COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Tadalafil ELC 5 mg, 10 mg and 20 mg film-coated tablets

(tadalafil)

NL/H/4387/002-004/DC

Date: 26 August 2019

This module reflects the scientific discussion for the approval of Tadalafil ELC 5 mg, 10 mg and 20 mg film-coated tablets. The procedure was finalised at 7 May 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

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 ELC 5 mg, 10 mg and 20 mg film-coated tablets, from ELC GROUP s.r.o.

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 ELC 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 5 mg, 10 mg and 20 mg, film-coated tablets (EU/1/02/237) 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 state (CMS) involved in this procedure was Spain

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

II. QUALITY ASPECTS

II.1 Introduction

Tadalafil ELC 5 mg is a yellow, almond shaped film-coated tablet debossed with “T5” on one side and plain on the other side.
Tadalafil ELC 10 mg is a yellow, almond shaped film-coated tablet debossed with “T10” on one side and plain on the other side.
Tadalafil ELC 20 mg is a yellow, almond shaped film-coated tablet debossed with “T20” on one side and plain on the other side.

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

The film-coated tablets are packed in Aluminium/PVDC coated rigid PVC/PE laminate blisters

The excipients are:
Tablet core - lactose monohydrate, low substituted hydroxypropylcellulose, hydroxypropylcellulose (E463), microcrystalline cellulose (E460), sodium laurilsulfate (E487) and magnesium stearate (E470b)
Tablet coating - hypromellose (E464), lactose monohydrate, triacetin (E1518), talc (E553b), titanium dioxide (E171) and yellow iron oxide (E172)

The three 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 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. with additional requirements indicated on the CEP. In addition, additional route-specific impurities with acceptable limits have been specified. Batch analytical data demonstrating compliance with this specification have been provided for three batches.

Stability of drug substance
No retest period is claimed on the CEP. A stability study was performed for three batches stored at 30°C/75% RH (36 months) and 40 °C/75% RH (6 months) and three more recent batches stored at 30 °C/75% RH (18 months) and 40 °C/75% RH (6 months). A commitment from the CEP holder to test microbiological quality in three batches at the end of shelf life and yearly in long term stability studies is included. Particle size distribution will be monitored during the stability program until end of shelf life. Sufficient data is available to

support the 12 month re-test period of the MAH when stored in well-closed containers between 15°C to 30°C.

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 choices of the packaging and manufacturing process are sufficiently justified. The development focused mainly on assay, content uniformity, dissolution and degradation products and particle size limits of the drug substance and was performed in line with ICH guideline on Pharmaceutical Development Q8(R2).

Bioequivalence was demonstrated, for the highest strength. Comparative dissolution studies with the test and reference product used in the bioequivalence study without the addition of a surfactant and with sufficient test time points have been performed. As reference product, a different batch as the one used in the bioequivalence study has been used, because the latter was not available any more. The results sustain the similarity of dissolution profiles between the biobatch and a representative batch of the reference product and are considered acceptable as in vitro data complementary to the bioequivalence study.

Given the dose proportionality of all the strengths, *in vitro* dissolution data were used in support of biowaiver of strengths. The comparative dissolution studies between the biobatch and representative batches of the lower strengths have been performed without the addition of a surfactant to the dissolution medium, comparing one tablet each and comparing equal dosages. In addition, each strength of the test product was compared with the same strength of the reference product. The results in buffers pH 1.2, 4.5 and 6.8 without surfactant met the conditions for calculation of f2 as outlined in the Guideline on bioequivalence. The results of the comparisons at equal dosage confirmed the similarity of the dissolution profiles for the strengths 5 mg and 10 mg. The biowaiver of strengths is acceptable from a pharmaceutical point of view for these two strengths.

Manufacturing process

The main steps of the manufacturing process are preparation of first blend, sifting and dry mixing, wet granulation, drying, sifting and milling, sifting extra granular excipients, pre-lubrication and lubrication, compression and film-coating. The manufacturing process has been adequately validated according to relevant European guidelines. Process validation data on the product have been presented for three commercial batches for each strength in accordance with the relevant European guidelines.

Control of excipients

The excipients comply with the Ph. Eur. requirements. For several excipients the MAH has included additional tests and limits. Some of the test used to control the excipients and coating are performed according to in-house procedures, which were provided together with the validation reports.

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, content uniformity, disintegration time, dissolution, water content, assay, impurities 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 submission 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 have been provided for three submission batches per strength, stored at 25°C/60% RH (24 months) and 40°C/75% RH (6 months). The conditions used in the stability studies are in line with the ICH stability guideline. The batches were stored in PVC/Al blisters. Photostability studies were conducted on one drug product batch per strength. The drug product remains stable throughout the evaluated period under all conditions tested; no specific up or downward trends are observed.
Based on this and on the provided stability studies results the proposed shelf life of 24 months not requiring any special storage conditions is acceptable.

Specific measures concerning 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 Tadalafil ELC 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 ELC 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 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 20 mg, film-coated tablets (ELC GROUP s.r.o., CZ) is compared with the pharmacokinetic profile of the reference product Cialis 20 mg, film-coated tablets (Eli Lilly Nederland B.V., NL).

The choice of the reference product in the bioequivalence studies 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.

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.

Design
The MAH submitted for the 20 mg strength a fasted and fed study. According to 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 is in accordance with the guidance

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 5 mg – 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 studies

Study I – 20 mg under fasting conditions

Design

A single-dose, randomised, two-period, two-treatment, two-sequence, crossover bioequivalence study was carried out under fasted conditions in 44 healthy male subjects, aged 21-44 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 withdrew consent on his own accord. Therefore, a total of 43 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 tadalafil under fasted conditions.

Treatment N=43	**AUC_{0-72} (ng.h/ml)**	**C_{max} (ng/ml)**	**t_{max} (h)**
Test	12910 ± 4769	485 ± 165	2.67 (0.67-8.02)
Reference	12622 ± 4209	458 ± 130	3.00 (1.00-4.50)
***Ratio (90% CI)**	1.02 (0.99-1.12)	1.05 (0.96-1.09)	--

CV (%)	16.96	18.14	--

$AUC_{0-\infty}$ 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
CV coefficient of variation

**ln-transformed values*

Study II – 20 mg under fed conditions

Design

A single-dose, randomised, two-period, two-treatment, two-sequence, crossover bioequivalence study was carried out under fed conditions in 44 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 30 minutes after the start of a standardized, high-fat, high-calorie breakfast (consisting of milk, egg omelette, chicken tikka, bread with butter and a hash brown potato). 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 after administration of the products.

Results

Two subjects were withdrawn from the study due to vomiting, one subject withdrew consent on his own accord and two subjects did nog report to the clinical facility for the second period. Therefore, a total of 39 subjects completed the study and 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=39	**AUC_{0-72} (ng.h/ml)**	**C_{max} (ng/ml)**	**t_{max} (h)**
Test	14123 ± 3576	586 ± 118	3.00 (1.67-4.50)
Reference	13886 ± 3535	537 ± 139	3.33 (1.33-5.00)
***Ratio (90% CI)**	1.02 (0.94-1.11)	1.10 (1.03-1.18)	--
CV (%)	20.80	18.05	--

$AUC_{0-\infty}$ 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
CV coefficient of variation

**ln-transformed values*

Conclusion on bioequivalence studies

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 studies Tadalafil ELC 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).

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 ELC.

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 ischaemic optic neuropathy (NAION) • Sudden hearing loss
Missing information	• Characterisation of adverse events in elderly patients (over 65 years of age)

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 two bioequivalence studies 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) of the 5 mg strength 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 results show that the PL 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. For the 10 mg and 20 mg strength bridging reports have been submitted. It is concluded that no separate readability tests are required for these leaflet.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Tadalafil ELC 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 ELC with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 7 May 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