COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Lehasofu 2.5 mg, 5 mg, 10 mg and 20 mg, film-coated tablets

(tadalafil)

NL/H/4707/001-004/DC

Date: 9 July 2020

This module reflects the scientific discussion for the approval of Lehasofu. The procedure was finalised on 12 April 2020. 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 Lehasofu 2.5 mg, 5 mg, 10 mg and 20 mg, film-coated tablets from Stada Arzneimittel AG.

The product is indicated for:

- Treatment of erectile dysfunction in adult males (all strengths). 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 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 product Cialis 2.5 mg, 5 mg, 10 mg and 20 mg tablets which has been registered in the EEA through centralised procedure EU/1/02/237 by Eli Lilly Nederland B.V. since 12 November 2002.

The concerned member states (CMS) involved in this procedure were Austria, Belgium and Luxembourg (5 mg, 10 mg and 20 mg); Ireland (10 mg and 20 mg), France, Germany and Spain (all strengths).

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

II. QUALITY ASPECTS

II.1 Introduction

Lehasofu 2.5 mg is a light orange-yellow, round, biconvex, film-coated tablet.
Lehasofu 5 mg is a light yellow, round, biconvex, film-coated tablet.
Lehasofu 10 mg is a yellow, round, biconvex, film-coated tablet with score line on one side, white at the cross section. The tablet can be divided into equal doses.
Lehasofu 20 mg is a yellow, round, biconvex, film-coated tablet with cross line on both sides, white at the cross section. The tablet can be divided into equal doses.

Lehasofu contains as active substance 2.5 mg, 5 mg, 10 mg or 20 mg of tadalafil.

The film-coated tablets are packed in PVC/PCTFE/PVC/ Aluminium blisters (unit-dose).

The excipients are:
Tablet core - lactose monohydrate, croscarmellose sodium, sodium laurilsulfate (E487), hydroxypropyl cellulose, polysorbate, microcrystalline cellulose, magnesium stearate
Coating – hypromellose, lactose monohydrate, titanium dioxide (E171), triacetin, iron oxide yellow (E172), iron oxide red (E172), talc

The cores of the four tablet strengths are fully dose proportional. Only the hydrophilic coatings are not fully dose-proportion.

II.2 Drug Substance

The active substance is tadalafil, an established active substance described in the European Pharmacopoeia (Ph. Eur.). The active substance is a white or almost white powder. Tadalafil is practically insoluble in water, freely soluble in dimethyl sulfoxide, slightly soluble in methylene chloride. As the molecule includes chiral centres, stereochemistry issues may be relevant. Sufficient information was provided on polymorphism.

The CEP procedure is used for both manufacturers of 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
CEPs have been submitted; therefore no details on the manufacturing process have been included.

Quality control of drug substance
The active substance specification and methods are in line with the Ph. Eur. monograph, with additional tests as per CEP and for particle size. The additional methods have adequately been described and where applicable, also validated. Provided batch results show compliance to the specification. Omission of a test for microbial contamination is justified. The specification is acceptable.

Stability of drug substance
The active substance is stable for 5 years 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 development of the product has been described, the choice of excipients is justified and their functions explained. Further formulation optimisations were performed by changing the binder concentration, solubiliser concentration and intragranular/extragranular ratio of the constituents. High shear granulation was selected as the technological process of choice. The discriminatory nature of the QC dissolution test has been adequately demonstrated.

Tadalafil 10 mg film-coated tablets with score-line and 20 mg film-coated tablets with score-cross were developed to allow division of tablet into equal halves (10 mg) or equal quarters or halves (20 mg). Several trials were done in order to obtain tablets that will be in accordance with test of breakability (Ph. Eur. ″Tablets″) and specified in-process parameters for Tadalafil 10 and 20 mg film-coated tablets. Tested parameters (Breakability and uniformity of dosage units) of the tablets appeared to comply with requirements of Ph. Eur. monograph 0478 Tablets.

The pivotal bioequivalence (BE) study has been done with a small-scale batch. The MAH has however confirmed that comparative dissolution profile testing will be undertaken with the approved QC dissolution method on the first three production batches and, in line with the BE Guideline, full scale batches will not be marketed until comparative dissolution profile testing has been completed with acceptable results.

The bioequivalence study was performed with unscored 20 mg tablets, while the commercial tablets contain a score. A biowaiver was requested for the other strengths. Adequate results of comparative dissolution testing have been provided. Also comparison of tablets (20 mg) with and without score-cross was performed in the QC method and over the physiological range (pH 1.2, 4.5 and 6.8). It has been demonstrated that the score-cross has no impact on dissolution over the physiological range nor in the QC medium.

Manufacturing process

The description of the manufacturing process is described in a sufficient matter as is outlined *Guideline on Manufacture of the finished dosage form (EMA/CHMP/QWP/245074/2015*). The process includes the preparation of granulation mixture, blending, tableting, film coating and packaging. Sufficient controls are adopted. The process is considered a standard manufacturing process and, in view of the similarity of the four tablet strengths, is considered adequately validated for six common blend batches and at least two batches of each tablet strength.

Control of excipients

The MAH included a certificate of analysis of each excipient including relevant functionality related characteristics. The specifications are acceptable.

Quality control of drug product

The product specification includes tests for appearance, identification, average mass, uniformity of dosage units, dissolution, assay, related substances and microbiological quality. Resistance to crushing and water are monitored during stability studies, it is

adequately justified not to include them in the specification. The analytical methods have been adequately described and validated.
Batch analytical data from the proposed production site have been provided on at least two pilot-scale batches, demonstrating compliance with the release specification.

Stability of drug product
Stability data has been provided for at least two pilot-size batches of each strength, stored at 25°C/60% RH for 6-24 months and at 40°C/75% RH for 6 months. The conditions used in the stability studies are according to the ICH stability guideline. The batches were stored in PVC/PCTFE /PVC//Al transparent blister packaging. Photostability studies were performed in accordance with ICH recommendations and showed that the product is stable when exposed to light.
Tested parameters remained within set specifications, current results are considered sufficient to justify a shelf life of 3 years and storage condition: 'This medicinal product does not require any special storage conditions'.
On the basis of the currently available in-use stability data, the proposed in-use stability period of 4 weeks for the divided tablet has been granted.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies
The components with possible TSE risk are lactose monohydrate and magnesium stearate. Lactose monohydrate complies with the CPMP "Note for guidance on minimizing the risk of transmitting animal spongiform encephalopathy agents via human or veterinary medicinal products". Stearic acid used for the manufacturing of magnesium stearate is of vegetable origin. Herewith, safety with respect to the possibility of transmitting TSE is considered justified.

II.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the member states consider that Lehasofu 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 Lehasofu 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 Lehasofu 20 mg (Stada Arzneimittel AG, Germany) is compared with the pharmacokinetic profile of the reference product Cialis 20 mg film-coated tablets (Eli Lilly Nederland B.V., the Netherlands). A study under fasted and under fed conditions was conducted. 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 micronisation) a difference in bioavailability may be observed under fed conditions.

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.

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

Biowaiver

Bioequivalence studies were performed with the 20 mg strength only. The MAH applied for a biowaiver for the 2.5 mg, 5 mg and 10 mg strengths. The biowaiver has been granted, as the following criteria have been fulfilled:

- the formulations are manufactured by the same manufacturer and manufacturing process
- the tadalafil tablets have the same qualitative composition
- the composition of the tablets is quantitatively proportional
- tadalafil shows linear pharmacokinetics over the therapeutic dose range of 2.5 – 20 mg
- dissolution data at pH 1.2, 4.5 and 6.8 have been provided, showing comparable dissolution.

Bioequivalence studies

Study I – 20 mg under fasted 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 18-55 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 of at least 10 hours. 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, 48 and 72 hours after administration of the products.

The design of the study is acceptable. Given the expected t_{max} of 2 hours and the half-life of tadalafil of 16 hours, the sampling period and washout period are long enough. The absorption process is likely covered with the given sampling schedule.

Results

Three subjects were withdrawn due to personal reasons after drug administration in the first treatment period. A total of 35 subjects finished the study and were included in the statistical evaluation.

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

Treatment N=35	**AUC_{0-72} (ng.h/ml)**	**C_{max} (ng/ml)**	**t_{max} (h)**	**$t_{1/2}$ (h)**
Test	10543 ± 2938	393 ± 85	3.0 (0.7-6.0)	--
Reference	10306 ± 3176	400 ± 98	2.7 (0.7-4.5)	--

***Ratio (90% CI)**	1.03 (0.95-1.11)	1.00 (0.92-1.07)	--	--
CV (%)	20.14	18.29	--	--

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*

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 36 healthy male subjects, aged 18-55 years. After an overnight fast of at least 10 hours, subjects were served a standardized, high-fat, high-calorie breakfast which they consumed completely within 30 minutes (the composition of the meal corresponds approximately to 150 kcal from protein, 250 kcal from carbohydrate and 500 – 600 kcal from fat with a total caloric content of approximately 800 – 1000 kcal) according to the Guideline on the Investigation of Bioequivalence and FDA recommendation. Exactly 30 minutes after the actual start time of the high-fat, high-calorie breakfast, the subjects received a single dose (20 mg) of one of the 2 tadalafil formulations. For each subject there were 2 dosing periods, separated by a washout period of 14 days.

Blood samples were collected pre-dose and at 0.5, 1, 1.33, 1.67, 2, 2.33, 2.67, 3, 3.5, 4, 4.5, 5, 5.5, 6, 8, 12, 24, 48 and 72 hours after administration of the products.

The design of the study is acceptable. Given the expected t_{max} of 2 hours and the half-life of tadalafil of 16 hours, the sampling period and wash-out period are long enough. The absorption process is likely covered with the given sampling schedule.

Results

One subject was excluded from the pharmacokinetic data evaluation and statistical analysis due to observed non-zero baseline values > 5 % of C_{max} in the second treatment period. A total of 35 subjects were included in the statistical evaluation.

Table 2. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of 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	11538 ± 3723	494 ± 122	3.0 (1.0-5.0)	--

Reference	12177 ± 3736	493 ± 122	3.0 (1.0-6.0)	--
***Ratio (90% CI)**	0.95 (0.91-0.99)	1.00 (0.96-1.04)	--	--
CV (%)	11.14	9.95	--	--

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 studies

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 Lehasofu 20 mg is considered bioequivalent with Cialis 20 mg film-coated tablets under fasted and fed conditions.

The MEB has been assured that the bioequivalence studies have 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 Lehasofu.

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
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 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

The package leaflet (PL) 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 10 participants each. The questions covered the following areas sufficiently: traceability, comprehensibility and applicability.
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.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Lehasofu 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. 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 Lehasofu with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 12 April 2020.

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