytical/statistical methods

The analytical methods have been adequately validated and is considered acceptable for analysis of the plasma samples. The methods used in these studies for the pharmacokinetic calculations and statistical evaluation are considered acceptable.

In the Bioequivalence Guideline (CHMP/QWP/EWP/1401/98 Rev. 1 section 4.1.4 Fasting or fed conditions) it is stated that both fasted and fed studies are required for products with specific formulation characteristics. 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. This is because for Cialis, the MAH showed that due to a difference in manufacturing process (co-precipitation or micronization) a difference in bioavailability may be expected under fed conditions. As such, the submission of a bioequivalence study under fasting conditions and a bioequivalence study under fed conditions under fed conditions is in accordance with these guidances.

Bioequivalence study under fasting conditions

Design

A single-dose, randomised, two-period, two-treatment, two-sequence, 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 two tadalafil formulations. The tablet was orally administered with 240 ml water after an overnight fast. There were two 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). Therefore, 37 subjects were eligible for pharmacokinetic analysis.

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

Treatment N=37	**AUC_{0-t} (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	--	--

$AUC_{0-\infty}$ 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*

Bioequivalence study under 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 two 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 two 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 tadalafil under fasted conditions.

Treatment N=35	**AUC_{0-t} (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	--	--

$AUC_{0-\infty}$ 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 studies
The 90% confidence intervals calculated for AUC_{0-t}, $AUC_{0-\infty}$ and C_{max} are within the bioequivalence acceptance range of 0.80 – 1.25. Based on the submitted bioequivalence studies Tadalafil AOP 20 mg is considered bioequivalent with Cialis 20 mg.

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 Tadalafil AOP.

Table 3. Summary table of safety concerns as approved in RMP

Important identified risks	• Priapism • Hypotension/Increased Hypotensive Effect
Important potential risks	• Non-Arteritic Anterior Ischemic Optic Neuropathy (NAION) • Sudden Hearing Loss • Increased uterine bleeding
Missing information	none

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

A user consultation with target patient groups on the package leaflet (PL) has been performed on the basis of a bridging report in which both content and lay-out/design are discussed. For content, the parent PL is defined as Adcirca, authorised by centralised procedure (EMEA/H/C/001021) and considerably amended in the type II variation (EMEA/H/C/1021/II/0001), in which the indication was changed from erectile dysfunction to PAH. In terms of layout and design it is bridged to the AOP in-house style, as positively tested in various national and decentralised marketing authorisation procedures. The bridging report submitted by the MAH has been found acceptable; bridging is justified for both content and layout of the leaflet.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Tadalafil AOP 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 Tadalafil AOP with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 29 January 2019.

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