CBG MEB

Public Assessment Report

Scientific discussion

Tadalafil 1A Pharma 2.5 mg, 5 mg, 10 mg and 20 mg, film-coated tablets

(tadalafil)

NL/H/3614/001-004/DC

Date: 24 May 2017

This module reflects the scientific discussion for the approval of Tadalafil 1A Pharma 2.5 mg, 5 mg, 10 mg and 20 mg, film-coated tablets. The procedure was finalised on 10 November 2016. 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 Tadalafil 1A Pharma 2.5 mg, 5 mg, 10 mg and 20 mg, film-coated tablets from 1A Pharma GmbH.

The product is indicated for:
- Treatment of erectile dysfunction in adult males. In order for tadalafil to be effective for the treatment of erectile dysfunction, sexual stimulation is required.
- Treatment of the signs and symptoms of benign prostatic hyperplasia in adult males (only the 5 mg strength).

Tadalafil 1A Pharma is not indicated for use by women.

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 products Cialis 2.5 mg, 5 mg, 10 mg and 20 mg, film-coated tablets which have been registered in the EEA through centralised procedure EMEA/H/C/000436 by Eli Lilly Nederland B.V. since 12 November 2002.

The concerned member states (CMS) involved in this procedure were Germany and Greece.

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

II. QUALITY ASPECTS

II.1 Introduction

Tadalafil 1A Pharma 2.5 mg is a ochre to yellow coloured, round shaped film-coated tablets debossed with “2.5” on one side and plain on the other side.
Tadalafil 1A Pharma 5 mg is a ochre to yellow, oval shaped film-coated tablet debossed with “5” on one side and plain on the other side.
Tadalafil 1A Pharma 10 mg is a ochre to yellow, oval shaped film-coated tablet. On one side it is scored and debossed with “1” on the left side of the score and with “0” on the right side of the score. The other side is plain. The tablet can be divided into equal halves.
Tadalafil 1A Pharma 20 mg is a ochre to yellow, oval shaped film-coated tablets. On one side it is scored and debossed with “2” on the left side of the score and with “0” on the right side of the score. The other side is plain. The tablet can be divided into equal halves.

Each film-coated tablet contains 2.5 mg, 5 mg, 10 mg or 20 mg tadalafil.

The film-coated tablets are packed in Alu-Alu(Al-OPA/Al/PVC), PVC/ACLAR/PVC-Al or PVC/ACLAR/PVdC/PVC-Al blisters

The excipients are:
Tablet core: lactose monohydrate, sodium laurilsilfate, povidone K-12, crospovidone (type B) and sodium stearyl fumarate
Tablet coating: polyvinyl alcohol, macrogol 3350, titanium dioxide (E171), talc, yellow iron oxide (E172)

The four different tablet strengths have a fully dose proportional composition.

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 from and exhibits polymorphism. The manufacturer consistently produces the anhydrous 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, including tests for identity, heavy metals and residual solvents that have been adopted from the specification of the supplier and additional in-house tests for particle size, bulk- and tapped density. Batch analytical data demonstrating compliance with this specification have been provided for two 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.
A bioequivalence study under fasted conditions has been performed with the 20 mg strength. The dissolution studies showed similarity in dissolution between the test product and the reference product. For the additional strengths a biowaiver has been requested and has been justified based on *in vitro* dissolution data. The MAH has sufficiently demonstrated that this discrepancy was due to poor dissolution of the active substance and was not drug product related. The pharmaceutical development of the product has been adequately performed.

Manufacturing process
The main steps of the manufacturing process are premixing, wet granulation, drying, milling, blending, compression, coating and packaging. The manufacturing process has been adequately validated according to relevant European guidelines. Process validation data on the product has been presented for two pilot scaled batches of the 2.5 mg, 5 mg and 10 mg strengths and three pilot scaled batches for the 20 mg strength. 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 Opdary 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 for appearance, identity, dissolution, uniformity of dosage units, assay, optical purity, related substances, microbiological quality, loss on drying and uniformity of mass for subdivided parts (only 10 mg and 20 mg products). Except for optical purity and related substances, 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 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 for two pilot scaled batches of the 2.5 mg, 5 mg and 10 mg strengths and three pilot scaled batches for the 20 mg strength 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 impurities at accelerated storage conditions and some variability in some of the test parameters, 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 24 months without any special storage requirements is justified.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies
Specific measures for the prevention of the transmission of animal spongiform encephalopathies
Lactose monohydrate is of animal origin. Compliance with the Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via Medicinal Products has been confirmed.

II.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the member states consider that Tadalafil 1A Pharma 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 1A Pharma 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 Cialis 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 four bioequivalence studies, which are discussed below.

IV.2 Pharmacokinetics

The MAH conducted bioequivalence studies in which the pharmacokinetic profile of the test product Tadalafil 1A Pharma 20 mg (1A Pharma GmbH, Germany) is compared with the pharmacokinetic profile of the reference product 20 mg (Eli Lilly Nederland B.V., the Netherlands).

The choice of the reference product in the bioequivalence study is justified as the reference product was authorised in the EU through a centralised procedure.
The formula and preparation of the bioequivalence batch is identical to the formula proposed for marketing.

Biowaiver
The following criteria for extrapolation of the results obtained in the bioequivalence studies for the 20 mg to the 5 mg and 10 mg tablets have been fulfilled:

- the formulations are dose proportional.
- the formulations are manufactured by the same manufacturer and manufacturing process.
- tadalafil shows linear pharmacokinetics over the therapeutic dose range of 2.5 – 20 mg.
- comparable dissolution has been shown at pH 1.2, 4.5 and 6.8 using the same dose; the f2 factor was above 50 in all cases.

Bioequivalence study: 20 mg under fasted 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 20 healthy male subjects, aged 22-54 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 14 days.

Blood samples were collected pre-dose and at 0.33, 0.67, 1, 1.33, 1.67, 2, 2.33, 2.67, 3, 3.5, 4, 4.5, 5, 6, 8, 12, 24, 36, 48, 60 and 72 hours after administration of the products.

The design of the study is acceptable. Tadalafil can be taken regardless of food, according to the SmPC.

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
Two subjects withdrew consent due to personal reasons and one subject was withdrawn due to an adverse event. Therefore, 17 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=25	**AUC_{0-72}** ng.h/ml	**$AUC_{0-\infty}$** ng.h/ml	**C_{max}** ng/ml	**t_{max}** h	**$t_{1/2}$** h
Test	7706 ± 2566	9065 ± 3805	293 ± 45	3.0 (1.33 – 4.5)	23 ± 8
Reference	8649 ± 3254	10129 ± 4712	328 ± 91	3.0 (0.67 – 5.0)	23 ± 8
***Ratio (90% CI)**	0.90 (0.83 – 0.98)	--	0.91 (0.84 – 0.99)	--	--
CV (%)	14.1	--	14.3	--	--

$AUC_{0-\infty}$	area under the plasma concentration-time curve from time zero to infinity
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*

Conclusion on bioequivalence study

The 90% confidence intervals calculated for AUC0-t and C_{max} are within the bioequivalence acceptance range of 0.80 – 1.25. Based on the submitted bioequivalence studies Tadalafil 1A Pharma is considered bioequivalent with Cialis.

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 study 2013-3225 with the 20 mg formulation can be extrapolated to other strengths 2.5 mg, 5 mg, and 10 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 Tadalafil 1A Pharma.

Summary table of safety concerns as approved in RMP:

Important identified risks	• Prolonged and painful erection (priapism) • Low blood pressure (hypotension / increased hypotensive effect)
Important potential risks	• Non-arteritic anterior ischaemic optic neuropathy (NAION) • Sudden hearing loss
Missing information	• Use in older 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 Cialis. 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 bridging report was provided to support the readability of the package leaflet (PL) for Tadalafil 1A Pharma. The MAH has indicated that the wording of the PL is in line with that of the reference product Cialis, which is a centrally authorised product. Furthermore, the format of the leaflet is similar to that of other user tested leaflets of the MAH. Altogether, the Member States consider the bridging for user testing acceptable.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Tadalafil 1A Pharma 2.5 mg, 5 mg, 10 mg and 20 mg, film-coated tablets have a proven chemical-pharmaceutical quality and are generic forms of Cialis 2.5 mg, 5 mg, 10 mg and 20 mg, film-coated tablets. Cialis 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 1A Pharma with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 10 November 2016.

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