LÄKEMEDELSVERKET
MEDICAL PRODUCTS AGENCY

Public Assessment Report
Scientific discussion

Tadalafil Actavis
(tadalafil)

SE/H/1531/01-04/DC

This module reflects the scientific discussion for the approval of Tadalafil Actavis. The procedure was finalised on 2016-04-20. For information on changes after this date please refer to the module 'Update'.

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I. INTRODUCTION

The application for Tadalafil Actavis, film-coated tablets, 2.5 mg, 5 mg , 10 mg and 20 mg, 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 AT, CZ, SK (5 mg and 20 mg only), DK, EE, FI, IE, IS, LT, LV, NO, RO (5 mg, 10 mg and 20 mg only) and UK as concerned member states (CMS).

The reference medicinal product chosen for the purposes of establishing the expiry of the data protection period is Cialis, film-coated tablet, 20 mg, authorised in EU since 2002, with Eli Lilly Nederland BV, as marketing authorisation holder.
The reference product used in the bioequivalence study is Cialis, film-coated tablet, 2.5 mg and 20 mg from EU with Lilly S.A, 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 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

Bioequivalence was evaluated in three single-dose two-way crossover studies, two in the fasted state with the 2.5 mg and 20 mg strengths (Study 3057/13 and 3054/13) and one in the fed state with the 20 mg strength (Study 3735/15).

Study 3057/13was conducted in 42 healthy male volunteers, comparing Tadalafil, 2.5 mg, tablet with Cialis, 2.5 mg, tablet under fasting conditions. The study was conducted at Lotus Labs Pvt. Ltd., Chennai, India between 11th and 29th 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 3054/13 was conducted in 60 healthy male volunteers, comparing Tadalafil, 20 mg, tablet with Cialis, 20 mg, tablet under fasting conditions. The study was conducted at Lotus Labs Pvt. Ltd., Bangalore, India 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 3735/15 was conducted in 70 healthy male volunteers, comparing Tadalafil, 20 mg, tablet with Cialis, 20 mg, tablet under fed conditions. The study was conducted at Lotus Labs Pvt. Ltd., Bangalore, India 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 %.

The submitted study package including three single dose bioequivalence studies (2.5 mg fasted, 20 mg fasted and 20 mg fed) are considered sufficient. Bioequivalence are concluded in all three studies.
A bracketing approach is used because of a deviation from proportional composition and waiver of the strengths 5 mg and 10 mg is acceptable since the bioequivalence studies in the

fasted state have been performed with the extremes, the lowest and highest strengths, 2.5 and 20 mg. Since the reference product is considered to have specific formulation characteristics, bioequivalence studies in both fasted and fed state are required and a study with the 20 mg strength in the fed state have been submitted.

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, characterise, prevent or minimise risks relating to Tadalafil Actavis.

Safety specification
The RMP for the reference product **Cialis** is combined with the product **Adcirca**, also containing tadalafil, but indicated for Pulmonary Arterial Hypertension (PAH).

The RMP for **Tadalafil Actavis** has been updated in accordance with the table with Summary of safety specification below for Cialis and Adcirca, but the Important Potential Risks for the PAH indication has been omitted. Please see the table below.

Summary of safety concerns	
Important identified risks	*For all indications:* Hypotension/ Increased hypotensive effect Priapism
Important potential risks	*For all indications:* Non-arteritic anterior ischaemic optic neuropathy (NAION) Sudden hearing loss
Missing information	*For Once-a-Day ED and BPH:* Characterisation of adverse events in elderly patients (≥65 years of age)

- The RMP, version 2.2, for **Tadalafil Actavis (**MAH Actavis) is approvable.

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.

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

The package leaflet has been evaluated via a user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC. The language used for the purpose of user testing the PIL was English.
The results show that the package leaflet meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

The benefit/risk ratio is considered positive and Tadalafil Actavis, film-coated tablets, 2.5 mg, 5 mg, 10 mg and 20 mg, is recommended for approval.

List of recommendations not falling under Article 21a/22 of Directive 2001/83 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 Actavis, film-coated tablets, 2.5 mg, 5 mg, 10 mg and 20 mg was positively finalised on 2016-04-20.

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Public Assessment Report – Update

Scope	Procedure number	Product Information affected	Date of start of the procedure	Date of end of procedure	Approval/ non approval	Assessment report attached
						Y/N (version)

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