LÄKEMEDELSVERKET
SWEDISH MEDICAL PRODUCTS AGENCY

Public Assessment Report
Scientific discussion

Tadalafil Jubilant
tadalafil

SE/H/2061/01-04/DC

This module reflects the scientific discussion for the approval of Tadalafil Jubilant. The procedure was finalised on 2021-05-22. For information on changes after this date please refer to the module 'Update'.

Postadress/Postal address: P.O. Box 26, SE-751 03 Uppsala, SWEDEN
Besöksadress/Visiting address: Dag Hammarskjölds väg 42, Uppsala
Telefon/Phone: +46 (0)18 17 46 00 Fax: +46 (0)18 54 85 66
Internet: www.lakemedelsverket.se E-mail: registrator@lakemedelsverket.se

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, a marketing authorisation has been granted for Tadalafil Jubilant 2.5 mg, 5 mg, 10 mg and 20 mg, film-coated tablets.

The active substance is tadalafil. A comprehensive description of the indication and posology is given in the SmPC.

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

The application for Tadalafil Jubilant, 2.5 mg, 5 mg, 10 mg and 20 mg film-coated tablet, is a generic application made according to Article 10(1) of Directive 2001/83/EC. The applicant, Jubilant Pharmaceuticals N.V., applies through the Decentralised Procedure with Sweden acting as reference member state (RMS) and DE, DK, ES and UK (NI) as concerned member states (CMS).

The reference medicinal product chosen for the purposes of establishing the expiry of the data protection period is Cialis, 2.5 mg, 5 mg, 10 mg and 20 mg film-coated tablets authorised in the Union since 2002, with Eli Lilly Nederland B.V. as marketing authorisation holder.

The reference product used in the bioequivalence studies is Cialis, 20 mg, film-coated tablet from PT with Eli Lilly Nederland B.V. as marketing authorisation holder

Potential similarity with orphan medicinal products
According to the application form and a check of the Community Register of orphan medicinal products there is no medicinal product designated as an orphan medicinal product for a condition relating to the indication proposed in this application.

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

Pharmacodynamic, pharmacokinetic and toxicological properties of tadalafil are well known. As tadalafil is a widely used, well-known active substance, no further studies are required, and the applicant provides none. Overview based on literature review is, thus, appropriate.

Environmental Risk Assessment (ERA)
Since Tadalafil Jubilant is a generic product, it will not lead to an increased exposure to the environment. An environmental risk assessment is therefore not deemed necessary.

There are no objections to approval of Tadalafil Jubilant from a non-clinical point of view.

IV. CLINICAL ASPECTS

Pharmacokinetics
To support the marketing authorisation application the applicant has conducted two bioequivalence studies comparing Tadalafil with the reference product Cialis.

The reference product can be taken with or without food according to the SmPC. Since the specific formulation (e.g. particle size and excipients) is known to be critical to the performance of the formulation in fed conditions, it cannot be assumed that the impact of food will be the same regardless of formulation. Therefore, following the requirements for "specific formulation characteristics" described in the Guideline on Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev 1/Corr), both fasted and fed state comparisons of test to reference formulations are required.

Pharmacokinetic properties of the active substance
Absorption: Tadalafil is readily absorbed after oral administration and the mean maximum observed plasma concentration (C_{max}) is achieved at a median time of 2 hours after dosing. Absolute bioavailability of tadalafil following oral dosing has not been determined.

The rate and extent of absorption of tadalafil are not influenced by food, thus tadalafil may be taken with or without food. The time of dosing (morning versus evening) had no clinically relevant effects on the rate and extent of absorption.

Linearity: Tadalafil pharmacokinetics in healthy subjects are linear with respect to time and dose. Over a dose range of 2.5 to 20 mg, exposure (AUC) increases proportionally with dose. Steady-state plasma concentrations are attained within 5 days of once-daily dosing.

Elimination: The mean oral clearance for tadalafil is 2.5 l/h and the mean half-life is 17.5 hours in healthy subjects.

Study TADA-17-028 (20 mg Fasting)
Methods
This was a single-dose, two-way crossover study conducted in 40 healthy volunteers, comparing

Tadalafil, 20 mg, film-coated tablet with Cialis, 20 mg, film-coated tablet under fasting conditions. Blood samples for concentration analysis were collected pre-dose and up to 72 hours post-dose. Plasma concentrations of tadalafil were determined with a LC-MS/MS method. Analysis of variance (ANOVA) was performed on the log-transformed data for AUC_{0-72} and C_{max}. The study was conducted between 10/SEP/2019 and 14/OCT/2019.

Results
The results from the pharmacokinetic and statistical analysis are presented in Table 1 below.

Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, T_{max} median, range) for tadalafil, n=37.

Treatment	AUC_{0-72} ng*h/ml	C_{max} ng/ml	T_{max} h
Test	**13154.8 ± 3589.8**	**470.6 ± 95.3**	**1.670 (0.67-4.52)**
Reference	**12887.8 ± 3641.5**	**482.1 ± 108.2**	**1.330 (0.67-4.50)**
***Ratio (90% CI)**	**102.68 (97.45 -108.19)**	**98.33 (93.44 -103.48)**	**-**
AUC_{0-72} area under the plasma concentration-time curve from time zero to 72 hours **C_{max}** maximum plasma concentration **T_{max}** time for maximum plasma concentration			

**calculated based on ln-transformed data*

For AUC_{0-72} 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%. Comparable median and range for T_{max} between test and reference product have been demonstrated.

Study TADA-17-018 (20 mg Fed)
Methods
This was a single-dose, two-way crossover study conducted in 40 healthy volunteers, comparing Tadalafil, 20 mg, film-coated tablet with Cialis, 20 mg, film-coated tablet under fed conditions. Blood samples for concentration analysis were collected pre-dose and up to 72 hours post-dose. Plasma concentrations of tadalafil were determined with a LC-MS/MS method. Analysis of variance (ANOVA) was performed on the log-transformed data for AUC_{0-72} and C_{max}. The study was conducted between 21/OCT/2019 and 22/NOV/2019.

Results
The results from the pharmacokinetic and statistical analysis are presented in Table 2 below.

Table 2. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, T_{max} median, range) for tadalafil, n=34.

Treatment	AUC_{0-72} ng*h/ml	C_{max} ng/ml	T_{max} h
Test	**13293.6 ± 3795.0**	**450.2 ± 109.2**	**4.330 (2.00-8.02)**
Reference	**13902.8 ± 3884.0**	**443.9 ± 115.2**	**4.330 (1.67-12.00)**
***Ratio (90% CI)**	**95.33 (87.73 -103.60)**	**102.31 (96.68 -108.27)**	**-**
AUC_{0-72} area under the plasma concentration-time curve from time zero to 72 hours **C_{max}** maximum plasma concentration **T_{max}** time for maximum plasma concentration			

**calculated based on ln-transformed data*

For AUC_{0-72} 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%. Comparable median and range for T_{max} between test and reference product have been demonstrated.

A biowaiver was sought for the additional strengths of 2.5 mg, 5 mg and 10 mg.

Discussion and overall conclusion
The bioequivalence studies and their statistical evaluation were in accordance with accepted standards for bioequivalence testing, as stated in the Guideline on the investigation of bioequivalence (CPMP/EWP/QWP/1401/98 Rev 1/Corr) and the EMA product-specific bioequivalence guidance for tadalafil, 2.5 mg, 5 mg, 10 mg and 20 mg, film-coated tablets (EMA/CHMP/315234/2014/Rev.1[†]). The bioanalytical methods were adequately validated.

Absence of studies with the additional strengths of 2.5 mg, 5 mg and 10 mg is acceptable from a pharmacokinetic point of view as the pharmacokinetics of tadalafil is linear between 2.5 mg and 20 mg. For drugs with linear pharmacokinetics the bioequivalence study should in general be conducted at the highest strength. The highest strength has been studied which is in accordance with guideline recommendations.

Based on the submitted bioequivalence studies, Tadalafil is considered bioequivalent with Cialis.

Pharmacodynamics/Clinical efficacy/Clinical safety
No new studies on pharmacodynamics, clinical efficacy or clinical safety have been submitted. Provided that bioequivalence with the originator product is demonstrated, additional data is not necessary.

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 Jubilant.

Safety specification

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
Missing information	• Characterization of adverse events in elderly patients (≥65 years) (ED/BPH indications only)

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 1.0 signed 15 January 2020 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 an 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 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 quality of the generic product, Tadalafil Jubilant, is found adequate. There are no objections to approval of Tadalafil Jubilant, 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/22a/22 of Directive 2001/83/EC in case of a positive benefit risk assessment

A new version of the CEP was issued by the EDQM in March 2021. The applicant should commit to submit an appropriate variation within 30 days to reflect any changes.

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

N/A

VII. APPROVAL

The decentralised procedure for Tadalafil Jubilant 2.5 mg, 5 mg, 10 mg and 20 mg, film-coated tablets was positively finalised on 2021-05-22.

LÄKEMEDELSVERKET
SWEDISH MEDICAL PRODUCTS AGENCY

Public Assessment Report – Update

Procedure number*	Scope	Product Information affected (Yes/No)	Date of end of procedure	Approval/ non approval	Summary/ Justification for refuse

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

Postadress/Postal address: P.O. Box 26, SE-751 03 Uppsala, SWEDEN
Besöksadress/Visiting address: Dag Hammarskjölds väg 42, Uppsala
Telefon/Phone: +46 (0)18 17 46 00 Fax: +46 (0)18 54 85 66
Internet: www.lakemedelsverket.se E-mail: registrator@lakemedelsverket.se