LÄKEMEDELSVERKET
SWEDISH MEDICAL PRODUCTS AGENCY

Public Assessment Report
Scientific discussion

Tadalafil Teva Pharma B.V.
(tadalafil)

SE/H/1726/01/DC

This module reflects the scientific discussion for the approval of Tadalafil Teva Pharma B.V.. The procedure was finalised on 2018-10-10. For information on changes after this date please refer to the module 'Update'.

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I. INTRODUCTION

The application for Tadalafil Teva Pharma B.V., 20 mg, film-coated tablet, is a generic application made according to Article 10(1) of Directive 2001/83/EC. The applicant, Actavis Group PTC ehf. applies through the Decentralised Procedure with Sweden acting as reference member state (RMS) and ADE as CMS for Tadalafil Teva Pharma B.V. Withdrawal of application in IT was made by the applicant on 2018-08-22, i.e. after Day 120 of the procedure.

The reference medicinal product chosen for the purposes of establishing the expiry of the data protection period is ADCIRCA, 20 mg, film-coated tablet authorised in the European Union since 2008, with Eli Lilly Nederland B.V. as marketing authorisation holder.

The reference products used in the bioequivalence study are CIALIS, 20 mg, film-coated tablets from UK with Eli Lilly Nederland B.V. as marketing authorisation holder.

For approved indications, see the Summary of Product Characteristics.

For recommendations to the marketing authorisation not falling under Article 21a/22 of Directive 2001/83/EC and conditions to the marketing authorisation pursuant to Article 21a or 22 of Directive 2001/83/EC to the marketing authorisation, please see section VI.

II. QUALITY ASPECTS

II.1 Drug Substance

The structure of the drug substance has been adequately proven and its physico-chemical properties are sufficiently described.

The manufacture of the drug substance has been adequately described and satisfactory specifications have been provided for starting materials, reagents and solvents.

The drug substance specification includes relevant tests and the limits for impurities and degradation products have been justified. The analytical methods applied are suitably described and validated.

Stability studies confirm the retest period.

II.2 Medicinal Product

The medicinal product is formulated using excipients listed in section 6.1 in the Summary of Product Characteristics.

The manufacturing process has been sufficiently described and critical steps identified.

The tests and limits in the specification are considered appropriate to control the quality of the finished product in relation to its intended purpose.

Stability studies have been performed and data presented support the shelf life and special precautions for storage claimed in the Summary of Product Characteristics, sections 6.3 and 6.4.

III. NON-CLINICAL ASPECTS

III.1 Discussion on the non-clinical aspects

Since this product has been shown to be essentially similar and refer to a product approved based on a full application with regard to preclinical data, no further such data have been submitted or are considered necessary.

IV. CLINICAL ASPECTS

IV.1 Pharmacokinetics

Two single dose bioequivalence studies have been submitted for the 20 mg strength (fasted and fed state). Bioequivalence studies in both fasted and fed state are adequate since the reference product is considered to have specific formulation characteristics.

Study under fasting conditions: Bioequivalence was evaluated in one single-dose, three-way crossover study conducted in 60 healthy male volunteers, comparing Tadalafil, 20 mg, tablet, with Cialis, 20 mg, tablet from two different markets under fasting conditions. The study was conducted between 25th October and 26th November 2013. Blood samples were collected pre-dose and up to 72 hours post-dose. The study design is considered acceptable. Plasma concentrations of tadalafil were determined with an adequately validated LC-MS/MS method. For AUC_{0-t} and C_{max} the 90% confidence interval for the ratio of the test and reference products fell within the conventional acceptance range of 80.00-125.00 %.

Study under fed conditions: Bioequivalence was evaluated in one single-dose, two-way crossover study conducted in 70 healthy male volunteers, comparing Tadalafil, 20 mg, tablet with Cialis, 20 mg, tablet under fed conditions. The study was conducted between 27th May and 19th June 2015. Blood samples were collected pre-dose and up to 72 hours post-dose. The study design is considered acceptable. Plasma concentrations of tadalafil were determined with an adequately validated LC-MS/MS method. For AUC_{0-72h} and C_{max} the 90% confidence interval for the ratio of the test and reference products fell within the conventional acceptance range of 80.00-125.00 %.

Based on the submitted bioequivalence studies, Tadalafil Teva Pharma B.V. is considered bioequivalent with Cialis.

IV.2 Discussion on the clinical aspects

Since this product has been shown to be essentially similar and refer to a product approved based on a full application with regard to clinical efficacy/safety data, no further such data have been submitted or are considered necessary.

IV.3 Risk Management Plan

The MAH has submitted a risk management plan, in accordance with the requirements of Directive 2001/83/EC as amended, describing the pharmacovigilance activities and interventions designed to identify, characterize, prevent or minimize risks relating to Tadalafil Teva Pharma B.V..

Safety specification
Summary of Safety Concerns:

List of important risks and missing information	
Important identified risks	• Priapism • Hypotension/increased hypotensive effect
Important potential risks	• Non-arteritic anterior ischemic optic neuropathy (NAION) • Sudden hearing loss • Increased uterine bleeding
Missing information	None

Pharmacovigilance Plan
Routine pharmacovigilance is suggested and no additional pharmacovigilance activities are proposed by the applicant, which is endorsed.

Risk minimisation measures
Routine risk minimisation is suggested and no additional risk minimisation activities are proposed by the applicant, which is endorsed.

Summary of the RMP
The submitted Risk Management Plan, version 2.2 signed 31 July 2018 is considered acceptable.

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 RMS;
- 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 dates for submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time, but via different procedures.

V. USER CONSULTATION

A user consultation with target patient groups on the package leaflet (PL) has been performed on the basis of a bridging report making reference to Tadalafil Teva for content and Entecavir Teva for layout. The parent PLs were user tested and assessed by competent authorities in the procedures DE/H/4013/01-04/DC and NO/H/259/01-02/DC respectively. The bridging report submitted by the applicant has been found acceptable.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

The quality of the generic product, Tadalafil Teva Pharma B.V., is found adequate. There are no objections to approval of Tadalafil Teva Pharma B.V., from a non-clinical and clinical point of view. Bioequivalence between the test and reference product has been adequately demonstrated. The product information is acceptable.
The application is therefore recommended for approval.

List of recommendations not falling under Article 21a/22 of Directive 2001/83/EC in case of a positive benefit risk assessment

N/A

List of conditions pursuant to Article 21a or 22 of Directive 2001/83/EC

N/A

VII. APPROVAL

The Decentralised procedure for Tadalafil Teva Pharma B.V.
, 20 mg, Film-coated tablet was positively finalised on 2018-10-10.

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Public Assessment Report – Update

Procedure number*	Scope	Product Information affected	Date of end of procedure	Approval/ non approval	Summary/ Justification for refuse

*Only procedure qualifier, chronological number and grouping qualifier (when applicable)

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