Bundesinstitut
für Arzneimittel
und Medizinprodukte

PUBLIC ASSESSMENT REPORT

Decentralised Procedure

Tadalafil PMCS 5 mg
Tadalafil PMCS 10 mg
Tadalafil PMCS 20 mg

Procedure Number: DE/H/3777/01-03/DC

Active Substance:
Tadalafil

Dosage Form:
Film-coated Tablets

Marketing Authorisation Holder in the RMS, Germany:
PRO.MED.CS Praha a.s.

Publication:
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ADMINISTRATIVE INFORMATION

Proposed name of the medicinal product in the RMS	Tadalafil PMCS 5, 10 and 20 mg Filmtabletten
INN of the active substance	Tadalafil
Pharmaco-therapeutic group, ATC	G04BE08
Pharmaceutical form and strengths	5, 10 and 20 mg film-coated tablets
Reference Numbers for the Procedures	DE/H/3777/01-03/DC
Reference Member State	DE
Member States concerned	CZ, EE, LT, LV, PL, SE, SK
Marketing Authorisation Holder (name and address)	PRO.MED.CS Praha a.s. Telcská 1, CZ-140 00 PRAHA 4 ICN Polfa Rzeszow S.A. l. Przemyslowa 2, PL-35-959 Rzeszow
Name and address of manufacturers of dosage form and of manufacturers responsible for batch release in the EEA	PRO.MED.CS Praha a.s. Telcská 1 CZ-140 00 PRAHA 4

RECOMMENDATION

Based on the review of the data on quality, safety and efficacy, the RMS considers that the applications for Tadalafil PMCS, in the treatment of Treatment of erectile dysfunction in adult males

is approved.

I EXECUTE SUMMARY

I.1 Problem Statement

N/A

I.2 About the Product

The active substance is tadalafil. Tadalafil is a selective, reversible inhibitor of cyclic guanosine monophosphate (cGMP)-specific phosphodiesterase type 5 (PDE5).

Within the ATC system, tadalafil is coded G03BE08.

Therapeutic indications (as claimed by the applicant)

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.

Posology and method of administration (as claimed by the applicant)

Posology

Adult men

In general, the recommended dose is 10 mg taken prior to anticipated sexual activity and with or without food. In those patients in whom tadalafil 10 mg does not produce an adequate effect, 20 mg might be tried. It may be taken at least 30 minutes prior to sexual activity.

The maximum dose frequency is once per day.

Tadalafil 10 mg and 20 mg is intended for use prior to anticipated sexual activity and it is not recommended for continuous daily use.

In patients who anticipate a frequent use of tadalafil (i.e., at least twice weekly) a once daily regimen with the lowest doses of <Product name> might be considered suitable, based on patient choice and the physician's judgment. In these patients, the recommended dose is 5 mg taken once a day at approximately the same time of day. The dose may be decreased to 2.5 mg once a day based on individual tolerability (2.5 mg tablets are available on the market).

The appropriateness of continued use of the daily regimen should be reassessed periodically.

Special Populations

Elderly men

Dose adjustments are not required in elderly patients.

Men with renal impairment

Dose adjustments are not required in patients with mild to moderate renal impairment. For patients with severe renal impairment, 10 mg is the maximum recommended dose. Once-a-day dosing of tadalafil is not recommended in patients with severe renal impairment. (See sections 4.4 and 5.2.)

Men with hepatic impairment

The recommended dose of <Product name> is 10 mg taken prior to anticipated sexual activity and with or without food. There is limited clinical data on the safety of tadalafil in patients with severe hepatic impairment (Child-Pugh Class C); if prescribed, a careful individual benefit/risk evaluation should be undertaken by the prescribing physician. There are no available data about the administration of doses higher than 10 mg of tadalafil to patients with hepatic impairment. Once-a-day dosing has not been evaluated in patients with hepatic impairment; therefore if prescribed, a careful individual benefit/risk evaluation should be undertaken by the prescribing physician. (See sections 4.4 and 5.2.)

Men with diabetes

Dose adjustments are not required in diabetic patients.

Paediatric population

There is no relevant use of <Product name> in the paediatric population with regard to the treatment of erectile dysfunction.

Method of administration

Tadalafil is available as 5 mg, 10 mg and 20 mg film-coated tablets for oral use.

I.3 General Comments on the Submitted Dossier

The Application is submitted in accordance with Article 10 (1) Directive 2001/83/EC (generic application) as amended. The submitted documentation in relation to the proposed product is of sufficient quality and consistent with the current EU regulatory requirements from a quality, non-clinical and clinical point of view. To support the application, the applicant has submitted a bioequivalence study showing bioequivalence of the test product Tadalafil 20mg film-coated tablets (the highest strength) with the originator product Cialis 20mg film-coated tablets.

I.4 General Comments on Compliance with GMP, GLP, GCP and Agreed Ethical Principles

The RMS has been assured that acceptable standards of GMP are in place for these product types at all sites responsible for the manufacture and assembly of this product.

For manufacturing sites within the Community, the RMS has accepted copies of current manufacturer authorisations issued by inspection services of the competent authorities as certification that acceptable standards of GMP are in place at those sites.

GCP: For the pharmacokinetic study to demonstrate bioequivalence with the originator product the applicant declares that it was carried out according to GCP.

II SCIENTIFIC OVERVIEW AND DISCUSSION

II.1 Quality Aspects

Introduction

The chemical-pharmaceutical documentation Module 2.3 and 3 is of sufficient quality in view of the present European regulatory requirements.

Drug Substance

The active ingredient of Tadalafil PMCS 5, 10 and 20 mg Filmtabletten is Tadalafil which is monographed in the European Pharmacopoeia.

Both active substance manufacturers present an CEP.

Drug Substance manufactured by MSN

The applicant presents the CEP R0-CEP2011-366-Rev00 for MSN Organics. Tadalafil is tested according to the specification summarised in the current Certificate of Suitability showing conformity with the requirements of the Ph. Eur. monograph (current edition) and the following additional specifications:

The following impurity is detected by the test for related substances of the monograph and its limit is set at:

Chloroacetyl impurity: NMT 27 ppm

- Test for residual solvents by gas chromatography

Methanol	NMT 3 000 ppm
Toluene	NMT 890 ppm
Dimethylformamide	NMT 880 ppm

- Test for residual catalyst by ICP-OES

Palladium	NMT 10 ppm

The substance is packed in a double polyethylene bag (outer black) in 2a triple laminated bag placed in a polyethylene container.

The holder of the certificate has declared the absence of use of material of human or animal origin in the manufacture of the substance.

The synthesis is sufficiently described; all requirements of the ASMF Guideline are fulfilled.

Batch analysis results confirm batch to batch consistency.

The material is packed in a clear low-density polyethylene bag tied with a plastic strip and this bag is placed inside a black colour low-density polyethylene bag and this black colour bag is tied with a plastic strip. This double polyethylene bag is placed inside a triple laminated bag and then this triple laminated bag is sealed and kept inside a HDPE container.

The provided specifications and information for the proposed container closure systems are considered as sufficient.

Stability studies have been conducted according to the guideline for stability testing of existing ingredients and related finished products. No significant change has been observed with regard to the parameters tested. The re-test period of the substance is 48 months if stored in the container described in section S.6 is acceptable.

Drug Substance manufactured by Alembic Pharmaceuticals

The applicant presents the CEP R0-CEP2011-316-Rev01 for Alembic Pharmaceuticals. Tadalafil is tested according to the specification summarised in the current Certificate of Suitability showing conformity with the requirements of the Ph. Eur. monograph (current edition) and the following additional specifications:

- Test for residual solvents by gas chromatography

DCM	NMT 600 ppm
Methanol	NMT 3 000 ppm
Isoprpanol	NMT 5 000 ppm

The substance is packed in a double polyethylene bag in a triple laminated bag placed in a polyethylene container.

The holder of the certificate has declared the absence of use of material of human or animal origin in the manufacture of the substance.

Batch analysis results confirm batch to batch consistency.

The suitability of the reference standards has been shown.

The material is packed primarily with Plain LDPE)bag, twist tied & sealed with Plastic strip seal which is then packed Secondarily in HMHDPE, LDPE, LLDPE bag, heat sealed and then placed in Triple laminated bag and is heat sealed. The heat-sealed triple laminated bag is placed in HDPE drums and weighed. The HDPE drums are sealed with Pilfer proof plastic seal.

The provided specifications and information for the proposed container closure systems are considered as sufficient.

Stability studies have been conducted according to the guideline for stability testing of existing ingredients and related finished products. No significant change has been observed with regard to the parameters tested. The re-test period of the substance is 48 months if stored in the container described in section S.6 is acceptable.

Drug Substance controlled by DPM

The DPM presents a drug substance specification which includes the Ph. Eur. specification, particles size, residue solvents and microbial quality as well as the Chloroacetyl impurity specification.

The methods used by the ASM have been adequately described.

Certificates of analysis on four small commercial scale batches have been presented issued from the DPM and the corresponding ASM. The CoAs are accompanied by all analytical raw data obtained in the frame of the release control of the individual batches with exception of the particle size analysis. The particle size determination was not performed by DPM. The identification is additionally performed by the corresponding ASM.

The analytical results are in full compliance with the specified limits and show only little variability with respect to the individual parameters tested thus demonstrating a reliable and reproducible synthetic method with consistent results from batch to batch.

Sufficient information about the Reference Standards used by the DPM has been presented.

Drug Product

The goal of pharmaceutical development was to develop an immediate-release solid dosage form which is stable and essentially similar to the reference product Cialis® 5, 10 and 20 mg, film-coated tablets from Eli Lilly Nederland B.V., The Netherlands. The dosage form is a film-coated tablet for oral administration. The new medicinal product will be marketed in three strengths: Tadalafil 5, 10 and 20 mg FCTs. The development work of the formulation has been sufficiently described.

The composition of the drug product is satisfactorily described.

The finished product will be manufactured by PRO.MED.CS Praha a.s. The description of the manufacturing process is appropriate, all parameters have been listed. Holding times has been adequately set. The IPCs used are acceptable specified.

The manufacture of Tadalafil 5, 10 and 20 mg film-coated tablets is common standard process by wet granulation. The manufacturing process has been developed in order to verify the behaviour of the drug substance in the film-coated tablet as well as intra-batch homogeneity. Results of three subsequent pilot stability and validation batches of each strength demonstrate that the defined manufacturing process and controls ensure batch-to-batch consistency and confirm the feasibility of the drug product at pilot scale. The manufacturing process is robust.

The presented specifications of the finished products are satisfying.

The applied methods are in accordance with current technical and scientific requirements and have been adequately described.

The validation data provided are in accordance with the requirements of the relevant ICH guidelines.

Satisfactory batch analyses have been presented. The batch analyses data together with the results obtained from the stability testing confirm consistency and uniformity of the product based on the parameters tested and indicate the reproducibility of the manufacturing process for the drug product.

The suitability of the reference standards has been shown.

The applied primary packaging systems, PVC/PVdC//Al and OPA/Al/PVC//Al, are standard for solid oral formulations. The provided specifications and information for the proposed container closure systems are considered as sufficient.

The conditions used in stability studies are according to the ICH stability guideline. Test results of stability testing at long-term and intermediate conditions up to 24/12 months and accelerated conditions up to 6 months have been provided for the new medicinal products. Based on the proposed specifications, the results show that at all conditions tested the product appears chemically and physically stable. Proposed shelf life is 3 years without special conditions for storage is accepted.

II.2 Nonclinical Aspects

Pharmacodynamic, pharmacokinetic and toxicological properties of tadalafil are well known. As tadalafil is a widely used, well-known active substance, the applicant has not provided additional studies and further studies are not required.

The applicant states that the product is intended to substitute a part of this product on the market. The product does not contain any component which results in additional hazard to the environment during storage, distribution, use and disposal. Based on the assumption this generic product should not result in an increase of the total quantity of tadalafil derivatives

released into the environment. Therefore it should not result in an increased risk to the environment during storage, distribution, use and disposal.

An ERA is not deemed necessary.

There are no objections to approval of Tadalafil PMCS from a non-clinical point of view, provided the SmPC is in accordance with the Originator Cialis.

II.3 Clinical Aspects

Pharmacokinetics and pharmacodynamics

No new data has been submitted and none are required for this generic application. The pharmacodynamic and pharmacokinetic claims in the SmPC are consistent with the innovator product. The pharmacodynamic and pharmacokinetic properties have been extensively studied in the past.

Clinical Efficacy and Safety

No new data have been submitted and none are required for this generic application.

The applicant has submitted a bioequivalence study showing bioequivalence of the test product Tadalafil 20mg film-coated tablets (the highest strength) with the originator product Cialis 20mg film-coated tablets.

The application is approvable from the clinical point of view.

Pharmacovigilance System

The Applicant/Proposed Future MAH has submitted a signed Summary of the Applicant's/Proposed Future MAH's Pharmacovigilance System and asked the RMS to replace the previously submitted DDPS with the new Summary of Pharmacovigilance System. Provided that the Pharmacovigilance System Master File fully complies with the new legal requirements as set out in the Commission Implementing Regulation and as detailed in the GVP module, the RMS accepts this substitution.

Risk Management Plan

The MAH/MAA has provided an updated RMP, dated 26/8/2013 answering the following questions and points:

Data lock point for this RMP 30 June 2013 Version number 1.1
Date of final sign off 26 August 2013
Product(s) concerned (brand name(s)):
Tadalafil PMCS

The respective sections of the RMP had been updated according to the RMP template and in accordance with GVP module V.:

1. RMP module VI.1 “Summary of Safety concerns” is now adequately mirrored as follows:

VI.1.1 Summary table of safety concern

Summary of safety concerns	
Important identified risks	•Hypotension/Increased hypotensive effect •Cardiovascular disorder •Visual impairment •Priapism •Sudden hearing loss •Drug interaction (with CYP3A4 inhibitors)
Important potential risks	•Use in patients with severe renal impairment
Important missing information	•Use in patients with severe hepatic impairment

The safety concerns had been identified based on the SmPC for tadalafil and Assessment report for Cialis® - EMEA/H/C/000436/II/0060.

2. RMP complies with the EU-format of the risk management plan (RMP) for Generics.

Common renewal date
5 years after the finalisation of the procedure.

Legal status
Medicinal product subject to medical prescription.

User Testing
The user test has been adequately designed in terms of subject recruitment, questionnaire and questions covering the key safety aspects of the leaflet, recording and analysis of answers and design and layout of the leaflet.

III BENEFIT RISK ASSESSMENT

The use of Tadalafil is well established. It has recognised efficacy and acceptable safety. The application is approvable from a clinical and non-clinical point of view.
The application is approved. For intermediate amendments see current product information.