CBG MEB

# Public Assessment Report

# Scientific discussion

# Tadalafil STADA 2.5 mg, 5 mg, 10 mg and 20 mg, film-coated tablets

# (tadalafil)

## NL/H/3650/001-004/DC

## Date: 18 May 2017

**This module reflects the scientific discussion for the approval of Tadalafil STADA 2.5 mg, 5 mg, 10 mg and 20 mg, film-coated tablets. The procedure was finalised on 25 October 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

| | |
|---|---|
| CEP | Certificate of Suitability to the monographs of the European Pharmacopoeia |
| 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 STADA 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. 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 STADA 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 EMEA/H/C/000436 by Eli Lilly Nederland B.V. since 12 November 2002.

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

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

# II. QUALITY ASPECTS

## II.1 Introduction

Tadalafil STADA is a film-coated tablet in four strengths:
- The 2.5 mg strength is a yellow-orange coloured, caplet shaped, biconvex, film coated tablet, debossed with “T 2” on one side and plain on the other.
- The 5 mg strength is a yellow coloured, caplet shaped, biconvex, film coated tablet, debossed with “T 5” on one side and plain on the other.
- The 10 mg strength is a yellow coloured, caplet shaped, biconvex, film coated tablet, debossed with “T 10” on one side and plain on the other.
- The 20 mg strength is a yellow coloured, caplet shaped, biconvex, film coated tablet, debossed with “T 20” on one side and plain on the other.

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

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

The excipients are:
*Tablet core* - anhydrous lactose, croscarmellose sodium, sodium laurilsulfate, hydroxypropylcellulose, polysorbate 80 and magnesium stearate
*Tablet coating* - hypromellose 2910 (E464), lactose monohydrate, titanium dioxide (E171), triacetin, talc (E553b) and iron oxide yellow (E172)

The 5 mg, 10 mg and 20 mg strengths are fully dose proportional.

## 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, slightly soluble in methylene chloride. Tadalafil exhibits polymorphism. The manufacturing process consistently produces the 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. It meets the requirements of the monograph in the Ph.Eur., the CEP, and additional requirement to test for particle size. 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 choices of the packaging and manufacturing are justified. The main development studies were the characterisation of the reference product, optimisation of the excipient levels in the formulation and the performance of comparative *in vitro* dissolution studies. The pharmaceutical development of the product has been adequately performed.

Bioequivalence studies under fasted and fed conditions have been performed with the 2.5 mg and the 20 mg product versus their respective reference product strength. The batches used in the bioequivalence studies were manufactured according to the finalised formulation and manufacturing process.
A biowaiver is claimed for the 5 mg and 10 mg strengths based on the *in vivo* study with the 20 mg product. Comparative dissolution is shown of the 5 mg, 10 mg and 20 mg test tablets in 0.1N HCl, acetate buffer pH 4.5 and phosphate buffer pH 6.8.

Manufacturing process
The main steps of the manufacturing process are dry mixing, 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 per strength. The product is manufactured using conventional manufacturing techniques. Process validation for full scaled batches will be performed post authorisation.

Control of excipients
The excipients comply with their Ph.Eur. monographs or in-house specification. 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. Except for water content and total impurities, 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 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 per strength stored at 25°C/60% RH (18 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. 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. Based on the presented stability data, a shelf-life of 30 months without any special storage requirements is justified.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies
Anhydrous lactose and lactose monohydrate are the only materials of animal origin included in the drug product. Scientific data and/or certificates of suitability issued by the EDQM 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.

### 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 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

Bioequivalence studies
In total the MAH conducted four bioequivalence studies in which the pharmacokinetic profile of the test product Tadalafil STADA (Stada Arzneimittel AG, Germany) is compared with the pharmacokinetic profile of the reference product Cialis (Eli Lilly, UK):

- Single dose bioequivalence study with the 2.5 mg tablet under fasting conditions.
- Single dose bioequivalence study with the 2.5 mg tablet under fed conditions.
- Single dose bioequivalence study with the 20 mg tablet under fasting conditions.
- Single dose bioequivalence study with the 20 mg tablet under fed conditions.

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. As such, the submission of bioequivalence studies under fasting and fed conditions is in accordance with these guidelines.

*The choice of the reference product*
The choice of the reference product from the UK in the bioequivalence studies has been justified. 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.

*Biowaiver*
The biowaiver for tadalafil 5 mg and 10 mg film-coated tablets is acceptable, as the following criteria have been fulfilled:

- The formulations are manufactured by the same manufacturer and manufacturing process.
- The 5 mg, 10 mg and 20 mg formulations are dose-proportional.
- Tadalafil shows linear pharmacokinetics over the therapeutic dose range of 5–20 mg.
- Dissolution data without the use of sodium lauryl sulphate (SLS) at a pH 1.2, 4.5 and 6.8 have been provided showing comparable dissolution using the same dose, due to the fact that sink conditions could not be reached.

***Single dose bioequivalence study with the 2.5 mg tablet under fasting conditions***
*Design*
An open-label, balanced, randomised, single-dose, two-treatment, two-sequence, two-period, crossover bioequivalence study was carried out under fasted conditions in 38 healthy male subjects, aged 20-44 years. Each subject received a single dose (2.5 mg) of one of the two tadalafil formulations. The tablet was orally administered with 240 ml 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 withdrew consent before check-in of period II due to a personal problem. Therefore 37 subjects were eligible for pharmacokinetic analysis.

**Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, $t_{max}$ (median, range)) of tadalafil 2.5 mg under fasting conditions.**

| Treatment N=37 | $AUC_{0-t}$ ng.h/ml | $C_{max}$ ng/ml | $t_{max}$ h | $t_{1/2}$ h |
|---|---|---|---|---|

| | | | | |
|---|---|---|---|---|
| **Test** | 1718 ± 624 | 76 ± 19 | 1.67<br>(0.67 – 6.0) | 35 ± 13 |
| **Reference** | 1683 ± 469 | 79 ± 17 | 1.67<br>(0.33 – 5.0) | 34 ± 16 |
| ***Ratio<br>(90% CI)** | 0.99<br>(0.91 - 1.06) | 0.95<br>(0.90 - 1.00) | -- | -- |
| **CV (%)** | 17.7 | 13.9 | -- | -- |

**$AUC_{0-t}$** 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*

Two subjects did not report for the 72 hour ambulatory sample in period I and four subjects did not report for the 72 hour ambulatory sample in period II. For these subjects, the primary pharmacokinetic parameter $AUC_{0-h}$ could not be estimated precisely due to the missed 72 hour blood draw. These subjects were identified before bio-analysis and their data was excluded from the statistical analysis of $AUC_{0-h}$. However, these subjects were included in the statistical calculations of $C_{max}$. This is considered acceptable.

***Single dose bioequivalence study with the 2.5 mg tablet under fed conditions***

*Design*

An open-label, balanced, randomised, single-dose, two-treatment, two-sequence, two-period, crossover bioequivalence study was carried out under fasted conditions in 38 healthy male subjects, aged 18-41 years. Each subject received a single dose (2.5 mg) of one of the two tadalafil formulations. The tablet was orally administered with 240 ml water 30 minutes after starting the 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 and three subjects did not report for check-in for period II. Therefore, 34subjects were eligible for pharmacokinetic analysis.

**Table 2. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, $t_{max}$ (median, range)) of tadalafil 2.5 mg under fed conditions.**

| **Treatment<br>N=34** | **$AUC_{0-t}$<br>ng.h/ml** | **$C_{max}$<br>ng/ml** | **$t_{max}$<br>h** | **$t_{1/2}$<br>h** |
|---|---|---|---|---|
| **Test** | 1574 ± 558 | 61 ± 11 | 3.0<br>(1.0 – 5.0) | 33 ± 15 |
| **Reference** | 1486 ± 478 | 59 ± 15 | 3.5<br>(1.0 – 5.0) | 32 ± 12 |
| ***Ratio<br>(90% CI)** | 1.05<br>(0.99 - 1.12) | 1.06<br>(1.00 - 1.13) | -- | -- |
| **CV (%)** | 14.6 | 14.8 | -- | -- |

**$AUC_{0-t}$** 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*

***Single dose bioequivalence study with the 20 mg tablet under fasting conditions***

*Design*

An open-label, balanced, randomised, single-dose, two-treatment, two-sequence, two-period, 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 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) in period I. Therefore 37 subjects were eligible for pharmacokinetic analysis.

**Table 3. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, $t_{max}$ (median, range)) of tadalafil 20 mg under fasting 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 | -- | -- |

**$AUC_{0-t}$** 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*

Nine subjects did not report for the 72 hour ambulatory sample in period I and two subjects did not report for the 72 hour ambulatory sample in period II. For these subjects, the primary pharmacokinetic parameter $AUC_{0-h}$ could not be estimated precisely due to the missed 72 hour blood draw. These subjects were identified before bio-analysis and their data was excluded from the statistical analysis of $AUC_{0-h}$. However, these subjects were included in the statistical calculations of $C_{max}$. This is considered acceptable.

***Single dose bioequivalence study with the 20 mg tablet under fed conditions***

*Design*

An open-label, balanced, randomised, single-dose, two-treatment, two-sequence, two-period, crossover bioequivalence study was carried out under fasted 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 starting the 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 4. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, $t_{max}$ (median, range)) of tadalafil 20 mg under fed 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 | -- | -- |

**$AUC_{0-t}$** 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*

Nine subjects did not report for the 72 hour ambulatory sample in period I. For these subjects, the primary pharmacokinetic parameter $AUC_{0-h}$ could not be estimated precisely due to the missed 72 hour blood draw. These subjects were identified before bio-analysis and their data was excluded from the statistical analysis of $AUC_{0-h}$. However, these subjects were included in the statistical calculations of $C_{max}$. This is considered acceptable.

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 STADA 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 STADA.

Summary table of safety concerns as approved in RMP:

| | |
|---|---|
| Important identified risks | • Priapism<br>• Hypotension, increased hypotensive effect |
| Important potential risks | • Non-arteritic anterior ischaemic optic neuropathy (NAION)<br>• 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

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 test consisted of: a pilot test with two 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 package leaflet 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.

A user consultation with target patient groups on the PL of the 10 mg and 20 mg strengths has been performed on the basis of a bridging report making reference to PL of the 5 mg strength. 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 STADA 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 STADA with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 25 October 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 |
|---|---|---|---|---|---|---|
| | | | | | | |