Bundesinstitut
für Arzneimittel
und Medizinprodukte

PUBLIC ASSESSMENT REPORT

Decentralised Procedure

Tadalafil-ratiopharm 2.5 mg; 5mg; 10mg; 20mg Filmtabletten

Procedure Number: DE/H/4013/01-04/DC

Tadalafil AbZ 2.5 mg; 5mg; 10mg; 20mg Filmtabletten

Procedure Number: DE/H/4053/01-04/DC

Tadalafil PAH-ratiopharm 20 mg Filmtabletten

Procedure Number: DE/H/4054/01/DC

Active Substance:
Tadalafil

Dosage Form:
Film-coated tablet

Marketing Authorisation Holder in the RMS, Germany:
ratiopharm GmbH (DE/H/4013/01-04/DC + DE/H/4054/01/DC)
AbZ-Pharma GmbH (DE/H/4053/01-04/DC)

Publication:
12.09.2019

This module reflects the scientific discussion for the approval of Tadalafil-ratiopharm / AbZ 2.5 mg; 5mg; 10mg; 20mg; Tadalafil PAH-ratiopharm 20 mg Filmtabletten. The procedures were finalised on 29.04.2015.

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ADMINISTRATIVE INFORMATION

Proposed name of the medicinal product in the RMS	Tadalafil-ratiopharm 2,5 mg, 5mg, 10mg, 20mg Filmtabletten Tadalafil AbZ 2,5 mg, 5mg, 10mg, 20mg Filmtabletten Tadalafil PAH-ratiopharm 20 mg Filmtabletten
INN (or common name) of the active substance(s):	tadalafil
Pharmaco-therapeutic group (ATC Code):	G04BE08
Pharmaceutical form(s) and strength(s):	Film coated tablet
Reference Number(s) for the Decentralised Procedure	DE/H/4013/01-04/DC ; DE/H/4053/01-04/DC ; DE/H/4054/01/DC
Reference Member State:	DE
Member States concerned:	AT; BE; CZ; DK; ES; FI; FR; HR; IS; IT; LU; NL; NO; PL; PT; RO; SE; UK (DE/H/4013/01-04/DC); ES; PT (DE/H/4053/01-04/DC); AT; CZ; LU; NL; PT; UK (DE/H/4054/01/DC)
Martketing Authorisation Holder (name and address)	*DE/H/4013/01-04/DC & DE/H/4054/01/DC* ratiopharm GmbH Graf-Arco-Str. 3 89079 Ulm Germany *DE/H/4053/01-04/DC* AbZ-Pharma GmbH Graf-Arco-Str. 3 89079 Ulm Germany
Names and addresses of manufacturer(s) responsible for batch release in the EEA	TEVA Gyógyszergyár Zrt. TEVA Pharmaceutical Works Private Limited Company Debrecen Pallagi út 13, H-4042 Hungary TEVA UK Ltd Brampton Road, Hampden Park, Eastbourne, East Sussex, BN22 9AG United Kingdom TEVA Santé Rue Bellocier, Sens 89100 France Teva Operations Poland Sp. z.o.o. ul. Mogilska 80. , Krakow 31-546 Poland Teva Operations Poland Sp. z.o.o Ul. Sienkiewicza 25, Kutno 99-300 Poland TEVA PHARMA S.L.U. C/C, n. 4, Poligono Industrial Malpica, Zaragoza 50016 Spain Merckle GmbH

	Graf-Arco-Str. 3, Ulm 89079 Germany Merckle GmbH Ludwig-Merckle-Straße 3, Blaubeuren 89143 Germany PLIVA Hrvatska d.o.o. (PLIVA Croatia Ltd.) Prilaz baruna Filipovica 25, Zagreb 10000 Croatia Teva Pharma B.V. Swensweg 5, Haarlem 2031 GA The Netherlands

I. INTRODUCTION

Based on the review of the data on quality, safety, and efficacy the RMS considers that the application for Tadalafil-ratiopharm 2.5 mg, 5mg, 10mg, 20mg and Tadalafil AbZ 2,5 mg, 5mg, 10mg, 20mg in the treatment of erectile dysfunction in adult males and (5 mg only) treatment of the signs and symptoms of benign prostatic hyperplasia in adult males; and Tadalafil PAH-ratiopharm 20 mg in adults for the treatment of pulmonary arterial hypertension (PAH) classified as WHO functional class II and III, to improve exercise capacity; efficacy has been shown in idiopathic PAH (IPAH) and in PAH related to collagen vascular disease

is approved.

Please note, that there are commitments on RMP in Section V.

II. EXECUTIVE SUMMARY

II.1 Problem statement

N/A

II.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 as G03BE08 for all indications approved.

Therapeutic indications as claimed by the applicant

DE/H/4013/01-04/DC and DE/H/4053/01-04/DC
(Urological Indications)
Treatment of erectile dysfunction in adult males. In order for tadalafil to be effective, sexual stimulation is required.
Treatment of the signs and symptoms of benign prostatic hyperplasia in adult males. (5 mg only)
Tadalafil is not indicated for use by women.

DE/H/4054/01/DC
(Cardiologic Indication – PAH)

Tadalafil is indicated in adults for the treatment of pulmonary arterial hypertension (PAH) classified as WHO functional class II and III, to improve exercise capacity.
Efficacy has been shown in idiopathic PAH (IPAH) and in PAH related to collagen vascular disease.

Posology and method of administration as claimed by the applicant

DE/H/4013/01-04/DC and DE/H/4053/01-04/DC
(Urological Indications)

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 [Invented name] (i.e., at least twice weekly) a once daily regimen with the lowest doses of [Invented name] might be considered suitable, based on patient choice and the physician's judgement.
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.
The appropriateness of continued use of the daily regimen should be reassessed periodically.

(5 mg) Benign prostatic hyperplasia in adult men
The recommended dose is 5 mg, taken at approximately the same time every day with or without food.
For adult men being treated for both benign prostatic hyperplasia and erectile dysfunction the recommended dose is also 5 mg taken at approximately the same time every day. Patients who are unable to tolerate tadalafil 5 mg for the treatment of benign prostatic hyperplasia should consider an alternative therapy as the efficacy of tadalafil 2.5mg for the treatment of benign prostatic hyperplasia has not been demonstrated.

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.

Men with hepatic impairment
The recommended dose of Tadalafil is 10 mg taken prior to anticipated sexual activity and with or without food. There is limited clinical data on the safety of [Invented name] 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.

Men with diabetes
Dose adjustments are not required in diabetic patients.

Paediatric population
There is no relevant use of Tadalafil in the paediatric population with regard to the treatment of erectile dysfunction.

Method of administration
Tadalafil is available as 2.5, 5, 10, and 20 mg film-coated tablets for oral use.

DE/H/4054/01/DC
(Cardiologic Indication – PAH)

Treatment should only be initiated and monitored by a physician experienced in the treatment of PAH.

Posology
The recommended dose is 40 mg (2 x 20 mg) taken once daily with or without food.

Elderly patients
Dose adjustments are not required in elderly patients.

Renal impairment
In patients with mild to moderate renal impairment a starting dose of 20 mg once per day is recommended. The dose may be increased to 40 mg once per day, based on individual efficacy and tolerability. In patients with severe renal impairment the use of tadalafil is not recommended.

Hepatic impairment
Due to limited clinical experience in patients with mild to moderate hepatic cirrhosis (Child-Pugh Class A and B), following single doses of 10 mg, a starting dose of 20 mg once per day may be considered. If tadalafil is prescribed, a careful individual benefit/risk evaluation should be undertaken by the prescribing physician. Patients with severe hepatic cirrhosis (Child-Pugh Class C) have not been studied and therefore dosing of tadalafil is not recommended.

Paediatric population
The safety and efficacy of Tadalafil in individuals below 18 years of age has not yet been established. No data are available.

Method of administration
Tadalafil is for oral use.

II.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 is consistent with the current EU regulatory requirements.

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.

II.4 General comments on compliance with GMP, GLP, GCP, and agreed ethical principles

A QP statement is provided on behalf of the ratiopharm / AbZ qualified persons responsible for batch release in Europe.

Several alternate testing sites, batch release sites, primary and secondary packaging sites are also involved.

III. SCIENTIFIC OVERVIEW AND DISCUSSION

III.1 Quality aspects

Drug substance
Tadalafil is a compendial substance. An ASMF has been submitted. The ASMF holder has recently submitted an application for a CEP.
A three step synthesis process with subsequent purification is described.
The specifications are those described in the Ph. Eur. monograph with additional tests for chiral purity and residual solvents. FPM specifications include limits for particle size distribution, bulk and tapped density. Adequate controls are in place. A re-test period of 48 months without any special storage conditions has been justified by stability results.

Drug Product
The drug product is manufactured using a conventional wet granulation process. The four strengths (2.5 mg, 5 mg, 10 mg, and 20 mg film-coated tablets) are dose proportional. The presented in-process controls are sufficient for immediate release tablets and the process has been adequately validated. Results from batch analysis, pilot scale validation and ongoing stability demonstrate that the defined manufacturing process and controls ensure batch-to-batch consistency.
Results of 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. Appropriate specifications using validated methods are provided for the finished product.
Alternate blister packs are described: Al-Al; PVC/ACLAR/PVC -Al; and PVC/ACLAR/PVdC/PVC KPMAX-Al. Ongoing stability studies are provided justifying a shelf life of 24 months without any special storage conditions in when packaged in PVC/ACLAR/PVdC/PVC KPMAX-aluminium blisters

III.2 Non-clinical 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. Overview based on literature review is, thus, appropriate.

The non-clinical overview is well written. Report refers 56 publications up to year 2013.

The non-clinical overview on the pre-clinical pharmacology, pharmacokinetics and toxicology is adequate

Environmental Risk Assessment (ERA)
Since Tadalafil-ratiopharm/Tadalafil AbZ/ Tadalafil PAH-ratiopharm 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.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 these generic applications.

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

As the marketing application for Adcirca (Cardiologic Indication – PAH) has been based on informed consent and there are no issues as regards quality aspects of the current applications the bioequivalence studies are also considered valid for procedure DE/H/4054/01/DC (Cardiologic Indication – PAH).

For clarification concerning the indication for PAH the applicant has updated the information relating to orphan market exclusivity – similarity by a similarity assessement of tadalafil as compared to two other applications. The applicant concluded on dissimilarity in both cases.

Pharmacovigilance system
The Applicant/Proposed Future MAH has submitted a signed Summary of the Applicant's/Proposed Future MAH's 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 considers the Summary acceptable.

Risk Management Plan

DE/H/4013 and 4053/001-004/DC
The Applicants have submitted a Risk management plan (RMP), Version 1, data lock point 30 October 2013, date of final sign off 6 December 2014.

The following safety concerns are listed. These are in line with the EU reference product:

Table 1. Summary of safety concerns

Summary of safety concerns	
Important identified risks	• Priapism • Hypotension/increased hypotensive effect
Important potential risks	• Nonarteritic anterior ischemic optic neuropathy (NAION) • Sudden hearing loss
Missing information	• Characterization of adverse events in elderly patients (≥65 years)

The RMP is widely in line with the requirements of current GVP module V and the "Guidance on format of the risk management plan in the EU". There are some minor points concerning the RMP which will be addressed by the MAH with the next formal update of the RMP:

DE/H/4054/001/DC (PAH indication)
This is the first submission of a Risk management Plan (version 1.0, date of final sign off 06-Dec-2013) for Tadalafil 20 mg film-coated tablets for the treatment of pulmonary arterial hypertension (PAH). The applicant proposes the following 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 • Increased uterine bleeding (menorrhagia/vaginal hemorrhage)
Missing information	None

The RMP is widely in line with the requirements of current GVP module V and the "Guidance on format of the risk management plan in the EU". There are some minor points concerning the RMP which will be addressed by the MAH with the next formal update of the RMP:

Periodic Safety Update Report (PSUR)
The next PSUR should be submitted in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal.

Common renewal date
A prposed common renewal date of 5 years after finalisation of the procedure was accepted.

Legal status
Medicinal product subject to medical prescription.

User Test
The applicant does not present the results of a used test according to Art. 59 (3) and 61(1) of Directive 20021/83/EC.

Instead, the applicant presents a bridging report, which is based on the availability of the user testing for several products of the applicant with other active substances.

This bridging is considered adequate, because compliance with the requirements of the Art. 59 (3) and 61 (1) have been documented by the publicly available PARs of the products referenced.

IV. BENEFIT RISK ASSESSMENT

The use of tadalafil is well established and has recognised efficacy and acceptable safety.

Bioequivalence has been shown between the 20 mg product to be marketed and the 20 mg reference product in both fasted and fed condition. The results obtained in these studies for the 20 mg strength can be extrapolated to the other strengths 2.5, 5 and 10 mg.

The two risk management plans for the two different indications are accepted.

The application is approved. For intermediate amendments see current product information.

V. PROPOSED CONDITIONS FOR MARKETING AUTHORISATION AND PRODUCT INFORMATION

V.1 Proposed list of follow-up measures and specific obligations in case of a positive benefit risk assessment

Commitments in case of a positive benefit risk assessment

Area[1]	**Description**
01. RMP	The MAH committed to amend the RMP for DE/H/4013,4053 an 4054 with the next update to address the following: • RMP Part V, V.1. Table "Effectiveness of risk minimisation measures" should be described separately for each safety concern listed in the RMP.
0.2.RMP	The MAH committed to amend the RMP for DE/H/4013,4053 an 4054 with the next update to address the following: • RMP Part V.3 Table "Summary of risk minimization measures" and RMP Part VI.1.4 "Summary table of safety concerns" should include a classification of the safety concerns, i.e. either important identified or potential risks or missing information.

Areas: Pharmacovigilance