LÄKEMEDELSVERKET
MEDICAL PRODUCTS AGENCY

Public Assessment Report
Scientific discussion

Tadalafil Sigillata
(tadalafil)

SE/H/1646/01-03/DC

This module reflects the scientific discussion for the approval of Tadalafil Sigillata. The procedure was finalised on 2017-05-24. For information on changes after this date please refer to the module 'Update'.

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I. INTRODUCTION

The application for Tadalafil Sigillata, film-coated tablets, 5 mg, 10 mg and 20 mg, is a generic application made according to Article 10(1) of Directive 2001/83/EC. The applicant, Sigillata Limited, applies through the Decentralised Procedure with Sweden acting as reference member state (RMS) and IT 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 Germed and duplicates.

Safety specification

Summary table of safety concerns as approved in RMP

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)

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 RMP is approved

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 information leaflet (PIL) has been performed on the basis of a bridging report making reference to Vixantus, SE/H/1532/01-04/DC and Fullreizn SE/H/1534/01-03/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 Sigillata, is found adequate. There are no objections to approval of Tadalafil Sigillata, 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 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 Sigillata, 5 mg, 10 mg and 20 mg, film-coated tablets was positively finalised on 2017-05-24.

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MEDICAL PRODUCTS AGENCY

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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