COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Tadalafil STADA 10 mg, film-coated tablets (tadalafil)

NL/H/5801/001/MR

Date: 10 June 2024

This module reflects the scientific discussion for the approval of Tadalafil STADA 10 mg, film-coated tablets. The procedure was finalised on 6 February 2024. 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
EMA	European Medicines Agency
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 Tadalafil STADA 10 mg, film-coated tablets from Stada Arzneimittel AG.

The product is indicated for treatment of erectile dysfunction in adult males. In order for tadalafil to be effective, sexual stimulation is required.

Tadalafil is not indicated for use by women.

A comprehensive description of the up-to-date indications and posology is given in the SmPC.

The marketing authorisation has been granted pursuant to Article 10(1) of Directive 2001/83/EC, which concerns a generic application.

In this mutual recognition procedure, essential similarity is proven between the new product and the innovator product Cialis 20 mg, film-coated tablets, which has been registered in the EEA via a centralised procedure (EU/1/02/237/002) by Eli Lilly Nederland B.V. since 12 November 2002.

The concerned member states (CMS) involved in this procedure were Italy and Spain.

II. QUALITY ASPECTS

II.1 Introduction

Tadalafil STADA 10 mg is a yellow, round, biconvex, film-coated tablet with score line on one side, white at the cross section. One tablet contains as active substance 10 mg of tadalafil. The tablet can be divided into equal doses.

The excipients are:
Tablet-core: lactose monohydrate, croscarmellose sodium, sodium lauryl sulfate (E487), hydroxypropyl cellulose, polysorbate 80, cellulose (microcrystalline), and magnesium stearate.
Film-coating: hypromellose 2910, lactose monohydrate, titanium dioxide (E171), triacetin, iron oxide yellow (E172), and talc.

The film-coated tablet is packed in polyvinyl chloride/polychlorotrifluoroethylene/polyvinyl chloride/aluminium (PVC/PCTFE/PVC/Alu) blisters.

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 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 tests as per CEP and for particle size. The additional methods have been described adequately and where applicable, also validated. Provided batch results show compliance to the specification. Omission of a test for microbial contamination is justified. Batch analytical data demonstrating compliance with this specification have been provided for two batches.

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 product is an established pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines.

The development of the product (based on the innovator 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. Tadalafil 10 mg, film-coated tablets with score-line were developed to allow division of tablet into equal halves. High shear granulation was selected as the technological process of choice. As the solubility of the drug substance in aqueous media over the pH range is low, phosphate buffer pH 6.8 was chosen for QC dissolution test. The discriminatory nature of the QC dissolution test has been adequately demonstrated.

Manufacturing process

The manufacturing process has been validated according to relevant European/ICH guidelines. The process includes the preparation of granulation mixture, blending, tableting, film coating and packaging. Sufficient controls are adopted. Process validation data on the product have been presented for two batches in accordance with the relevant European guidelines.

Control of excipients

The applicant included a certificate of analysis of each excipient including relevant functionality related characteristics. 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, average mass, uniformity of dosage units, dissolution, assay, related substances and microbiological quality. Limits in the specification have been justified and are considered appropriate for adequate quality control of the product. Resistance to crushing and water are monitored during stability studies, it is adequately justified not to include them in the specification. An adequate nitrosamines risk evaluation report has been provided. No risk for presence of nitrosamines in the drug product was identified.

Satisfactory validation data for the analytical methods have been provided.

Batch analytical data for two 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 two batches stored at 25°C/ 60% RH (6-24 months) and 40°C/75% RH (6 months) in accordance with applicable European guidelines. Photostability studies were performed in accordance with ICH recommendations and showed that the product is stable when exposed to light. On basis of the data submitted, a shelf life was granted of 3 years. No specific storage conditions needed to be included in the SmPC or on the label.

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

Scientific data and/or certificates of suitability issued by the EDQM for excipient lactose monohydrate have been provided and compliance with the Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via medicinal products has been satisfactorily demonstrated. Excipient magnesium stearate also carries a possible TSE risk, however stearic acid used for the manufacturing of magnesium stearate is claimed to be 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 Tadalafil STADA 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 STADA is intended for generic substitution, this will not lead to an increased exposure to the environment. An environmental risk assessment was therefore not deemed necessary.

III.2 Discussion on the non-clinical aspects

This product is a generic formulation of Cialis 20 mg which is available on the European market. Reference was made to the preclinical data obtained with the innovator product. A non-clinical overview on the pharmacology, pharmacokinetics and toxicology has been provided, which was 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 member states agreed that no further clinical studies are required, besides the 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 STADA 20 mg, film-coated tablets (STADA Arzneimittel AG, Germany) was compared with the pharmacokinetic profile of the reference product Cialis 20 mg, film-coated tablet (Eli Lilly Nederland B.V., Netherlands).

The choice of the reference product in the bioequivalence study has been justified by comparison of dissolution study results and composition. The formula and preparation of the bioequivalence batch was identical to the formula proposed for marketing.

The bioequivalence studies were performed with unscored 20 mg Tadalafil STADA tablets, while the commercial tablets contain a score. The current application is for the 10 mg strength, for this a biowaiver was requested. 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.

Biowaiver

The following general requirements must be met where a waiver for additional strength is claimed, according to the EMA Bioequivalence guideline:

a. the pharmaceutical products are manufactured by the same manufacturing process,
b. the qualitative composition of the different strengths is the same,
c. the composition of the strengths are quantitatively proportional, i.e. the ratio between the amount of each excipient to the amount of active substance(s) is the same for all strengths (for immediate release products coating components, capsule shell, colour agents and flavours are not required to follow this rule),
d. appropriate *in vitro* dissolution data should confirm the adequacy of waiving additional *in vivo* bioequivalence testing.

Based on the submitted bioequivalence studies, Tadalafil 20mg, film-coated tablets is considered bioequivalent with Cialis 20 mg tablet (Eli Lilly). The results obtained in these studies for the 20 mg strength can be extrapolated to the lower strength 10 mg as all conditions for a biowaiver were met.

Bioequivalence studies

Study 1 – tadalafil 20 mg, fasting conditions

Design

A single-dose, randomised, two-period, two-treatment, two-sequence, crossover open label bioequivalence study was carried out under fasted conditions in 38 healthy male subjects, aged 18-51 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 of at least 10 hours. There were two 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, 72 hours after administration of the products.

The design of the study is acceptable. Tadalafil may be taken with or without food

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

38 subjects enrolled in the study. Three subjects withdrew due to personal reasons after drug administration in period I. 35 subjects were eligible for pharmacokinetic analysis.

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

Treatment N=35	**AUC_{0-t} (ng.h/mL)**	**$AUC_{0-\infty}$ (ng.h/mL)**	**C_{max} (ng/mL)**	**t_{max} (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)	-

$AUC_{0-\infty}$	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 = 72 hours
C_{max}	Maximum plasma concentration
t_{max}	Time after administration when maximum plasma concentration occurs
CI	Confidence interval

**ln-transformed values*

Study 2 – tadalafil 20 mg, fed conditions

Design

A single-dose, randomised, two-period, two-treatment, two-sequence, crossover open label bioequivalence study was carried out under fed conditions in 36 healthy male subjects, aged 18-50 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 fasting of about 10 hours and 30 minutes after taking a standardised high fat, high calorie breakfast (150 kcal protein, 250 kcal carbohydrate, 500-600 kcal fat, 800-1000 kcal total caloric content). There were two 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 studies is acceptable.

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

36 subjects enrolled in and completed the study. One subject was excluded from the pharmacokinetic data evaluation and statistical analysis due to observed non-zero baseline

values > 5 % of Cmax in the second treatment period. 35 subjects were eligible for pharmacokinetic analysis.

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

Treatment N=35	AUC_{0-t} (ng.h/mL)	$AUC_{0-\infty}$ (ng.h/mL)	C_{max} (ng/mL)	t_{max} (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)	-

$AUC_{0-\infty}$	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 = 72 hours
C_{max}	Maximum plasma concentration
t_{max}	Time after administration when maximum plasma concentration occurs
CI	Confidence interval

**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 STADA is considered bioequivalent with Cialis under fasted and fed conditions.

The results of the studies with 20 mg formulation can be extrapolated to strength 10 mg, according to conditions in Guideline on the Investigation of Bioequivalence CPMP/EWP/QWP/1401/98 Rev. 1/Corr*, section 4.1.6.

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 STADA.

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. 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) has been evaluated (based on Tadalafil STADA 5 mg (NL/H/4707/002/DC) via a user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC. The language used for the purpose of user testing the PL was English.
The test consisted of: a pilot test with 3 participants, 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

Tadalafil STADA 10 mg, film-coated tablet has a proven chemical-pharmaceutical quality and is a generic form of Cialis 10 mg, film-coated tablet. 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 STADA with the

reference product, and have therefore granted a marketing authorisation. The mutual recognition procedure was finalised with a positive outcome on 6 February 2024.

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
-	-	-	-	-	-