EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

25 September 2014
EMA/707959/2014
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Tadalafil Mylan

International non-proprietary name: Tadalafil

Procedure No. EMEA/H/C/003787

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature delete

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Table of contents

List of abbreviations

CEP	Certificate of Suitability of the European Pharmacopoeia
CHMP	Committee for Medicinal Products for Human Use
DMF	N,N-Dimethylformamide
DMSO	dimethyl sulfoxide
EMA	European Medicines Agency
EU	European Union
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
Ph. Eur.	European Pharmacopoeia
SmPC	Summary of Medicinal Product Characteristics

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Generics (UK) Limited submitted on 3 December 2013 an application for Marketing Authorisation to the European Medicines Agency (EMA) for Tadalafil Mylan, through the centralised procedure under Article 3 (3) of Regulation (EC) No. 726/2004– 'Generic of a Centrally authorised product'. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 19 June 2013.

The application concerns a generic medicinal product as defined in Article 10(2)(b) of Directive 2001/83/EC and refers to a reference product for which a Marketing Authorisation is or has been granted in the Union on the basis of a complete dossier in accordance with Article 8(3) of Directive 2001/83/EC.

The applicant applied for the following indication:

For 2.5 mg, 10 mg and 20 mg:
Treatment of erectile dysfunction in adult males.
In order for tadalafil to be effective, sexual stimulation is required.
Tadalafil Mylan is not indicated for use by women.

For 5 mg:
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.
Tadalafil Mylan is not indicated for use by women.

The legal basis for this application refers to:

Generic application (Article 10(1) of Directive No 2001/83/EC).

The application submitted is composed of administrative information, complete quality data and a bioequivalence study with the reference medicinal product Cialis instead of non-clinical and clinical unless justified otherwise.

Information on paediatric requirements

Not applicable

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

The chosen reference product is:

■ Medicinal product which is or has been authorised in accordance with Community provisions in accordance with Community provisions in force for not less than 6/10 years in the EEA:

- Product name, strength, pharmaceutical form: Cialis 2.5 mg, 5 mg, 10 mg and 20 mg film-coated tablets
- Marketing authorisation holder: Eli Lilly Netherland B.V.
- Date of authorisation: 12-11-2002
- Marketing authorisation granted by:
  - Community
    - Community Marketing authorisation number: EU/1/02/237

■ Medicinal product authorised in the Community/Members State where the application is made or European reference medicinal product:

- Product name, strength, pharmaceutical form: Cialis 2.5 mg, 5 mg, 10 mg and 20 mg film-coated tablets
- Marketing authorisation holder: Eli Lilly Netherland B.V.
- Date of authorisation: 12-11-2002
- Marketing authorisation granted by:
  - Community
    - Community Marketing authorisation number: EU/1/02/237

■ Medicinal product which is or has been authorised in accordance with Community provisions in force and to which bioequivalence has been demonstrated by appropriate bioavailability studies:

- Product name, strength, pharmaceutical form: Cialis 20 mg film-coated tablets
- Marketing authorisation holder: Eli Lilly Netherland B.V.
- Date of authorisation: 12-11-2002
- Marketing authorisation granted by:
  - Community
  - Community Marketing authorisation number(s): EU/1/02/237
- Bioavailability study numbers: TADA-1K-622-13, TADA-1937-13

Scientific advice

The applicant did not seek scientific advice at the CHMP.

Licensing status

Tadalafil Mylan has been given a Marketing Authorisation in Canada on 16-08-2013.

An application was filed in the following countries: New Zealand, Australia.

1.2. Manufacturers

Manufacturers responsible for batch release

McDermott Laboratories Ltd. t/a Gerard Laboratories
35/36 Baldoyle Industrial Estate
Grange road

Dublin 13
Ireland

Mylan Hungary Kft.
Mylan utca. 1
H-2900 Komárom
Hungary

1.3. Steps taken for the assessment of the product

The Rapporteur appointed by the CHMP was Kolbeinn Guðmundsson.

- The application was received by the EMA on 3 December 2013.
- The procedure started on 26 December 2013.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 14 March 2014
- During the PRAC meeting on 10 April 2014, the PRAC adopted an RMP Advice and assessment overview.
- During the meeting on 25 April 2014, the CHMP agreed on the consolidated List of Questions to be sent to the applicant. The final consolidated List of Questions was sent to the applicant on 28 April 2014.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 22 July 2014.
- The Rapporteur circulated the Assessment Report on the applicant’s responses to the List of Questions to all CHMP members on 29 August 2014.
- During the PRAC meeting on 11 September 2014, the PRAC adopted an RMP Advice and assessment overview.
- The Rapporteur circulated the updated Assessment Report on the applicant’s responses to the List of Outstanding Issues on 22 September 2014.
- During the meeting on 22-25 September 2014, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a Marketing Authorisation to Tadalafil Mylan.

2. Scientific discussion

2.1. Introduction

Tadalafil Mylan is a generic medicinal product of Cialis which has been authorised in the EU since 12 November 2002.

The active substance of Tadalafil Mylan is tadalafil, a selective, reversible inhibitor of cyclic guanosine monophosphate (cGMP)-specific phosphodiesterase type 5 (PDE5). When sexual stimulation causes the local release of nitric oxide, inhibition of PDE5 by tadalafil produces increased levels of cGMP in the corpus cavernosum. This results in smooth muscle relaxation and inflow of blood into the penile tissues, thereby

producing an erection. Tadalafil has no effect in the treatment of erectile dysfunction in the absence of sexual stimulation. It is classified in the pharmaco-therapeutic group of Urologicals, Drugs used in erectile dysfunction, with ATC Code G04BE08.

The safety and efficacy profile of tadalafil has been demonstrated in several clinical trials details of which can be found in the EPAR for Cialis. In addition, there is extensive post-marketing experience contributing to the knowledge of the clinical use of this product. Since this application is a generic application referring to the reference medicinal product Cialis, summary of the clinical data of tadalafil is available and no new clinical studies regarding pharmacology, pharmacokinetics and efficacy and safety have been conducted.

Tadalafil Mylan is administered orally and its bioequivalence versus the reference product Cialis was demonstrated in two bioequivalence studies. The studies were performed in healthy male volunteers, with 20 mg dose in fed and fasting condition.

The approved indication is:

For 2.5 mg, 10 mg and 20 mg:

Treatment of erectile dysfunction in adult males.
In order for tadalafil to be effective, sexual stimulation is required.
Tadalafil Mylan is not indicated for use by women.

For 5 mg:

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.

Tadalafil Mylan is not indicated for use by women.

The indication proposed for Tadalafil Mylan is the same as authorized for the reference medicinal product. The proposed pack sizes are consistent with the dosage regimen and duration of use.

2.2. Quality aspects

2.2.1. Introduction

The finished product is presented as film-coated tablets containing 2.5 mg, 5 mg, 10 mg or 20 mg of tadalafil as active substance.

Other ingredients are:

Tablet core: lactose anhydrous, poloxamer 188, cellulose microcrystalline (pH101), povidone (K-25), croscarmellose sodium, magnesium stearate, sodium laurilsulfate, and silica colloidal anhydrous.

Film-coat: lactose monohydrate, hypromellose (E464), titanium dioxide (E171), iron oxide yellow (E172), and triacetin.

The product is available in PVC/PE/PVdC-Alu blisters.

2.2.2. Active substance

General information

The chemical name of tadalafil is (6*R-trans*)-6-(1,3-benzodioxol-5-yl)-2,3,6,7,12,12a-hexahydro-2-methyl-pyrazino [1', 2':1,6] pyrido[3,4-*b*]indole-1,4-dione.

The active substance is a white or almost white powder which is practically insoluble in water, freely soluble in dimethyl sulfoxide and slightly soluble in methylene chloride.

As there is a monograph of tadalafil in the European Pharmacopoeia, the manufacturer of the active substance has been granted a Certificate of Suitability of the European Pharmacopoeia (CEP) for tadalafil which has been provided within the current Marketing Authorisation Application.

Manufacture, characterisation and process controls

The relevant information has been assessed by the EDQM before issuing the Certificate of Suitability.

Specification

The control tests were carried out to comply with the specifications and test methods of the Ph. Eur. monograph.

Additional specifications have been set for methanol, acetone and DMF residual solvents, safrole, chloroacetyl and chloroacetyl chloride impurities (included in the CEP) as well as for methylene chloride, isopropyl ether, toluene, triethylamine residual solvents and particle size (not included in the CEP). The analytical method for particle size has been adequately validated and it was demonstrated that it is not a critical factor for either the finished product performance or the manufacturing process.

Batch analysis data on three batches of the active substance were provided. The results comply with the specifications and confirm consistency and uniformity of the manufacturing process.

Stability

The relevant information has been assessed by the EDQM before issuing the Certificate of Suitability.

2.2.3. Finished medicinal product

Description of the product and Pharmaceutical development

The finished product Tadalafil Mylan film-coated tablets was developed as a generic bioequivalent to Cialis by Eli Lilly Nederland B.V. from the European market. The formulation contains the active substance tadalafil, officially listed in the Ph. Eur. Tadalafil is a white or almost white powder, practically insoluble in water, freely soluble in DMSO and slightly soluble in methylene chloride. The excipients selected for the formulation development are based on literature survey, excipient compatibility studies and their functionality for development of a tablet dosage form. All of the excipients are conventional pharmaceutical ingredients that comply with the respective requirements of the Ph. Eur., with the exception of the film coating agent Opadry II yellow which complies with

Commission Regulation (EU) No. 231/2012. However, the individual components of the coating material are of Ph.Eur. or similar quality.

The formulation should have the following attributes: the product should be formulated as an immediate release tablets and it has to be pharmaceutically equivalent to the reference product, the formulation should have comparable dissolution profile with reference product and the product should have satisfactory pharmaceutical stability.

Prototype development was initiated with a weight proportional composition for Tadalafil 2.5, 5, 10 and 20 mg film coated tablets. As the active substance exhibits poor flow properties, a wet granulation process was selected for prototype formulation development.

The dissolution characteristics of the finished product (2.5 mg, 5 mg, 10 mg and 20 mg tablets) were compared to the reference medicinal product Cialis from the European market (2.5 mg, 5 mg, 10 mg and 20 mg tablets). The dissolution profiles in water resulted in a release > 85% after 15 minutes for all strengths of the test product. However, in 0.1 N HCl, acetate buffer pH 4.5 and phosphate buffer pH 6.8 without the addition of a surfactant, the dissolution is generally incomplete for all strengths of the test and reference products. Since the 20 mg strength of the test product has been demonstrated to be bioequivalent to the reference product Cialis of the same strength, the incomplete release observed in the in-vitro dissolution studies was not raised as an issue.

The formulation used in the clinical studies is the same as the formulation intended for commercial supply. Furthermore, the applicant confirmed that the manufacturing process as described in the dossier was followed in the manufacturing of Tadalafil 20 mg film coated tables used in the bioequivalence study, manufacturing process validation and stability studies.

A biowaiver for the lower 2.5 mg, 5 mg and 10 mg strengths on the basis of the successful "fed" and "fasting" bioequivalence studies conducted on the 20 mg strength was applied. The conditions for granting a biowaiver were considered fulfilled and no further bioequivalence studies for the lower strengths were considered necessary.

The manufacturing process development strategy was to design and develop stable and bioequivalent generic product of Tadalafil film coated tablets using commonly used excipients and similar to the reference product. As mentioned above, the active substance characterization has revealed that the active substance had poor flow properties. Therefore a wet granulation process was chosen. During development the manufacturing process was optimized with regard to the following parameters: solvent system for granulation, drying temperature, milling process, blending time, tableting speed and hardness.

The discriminatory power of the dissolution method has been demonstrated.

The primary packaging is PVC/PE/PVdC-Alu blisters. The material complies with Ph. Eur. and EC requirements. The choice of container closure system has been validated by stability data and is adequate for the intended use of the product.

Manufacture of the product and process controls

The product is manufactured using a wet granulation process. The manufacturing process consists of 11 main steps: dispensing, sifting, granulation and drying, milling, mixing of granules, sifting, blending, compression, coating, inspection and packaging. All four strengths (2.5 mg, 5 mg, 10 mg, and 20 mg film-coated tablets) are being produced from the same common blend. The process is considered to be a standard manufacturing process.

Major steps of the manufacturing process have been validated by a number of studies. It has been demonstrated that the manufacturing process is capable of producing the finished product of intended quality in a reproducible manner. The in-process controls are adequate for this pharmaceutical form.

Product specification

The finished product release specifications include appropriate tests for this kind of dosage form: description, identification (UV, IR), color identification, dissolution (HPLC), uniformity of dosage units (by content uniformity), assay (UV), related substances (HPLC), loss on drying, residual solvents (GC), and microbiological test (Ph. Eur.).

Batch analysis results are provided for three commercial scale batches confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification.

Stability of the product

Stability data of twenty commercial scale batches (5 of each strength) of finished product stored under long term conditions for 12 months at 25 ºC / 60% RH and for up to 6 months under accelerated conditions at 40 ºC / 75% RH according to the ICH guidelines were provided. The batches of the medicinal product are identical to those proposed for marketing and were packed in the primary packaging proposed for marketing.

Samples were tested for description, dissolution, assay, related substances, loss on drying and microbiological quality. The analytical procedures used are stability indicating.

In addition, 1 batch was exposed to light as defined in the ICH Guideline on Photostability Testing of New Drug Substances and Products.

Based on available stability data, the shelf-life and storage conditions as stated in the SmPC are acceptable.

Adventitious agents

It is confirmed that the lactose is produced from milk from healthy animals in the same condition as those used to collect milk for human consumption and that the lactose has been prepared without the use of ruminant material other than calf rennet according to the Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents Via Human and veterinary medicinal products.

2.2.4. Discussion on chemical, and pharmaceutical aspects

Information on development, manufacture and control of the active substance and the finished product has been presented in a satisfactory manner. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use. The applicant is applying for a biowaiver for the three lower strength tablets (2.5 mg, 5 mg and 10 mg), which is acceptable.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way.

2.2.6. Recommendation(s) for future quality development

Not applicable.

2.3. Non-clinical aspects

2.3.1. Introduction

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. The non-clinical aspects of the SmPC are in line with the SmPC of the reference product. The impurity profile has been discussed and was considered acceptable.

Therefore, the CHMP agreed that no further non-clinical studies are required.

2.3.2. Ecotoxicity/environmental risk assessment

No Environmental Risk Assessment was submitted. This was justified by the applicant as the introduction of Tadalafil Mylan manufactured by Generics [UK] Limited is considered unlikely to result in any significant increase in the combined sales volumes for all tadalafil containing products and the exposure of the environment to the active substance. Thus, the ERA is expected to be similar and not increased.

2.3.3. Discussion on non-clinical aspects

This is an article 10(1) generic application. All non-clinical aspects have been covered in the SmPC, there are no objections according to the CHMP to grant a marketing authorisation for Tadalafil Mylan.

2.3.4. Conclusion on the non-clinical aspects

From a non-clinical point of view there are no objections according to the CHMP to approve Tadalafil Mylan.

2.4. Clinical aspects

2.4.1. Introduction

This is an application for film-coated tablets containing tadalafil. To support the marketing authorisation application the applicant conducted two bioequivalence study which was open label, balanced,

laboratory-blinded, randomised, single dose, two-treatment, two-sequence, two-period, two-way crossover oral bioequivalence study comparing two different formulations of Tadalafil 20 mg film-coated tablets in healthy, adult, human male subjects under fasting conditions.. This study was the pivotal study for the assessment.

The SmPC is in line with the SmPC of the reference product. This is agreeable to the CHMP.

No CHMP scientific advice pertinent to the clinical development was given for this medicinal product.

For the clinical assessment the Guideline on the Investigation of Bioequivalence CPMP/EWP/QWP/1401/98 Rev. 1/ Corr.) as well as the Guideline on Bioanalytical method validation (EMEA/CHMP/EWP/192217/09 Rev.1 Corr.) are of particular relevance.

GCP

The Clinical trials were performed in accordance with GCP as claimed by the applicant

The applicant has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

Exemption

Two bioequivalence studies were conducted on the 20 mg film-coated tablet strength under fasting and fed conditions.

To fulfil the requirements of a biowaiver an updated in vitro dissolution data was submitted at three pH levels without the addition of surfactant into the dissolution media.

The results of studies TADA-1K-622-13 and TADA-1937-13 with 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.

1. Tabular overview of clinical studies

Study identifier	**Study Title**
TADA-1K-622-13	An open label, balanced, randomized, single-dose, two-treatment, two-sequence, two-period, two-way crossover, oral bioequivalence study of Tadalafil Film-coated Tablets 20 mg of Mylan Laboratories Limited, India and CIALIS® (Film-coated Tadalafil tablets) 20 mg of Eli Lilly Nederland B.V., Grootslag 1-5, NL-3991 RA, Houten, The Netherlands, in healthy, adult, human subjects under fasting conditions.
TADA-1937-13	AN OPEN LABEL, BALANCED, RANDOMIZED, SINGLE-DOSE, TWO-TREATMENT, TWO-PERIOD, TWO-SEQUENCE, TWO-WAY CROSSOVER, ORAL BIOEQUIVALENCE STUDY OF TADALAFIL FILM-COATED TABLETS 20 mg OF MYLAN

	LABORATORIES LIMITED, INDIA AND CIALIS® (FILM-COATED TADALAFIL TABLETS) 20 mg OF ELI LILLY NEDERLAND B.V., GROOTSLAG 1-5, NL-3991 RA, HOUTEN, THE NETHERLANDS, IN HEALTHY, ADULT, HUMAN SUBJECTS UNDER FED CONDITIONS.

Biowaiver justification for Tadalafil 2.5 mg, 5 mg and 10 mg film coated tablets

The selection of the dose, 20 mg, used in the bioequivalence studies is justified and according to guidelines.

According to the Guideline on the Investigation of Bioequivalence *(CPMP/EWP/QWP/1401/98 Rev. 1/Corr –effective since 1st August 2010),* Tadalafil 2.5 mg, 5 mg and 10 mg film coated tablets satisfy the conditions for waiver of bioequivalence studies conducted on Tadalafil 20 mg film coated tablets as discussed below:

-All the strengths of Tadalafil film coated tablets are manufactured by the same manufacturer at the same manufacturing site using similar manufacturing process.

-The qualitative composition of core tablets of Tadalafil 2.5 mg, 5 mg, 10 mg and 20 mg film coated tablets is the same.

-Tadalafil tablets 2.5 mg, 5 mg, 10 mg and 20 mg are direct scale up/scale down formulations and the ratio between the amounts of each excipient to the amount of the active substance is the same.

-The *in vitro* dissolution characteristics demonstrates that dissolution profiles of Tadalafil 2.5 mg, 5 mg, 10 mg and 20 mg film coated tablets of Mylan Laboratories Limited's are similar across the physiological pH range i.e. pH 1.2, pH 4.5 and pH 6.8.

More than 85% of the labelled amount of drug (Tadalafil) was released within 15 minutes from the batches of bioequivalence study strength i.e. Tadalafil 20 mg film coated tablets and the lower strengths of the test product i.e. Tadalafil 2.5 mg, 5 mg and 10 mg film coated tablets in all the dissolution media tested. Therefore as per the provisions mentioned in *CHMP Guideline on the Investigation of Bio-equivalence – CPMP/EWP/QWP/1401/98-Rev 01 Corr–effective since 1 August 2010*, the dissolution profiles can be considered as similar.

-As per Cialis SmPC, "*Tadalafil pharmacokinetics in healthy subjects are linear with respect to time and dose. Over a dose range of 2.5 to 20 mg, exposure (AUC) increases proportionally with dose*". The bioequivalence study performed on Tadalafil 20 mg film coated tablets can therefore be extended to Tadalafil 2.5 mg, 5 mg and 10 mg film coated tablets.

Since all the requirements to waive bioequivalence studies as mentioned in *CHMP Guideline on the Investigation of Bio-equivalence – CPMP/EWP/QWP/1401/98- Rev 01 Corr* –are fulfilled*,* the bioequivalence study results of Tadalafil 20 mg film coated tablets can be extended to Tadalafil 2.5 mg, 5 mg and 10 mg film coated tablets.

Clinical studies

To support the application, the applicant has submitted one bioequivalence study.

Table 1. Tabular overview of clinical study

Type of study	Study identifier	Location of study report	Objective(s) of the study	Study design and type of control	Test product(s); Dosage Regimen; Route of Administration	Number of subjects	Healthy subjects or diagnosis of patients	Duration of treatment	Study Status; Type of report
BA	Not Applicable								
BE	TADA-1K-622-13	Module 5, Volume 1 Section 5.3.1.2	To evaluate the single oral dose bioequivalence of Tadalafil 20 mg film coated tablets manufactured by Mylan Laboratories Limited, Nashik, India against CIALIS® (Tadalafil) 20 mg tablets of Eli Lilly Nederland B.V., Grootslag 1-5, NL-3991 RA, Houten, The Netherlands in healthy, adult, human male subjects under fasting conditions.	An open label, balanced, randomized, single dose, two-treatment, two-sequence, two period, two-way crossover, oral bioequivalence study of Tadalafil 20 mg film coated tablets manufactured by Mylan Laboratories Limited, Nashik, India and CIALIS® (Tadalafil) 20 mg tablets of Eli Lilly Nederland B.V., Grootslag 1-5, NL-3991 RA, Houten, The Netherlands in healthy, adult, human male subjects under fasting conditions.	**Reference Product:** CIALIS® (Tadalafil) 20 mg tablets (Lot No. C073766; Exp. date: June 2015) of Eli Lilly Nederland B.V., Grootslag 1-5, NL-3991 RA, Houten, The Netherlands. **Test Product:** Tadalafil 20 mg film coated tablets (B. No. 2001691; Exp date: Nov. 2014) Manufactured by Mylan Laboratories Limited, Nashik, India.	30 healthy adult, human male subjects were planned and 27 subjects were completed the study, data from 27 subjects is reported. Range: 18 - 55 years.	Healthy adult human male subjects	Single dose	Complete; abbreviated
PK		Not Applicable							
PD		Not Applicable							
Efficacy		Not Applicable							

2.4.2. Pharmacokinetics

Study TADA-1K-622-13: An open label, balanced, randomized, single-dose, two-treatment, two-sequence, two-period, two-way crossover, oral bioequivalence study of Tadalafil Film-coated Tablets 20 mg of Mylan Laboratories Limited, India and CIALIS® (Film-coated Tadalafil tablets) 20 mg of Eli Lilly Nederland B.V., Grootslag 1-5, NL-3991 RA, Houten, The Netherlands, in healthy, adult, human subjects under fasting conditions

Methods

Study design

The study was an open label, balanced, laboratory-blinded, randomised, single dose, two-treatment, two-sequence, two-period, two-way crossover oral bioequivalence study comparing two different formulations of Tadalafil 20 mg film-coated tablets in healthy, adult, human male subjects under fasting conditions. The basis of the bioequivalence study under fasting conditions is justified and the study design is agreed by the CHMP.

The applicant updated the first paragraph of section 2.5.6 of the clinical overview in Module 2.5 as requested and included information on the two bioequivalence studies submitted to support the application.

After an overnight fasting of at least 10.00 hours, in the morning of each period, a single dose of either test or the reference Tadalafil 20 mg film-coated tablets as per the randomization schedule were administered orally with 240 ml of water at ambient temperature to the subjects. A standard meal was provided at around 04.00,

09.00 and 13.00 hours post-dose to all subjects. Water was restricted from at least 01.00 hr pre-dose until 01.00 hr post dose except for water given during dosing. The subjects were housed in the clinical facility until 24.00 hrs post dose in each period and returned to the clinical facility for *the ambulatory blood draws. The washout period between the two periods of the study was 16 days. The wash-out period was adequate according to the CHMP, no pre-dose levels were detected. The study was conducted under standardised conditions.*

According to the CHMP, the sampling period was adequate and was more than 72 hrs. The AUC ratio was higher than 80% in all but two subjects with ratio 78% and 79%. The AUC_{0-t} was calculated up to 144 hrs.

The sampling scheme according to the CHMP was adequate to estimate the pharmacokinetic parameters. T_{max} was not observed in any subject in the first sample time point. A total of 23 blood samples were collected at specified time points: 00.00 hr (pre-dose), 00.50, 01.00, 01.50, 02.00, 02.50, 03.00, 03.50, 04.00, 04.50, 05.00, 06.00, 08.00, 10.00, 12.00, 16.00, 24.00, 36.00, 48.00, 72.00, 96.00, 120.00 and 144.00 hours post dose in labelled K_3EDTA vaccutainers. Tadalafil was measured in human plasma.

Safety was evaluated through assessment of adverse events, vital signs measurements, ECG, haematology and biochemistry.

There were no changes in the conduct of the study. The listed protocol deviations did not have any significant impact on the outcome of the study this is agreed by the CHMP.

The CRO, clinical, pharmacokinetics and statistical parts of the study were performed by Micro Therapeutic Research Labs Pvt. Ltd., No. 6, Kamarajar Salai, Selaiyur, East Tambaram, Chennai, 600 059 Tamil Nadu, India. The Principal Investigator was Dr. D. Sridevi Muthusivam, M.B.B.S, PGDCR, MHSC (DIAB). The Pharmacokinetic Investigator was Mr. K. Nehru, M.Pharm, PGDCR&DM and the Statistical Investigator was Ms. L. Sailakshmi, M.Sc.

The bioanalytical facility performing the validation and the bioanalytical parts is Mylan Laboratories Limited, Clinical Research Centre, Saradhi Chambers, Plot No. 4-A, Beside Poulomi Hospital, Rukminipuri, Dr. A.S. Rao Nagar, Hyderabad, 500062, India. The Bioanalytical Investigator / Director was Mr. Amarnath Jaiswal, M.Sc (Tech).

The sponsor of the study is Mylan Laboratories Limited, Clinical Research Centre, Saradhi Chambers, Plot No. 4-A, Beside Poulomi Hospital, Rukminipuri, Dr. A. S. Rao Nagar, Hyderabad – 500062, India.

The study protocol (no. TADA-1K-622-13, version 01, signed and dated 3 April 2013) and the informed consent documents were approved by an Independent Ethics Committee on 6 April 2013 and the protocol amendment (no. 01, dated 15 April 2013 and signed) approved on 16 April 2013.

The clinical part of the study was conducted between 17 April and 10 May 2013. The dosing dates in period 1 and 2 were 18 April and 4 May 2013, respectively. The final clinical study report version 01 is signed and dated 20 July 2013.

Test and reference products

The test product from the bioequivalence study is identical to the formulation intended to be marketed.
The applicant confirms that the composition and the manufacturing process of the test product formulation used in the bioequivalence study and the formulation proposed for commercial supplies to EEA is the same.
The certificates of analysis of the biobatches are provided.
Detailed information of the formulations is found in Module 3.

Tadalafil Mylan 20mg manufactured by Generics (UK) Limited (batch No.2001691, manufacturing date December 2012; exp. Date November 2014) has been compared to Cialis 20 mg manufactured by Lilly S.A., Avda, de la industria 30, 28108, Alcobendas, Madrid, Spain (Batch No: C073766, exp. date June 2015).

Population studied

The population is chosen according to guidelines. Tadalafil is only indicated for males and therefore only male subjects participated in the study.

Thirty-one (31) healthy adult, human male subjects (18-45 years; BMI 19.13-29.74 kg/m^2) of Asian origin were enrolled (inclusive of 01 standby subject). Out of 31 enrolled subjects, 30 subjects were randomized and participated in the study. The purpose of the standby subject was to ensure dosing of 30 subjects in period I of the study. There were no withdrawals prior to dosing and therefore the standby subject did not participate in the study. The intention was not to replace dosed subjects. The sample calculation is acceptable and the sample size is adequate. Twenty-seven (27) subjects completed both periods of the study and were included for pharmacokinetic and statistical analysis.

Subject no. S08 and S25 did not report to the facility for period II and S26 was withdrawn after dosing of period I due to failure in complying with restrictions and prohibitions.

Analytical methods

The bioanalytical method is acceptable according to the CHMP and was validated pre-study and within study. The method performance during study sample analysis was acceptable according to the CHMP.

Validation

The bioanalytical method validation report VR-117-00 is signed and dated 20 March 2013. Addendum-01-00 for long term stability of tadalafil in human plasma is signed and dated 24 June 2013.

A specific LC/MS/MS method was validated for the determination of tadalafil concentrations in K_3EDTA human plasma over a concentration range of 4.999 ng/ml to 599.878 ng/ml. Tadalafil was extracted from an aliquot of human plasma using solid phase extraction technique. The internal standard used was tadalafil-D3. Certificates of analysis of the test article (tadalafil) and the internal standard (tadalafil-D3) are provided. The quality control (QC) concentrations of tadalafil were 5.005 ng/ml, 16.016 ng/ml, 120.119 ng/ml, 220.219 ng/ml and 460.457 ng/ml.

The method was validated and met acceptance criteria with respect to specificity (including also haemolytic and lipemic lots) and selectivity, carry-over, sensitivity (LLOQ= 4.999 ng/ml tadalafil; signal to noise ratio >5), linearity ($r^2 \geq 0.9978$), between-run and within-run precision and accuracy, recovery, dilution integrity (1/2 and 1/4-fold), matrix effect (including also haemolytic and lipemic lots), ruggedness, re-injection reproducibility, short and long term stock and working solution stability of tadalafil and of the internal standard (tadalafil-D3), bench top stability of tadalafil in matrix, coolant stability of tadalafil (in matrix in dry ice), post extracted refrigerator stability in matrix, dry extract stability, freeze-thaw stability of tadalafil and in-injector stability in autosampler. Long term stability of tadalafil in plasma at -70±15°C and at -20±5°C was approved for 101 days (Addendum-01-00).

All integrations were performed by Applied Biosystems Analyst Software Version 1.5.1.

Bioanalysis

The bioanalytical study report TADA-1K-622-13 is signed and dated 17 July 2013. Handling of samples is adequate. There were a few missing samples in the later time points. The same anticoagulant was used during validation and study sample analysis. The samples were analysed from 5 to 14 June 2013, including repeats and incurred sample analysis.

Blood samples were centrifuged at 4000 rpm for 10 minutes at 04°C nominal to separate the plasma. The plasma was stored in a freezer at a temperature -70°C±20°C until transferred to the bioanalytical facility where they were kept at -70±15°C until they were analysed. The plasma samples were received frozen by the bioanalytical facility.

Tadalafil was extracted from an aliquot of human plasma using solid phase extraction technique. The internal standard used was tadalafil-D3. Certificates of analysis of the test article (tadalafil) and the internal standard (tadalafil-D3) are provided. A validated LC/MS/MS method was employed in determining sample concentrations of tadalafil in human plasma. The calibration curve range during study sample analysis was from 4.995 ng/ml to 599.399 ng/ml for tadalafil. The quality control (QC) sample concentrations of tadalafil were 16.035 ng/ml, 120.263 ng/ml, 220.482 ng/ml and 461.008 ng/ml.

The longest storage period of the study samples was 58 days at temperature -70±15°C (18 April 2013 to 14 June 2013).

A total of 1289 samples were collected but 1229 samples were analysed from the 27 evaluable subjects. A total of 11 samples (0.9% of the total samples analysed) were repeated for tadalafil due to the following reasons, bad chromatography, unacceptable internal standard response, sample concentration above upper limit of quantitation, concentration/response in zero hours subject samples and due to processing error (no analyte response was observed). A total of 128 samples were included in the incurred sample reanalysis (ISR). A total of 127 samples were considered for ISR calculations and all of them meet acceptance criteria. The one sample that was not taken into account was an incorrect sample being processed and analysed. The ISR is acceptable according to the CHMP. Sample chromatograms for 20% of the subjects and for the discrete repeated samples are submitted.

All integrations were performed by Applied Biosystems Analyst® Software Version 1.5.1.

Pharmacokinetic variables

The pharmacokinetic parameters for tadalafil were calculated using non-compartmental model of WinNonlin® software version 5.3 of Pharsight Corporation, USA for both the formulations. The primary pharmacokinetic parameters were C_{max}, AUC_{0-t} and $AUC_{0-\infty}$, and the secondary pharmacokinetic parameters t_{max}, K_{el}, $t_{1/2}$ and $AUC_{0-t}/AUC_{0-\infty}$. Standard methods were used.

Statistical methods

The statistics is adequately described and the methods are acceptable. The ln-transformed pharmacokinetic parameters C_{max}, AUC_{0-t} and $AUC_{0-\infty}$ were analysed using an analysis of variance (ANOVA) model. Ratio analysis was calculated for ln-transformed C_{max}, AUC_{0-t} and $AUC_{0-\infty}$ and the 90% confidence interval for the test to reference ratio of geometric least square means was calculated for ln-transformed C_{max} and AUC_{0-t} using mixed procedure of SAS statistical software version 9.2 from SAS® Institute Inc, USA. The ANOVA model included

sequence, period, treatment and subjects nested within sequence as fixed effect and tested at 5% level of the significance.

Criteria for Evaluation:

Standard acceptance criteria are proposed for conclusion of bioequivalence. The 90% confidence interval of the relative mean C_{max} and AUC_{0-t} (of tadalafil) of the test and reference product should be between 80.00% and 125.00% for ln-transformed data.

This is acceptable for tadalafil according to the CHMP. A few samples were missing for the later time points and they were reported as "M" and any non- reportable concentration was reported as "NR". A few deviations in blood collection times occurred, mostly in the later time points, but the actual time points of the sample collection was used in cases of sample collection deviations.

Results

Table 2. Pharmacokinetic parameters for tadalafil (non-transformed values)

Pharmacokinetic parameter	Test		Reference	
	arithmetic mean	SD	arithmetic mean	SD
$AUC_{(0-t)}$ (ng.hr/mL)	14757.9044	4371.4597	15626.1633	5265.2681
$AUC_{(0-\infty)}$ (ng.hr/mL)	16178.6944	5670.9124	16994.6122	6788.0285
C_{max} (ng/mL)	366.1138	96.2650	376.0056	86.1773
T_{max}*	3.00	(1.00-24.00)	2.50	(1.00-4.50)
AUC_{0-t}	area under the plasma concentration-time curve from time zero to t hours			
$AUC_{0-\infty}$	area under the plasma concentration-time curve from time zero to infinity			
C_{max}	maximum plasma concentration			
T_{max}	time for maximum concentration (* median, range)			

Table 3. Statistical analysis for <analyte> (ln-transformed values)

Pharmacokinetic parameter	Geometric Mean Ratio Test/Reference	Confidence Intervals	CV%*
$AUC_{(0-t)}$ (ng.hr/mL)	95.73%	90.99%-100.71%	10.95%
C_{max} (ng/mL)	96.17%	90.16%-102.59%	13.95%
* estimated from the Residual Mean Squares			

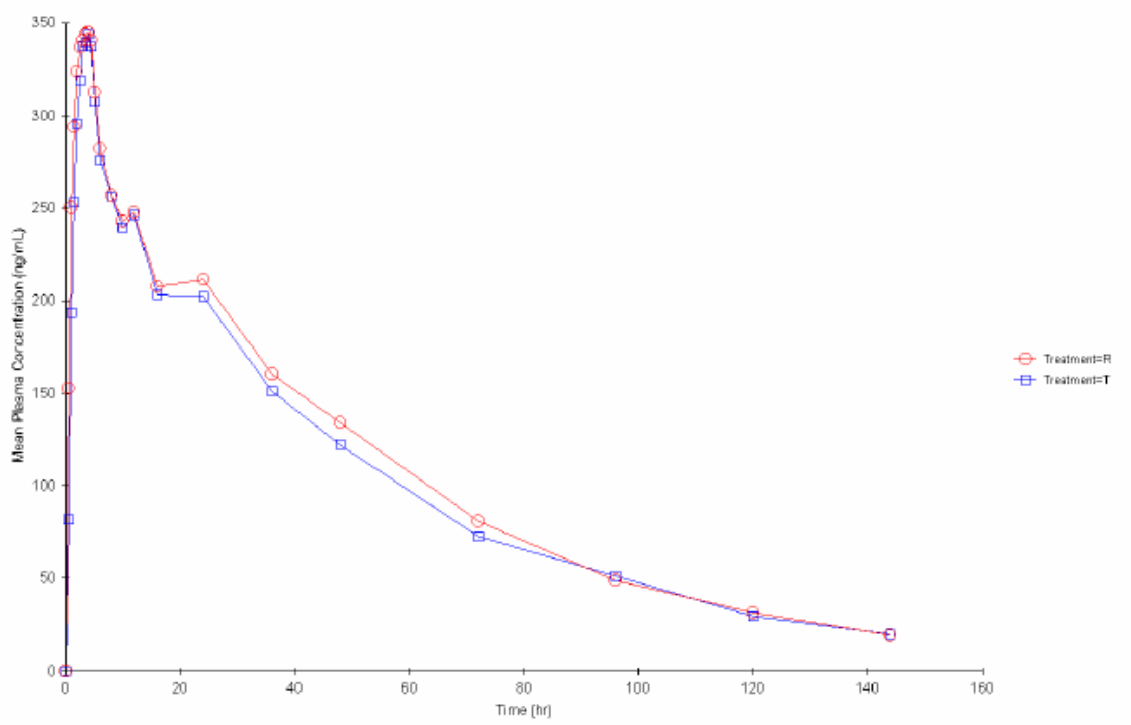

Figure 1: Linear plot of mean plasma tadalafil concentrations versus time in healthy adult male subjects (N=27).

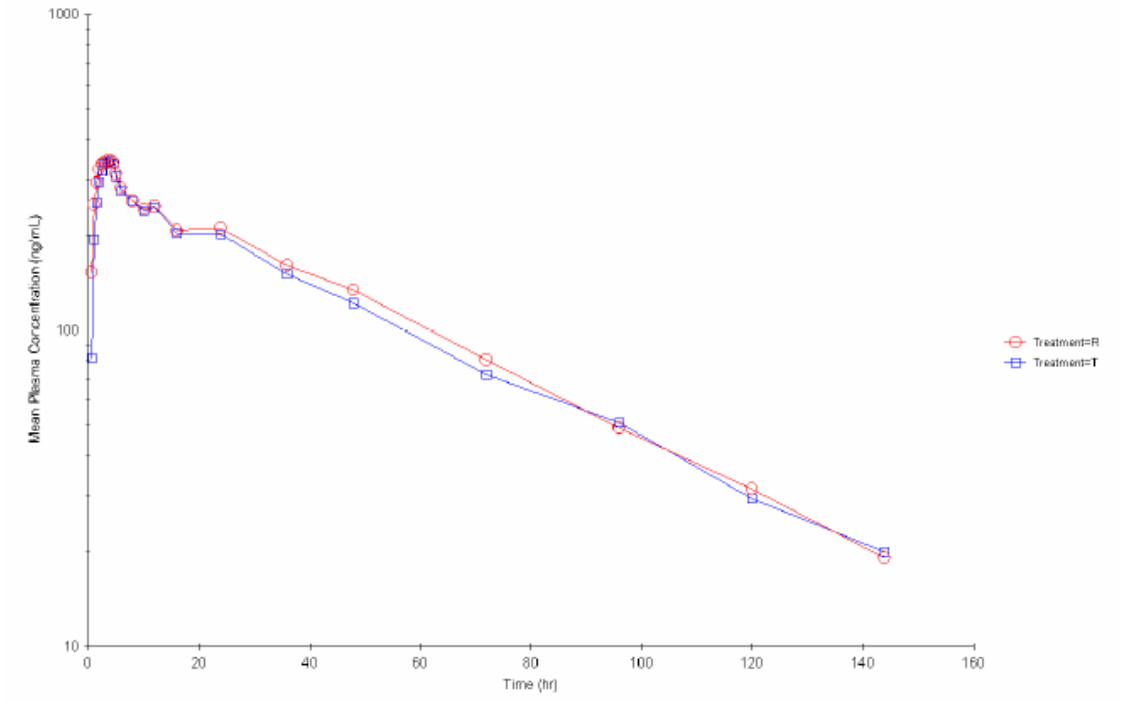

Figure 2: Semi-logarithmic plot of mean plasma tadalafil concentrations versus time in healthy adult male subjects (N=27).

The mean AUC ratio was 93% and 94% after administration of the test and the reference products, respectively. The AUC ratio is higher than 80% in all but two subjects where the ratio is 78% and 79%. The duration of sampling is sufficient. The AUC ratio was 78% in subject no. 09 after administration of the test product and 79% in subject no. 21 after administration of the reference product in period I.

No subject had detectable pre-dose plasma levels and no subject reached Cmax at the first sampling time point

T_{max} was not observed in any subject in the first sample time point. One subject observed Tmax at 24.00 hrs after administration of the test product. Other subjects observed Tmax in the range of 1.00 – 4.50 hrs after administration of the test product which is in line with the range found after administration of the reference product.

The Test to Reference ratio of geometric LSmeans and the corresponding 90% confidence interval for the C_{max} and AUC_{0-t} were all within the acceptance range of 80.00 to 125.00%. Therefore, the Test formulation (Tadalafil 20 mg film-coated tablets, Mylan Laboratories Limited F-4 & F-12, MIDC, Malegaon, Sinnar Nashik-422 113, Maharashtra, India) is judged to be bioequivalent to the Reference formulation (CIALIS® (tadalafil) 20 mg film-coated tablets, Eli Lilly Nederland B.V., Grootslag 1-5, NL-3991 RA, Houten, The Netherlands) in healthy, adult human male subjects under fasting conditions.

The samples where the plasma concentration was above upper limit of quantitation were diluted and repeated. The dilution integrity was validated and the reported values are acceptable.

The test to reference ratio of geometric LSmeans and corresponding 90% confidence interval for the Cmax and AUC0-t were all within the acceptance range of 80.00 to 125.00%.

The bioequivalence has been shown appropriately under fasting conditions.

Section 2.5.2 of the clinical overview Module 2.5 includes information on the two bioequivalence studies under fasting and fed conditions. The text after the synopsis in the same section has also been updated with information on the two bioequivalence studies.

In vitro dissolution

In vitro dissolution tests were conducted using USP Type – II apparatus (Paddle), comparing the test and the reference products used in the bioequivalence study (the biobatches) as well as the test biobatch with the lower strengths of the applied product.

In vitro dissolution tests complementary to the bioequivalence study

More than 85% of the labelled amount of the drug was released within 15 minutes from the test and the reference biobatches in 0.5% SLS in water (release media).

For the dissolution tests comparing the test and the reference biobatches in 0.5% SLS in 0.1N HCl, 0.5% SLS in pH 4.5 Acetate buffer and 0.5% SLS in pH 6.8 Phosphate buffer the calculated similarity factor was 39.30, 48.16 and 31.85, respectively. The drug release was found to be faster in the test product when compared to the reference product and it leads to the lower f2 value (less than 50), this may be attributed by the difference in the composition between the test and reference product. Though, the f2 value between the test and reference product is found to be below 50, these two products have been proven to be bioequivalent.

In vitro dissolution tests in support of a biowavier of strengths

More than 85% of the labelled amount of the drug was released within 15 minutes from the test biobatch and the lowers strengths of the Tadalafil Mylan product in 0.5% SLS in water (release media), 0.5% SLS in 0.1N HCl, 0.5% SLS in 0.1N HCl, 0.5% SLS in pH 4.5 Acetate buffer and 0.5% SLS in pH 6.8 Phosphate buffer.

Safety data

There were no adverse events or serious adverse events reported in the bioequivalence study.

Vital signs measurements and post-laboratory tests confirmed the absence of significant changes in the subjects´ state of health.

Both the products were safe and well tolerated at selected dose level in the participated subjects.

Conclusions

The application contains an adequate review of published clinical data

Based on the presented bioequivalence study Tadalafil Mylan 20 mg film-coated tablets and Cialis 20 mg film-coated tablets under fasting conditions.

2.4.3. Pharmacodynamics

No new pharmacodynamic studies were presented and no such studies are required for this application.

2.4.4. Post marketing experience

No post-marketing data are available. The medicinal product has not been marketed in any country.

2.4.5. Discussion on clinical aspects

The clinical overview on the clinical pharmacology, efficacy and safety has been provided and is adequate .

To support the application, the applicant has submitted two of bioequivalence studies. Statement of GCP compliance and compliance with applicable principles of GLP is provided. A statement is provided to confirm that the bioequivalence study carried out outside the European Union meets the ethical requirements of the European Union Directive 2001/20/EC.

The studies were open label, balanced, laboratory-blinded, randomised, single dose, two-treatment, two-sequence, two-period, two-way crossover oral bioequivalence study comparing two different formulations of tadalafil 20 mg film-coated tablets, Tadalafil Mylan and CIALIS®, in 30 healthy, adult, human male subjects under fasting conditions. After an overnight fasting of at least 10 hours the subjects received either the test or the reference formulation according to the randomization schedule. The study was conducted under standardised conditions. The sampling points, overall sampling time as well as the wash-out period of 16 days were adequate. Tadalafil was measured in human plasma using a validated LC/MS/MS method. The pharmacokinetic and statistical methods applied were adequate. The test to reference ratio of geometric LS means and the corresponding 90% confidence interval for the C_{max} and AUC_{0-t} were all within the acceptance range of 80.00 to 125.00%. Bioequivalence of the two formulations was demonstrated under fasting conditions. Both products were safe and well tolerated at selected dose level in the participated subjects. The *in vitro* dissolution tests complimentary to the bioequivalence study comparing the test and the reference biobatches at different pH levels were conducted using solubility enhancer (surfactants) that was added to the dissolution media used. Comparative *in vitro* dissolution tests are generally expected to be conducted in simple aqueous buffers without the addition of solubility enhancer (surfactants).

The results of study TADA-1K-622-13 and study no. TADA-1937-13 with 20 mg formulation can be extrapolated to other strengths 2.5 mg, 5 mg and 10 mg, according to conditions in the relevant Guidelines.

2.4.6. Conclusions on clinical aspects

The application contains an adequate review of published clinical data.

Bioequivalence has been shown between Tadalafil Mylan 20 mg film-coated tablets and Cialis 20 mg film-coated tablets under fasting conditions. Section 2.5.2 of the clinical overview Module 2.5 has been updated to include in the introduction text information on the two bioequivalence studies under fasting and fed conditions. The text after the synopsis in the same section has also been updated with information on the two bioequivalence studies.

Clinical Study Report for study no. TADA-1K-622-13 in Module 5.3.1.2. was updated during the evaluation procedure to include the updated dissolution data without surfactant at the beginning of the document. This update was found to be acceptable by the CHMP.

Clinical Study Report for study no. TADA-1937-13 in Module 5.3.1.2 was updated during the evaluation procedure to include the updated dissolution data without surfactant at the beginning of the document. This update was found to be acceptable by the CHMP.

Therefore, Tadalafil Mylan is approvable.

2.5. Pharmacovigilance

Detailed description of the pharmacovigilance system

The CHMP considered that the Pharmacovigilance system as described by the applicant fulfils the legislative requirements.

2.6. Risk management plan

The CHMP received the following PRAC Advice on the submitted Risk Management Plan:

The PRAC considered that the risk management plan version 2.0 is acceptable. The PRAC endorsed PRAC Rapporteur assessment report is attached.

The CHMP endorsed this advice without changes.

Safety concerns

The applicant identified the following safety concerns in the RMP:

Table 1: Summary of the safety concerns

Summary of safety concerns	
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 PRAC agreed.

Pharmacovigilance plan

The PRAC, having considered the data submitted, was of the opinion that routine pharmacovigilance is sufficient to identify and characterise the risks of the product.

The PRAC also considered that routine PhV is sufficient to monitor the effectiveness of the risk minimisation measures.

Risk minimisation measures

Table 2: Summary table of Risk Minimisation Measures

Safety concern	**Routine risk minimisation measures**	**Additional risk minimisation measures**
Priapism	Sections 4.4, and 4.8 of the SmPC contain warnings on this risk	None

	Sections 2 and 4 of the PIL explain this issue to patients adequately Product is a prescription medicine	
Hypotension/Increased hypotensive effect	Sections 4.3, 4.4, 4.5 and 4.8 of the SmPC contain warnings on this risk. Sections 2 and 4 of the PIL explain this issue to patients in adequate details Product is a prescription medicine	None
Non-arteritic anterior ischemic optic neuropathy (NAION)	Sections 4.3, 4.4 and 4.8 of the SmPC contain warnings on this risk Section 2 of the PIL explains this issue to patients in adequate details Product is a prescription medicine	None
Sudden hearing loss	Section 4.8 of the SmPC contains warnings of this risk Section 4 of the PIL explains this issue to patients adequately Product is a prescription medicine	None
Characterisation of adverse events in elderly patients (≥65 years)	Sections 4.2, 4.8 and 5.2 of the SmPC contains warnings of this risk Product is a prescription medicine	None

The PRAC, having considered the data submitted, was of the opinion that the proposed risk minimisation measures are sufficient to minimise the risks of the product in the proposed indication.

2.7. PSUR submission

At the time of granting the marketing authorisation, the submission of periodic safety update reports is not required for this medicinal product. However, the marketing authorisation holder shall submit periodic safety update reports for this medicinal product if the product is included in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83 and published on the European medicines web-portal.

2.8. Product information

The applicant updated the PI for Tadalafil Mylan as requested by the CHMP.

2.8.1. User consultation

No full user consultation with target patient groups on the package leaflet has been performed on the basis of a bridging report making reference to originator product for content and Sildenafil Mylan for design and layout. The bridging report submitted by the applicant has been found acceptable.

3. Benefit-risk balance

This application concerns a generic version of tadalafil film-coated tablets. The reference product Cialis is indicated as follows:

For 2.5 mg, 10 mg and 20 mg:
Treatment of erectile dysfunction in adult males.

In order for tadalafil to be effective, sexual stimulation is required.
CIALIS is not indicated for use by women.
For 5 mg:
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.
CIALIS is not indicated for use by women.

No nonclinical studies have been provided for this application but an adequate summary of the available nonclinical information for the active substance was presented and considered sufficient. From a clinical perspective, this application does not contain new data on the pharmacokinetics and pharmacodynamics as well as the efficacy and safety of the active substance; the applicant's clinical overview on these clinical aspects based on information from published literature was considered sufficient.

The results of studies TADA-1K-622-13 and TADA-1937-13 with 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.

The bioequivalence study forms the pivotal basis with a study design considered adequate to evaluate the bioequivalence of this formulation and was in line with the respective European requirements. Choice of dose, sampling points, overall sampling time as well as wash-out period were adequate. The analytical method was validated. Pharmacokinetic and statistical methods applied were adequate.

The test formulation of [applied product] met the protocol-defined criteria for bioequivalence when compared with the [reference product]. The point estimates and their 90% confidence intervals for the parameters AUC_{0-t},, $AUC_{0-\infty}$, and C_{max} were all contained within the protocol-defined acceptance range of [range, e.g. 80.00 to 125.00%]. Bioequivalence of the two formulations was demonstrated.

A benefit/risk ratio comparable to the reference product can therefore be concluded.

4. Recommendation

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of Tadalafil Mylan in the treatment of approved indication is favourable and therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to medical prescription.

Conditions and requirements of the Marketing Authorisation

- **Periodic Safety Update Reports**

At the time of granting the marketing authorisation, the submission of periodic safety update reports is not required for this medicinal product. However, the marketing authorisation holder shall submit periodic safety update reports for this medicinal product if the product is included in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83 and published on the European medicines web-portal.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

- **Risk Management Plan (RMP)**

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

If the submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time.

Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States.

Not applicable.