Public Assessment Report

Scientific discussion

Tadalafil Farmalter 5 mg, 10 mg and 20 mg orodispersible tablets (tadalafil)

ES/H/0905/001-003/DC

Date: 19/11/2024

This module reflects the scientific discussion for the approval of Tadalafil Farmalter 5 / 10 / 20 mg orodispersible tablets. The procedure was finalised at 18/07/2024.

I. INTRODUCTION

This application refers to a decentralized procedure following the Article 10(1) generic application of Directive 2001/83/EC, with Spain as reference member state and Italy as concerned member state.
The product is an immediate release orodispersible tablet, containing 5 mg, 10 mg or 20 mg of Tadalafil.
The proposed indications for Tadalafil 5 mg orodispersible tablets are: Treatment of erectile dysfunction in adult males. Treatment of the signs and symptoms of benign prostatic hyperplasia in adult males.
The proposed indications for Tadalafil 10 mg and 20 mg orodispersible tablets are: Treatment of erectile dysfunction in adult males.
The maximum daily dose according to the SmPC is 20 mg of tadalafil.
A comprehensive description of the indications and posology is given in the SmPC.

II. QUALITY ASPECTS

II.1 Introduction

The finished product is presented as a orodispersible tablet containing 5 mg, 10 mg and 20 mg of tadalafil as active substance. The maximum daily dose is 20 mg.

The product is available in PVC-PCTFE - aluminium blister as described in section 6.5 of the SmPC.

II.2 Drug Substance

The drug substance is described in the Ph. Eur. CEP procedure is used to support the quality of the active substance.

General Information

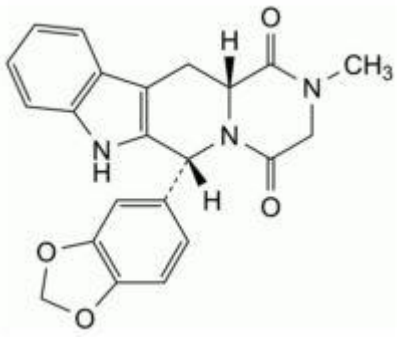
Nomenclature:

INN:	Tadalafil
Chemical name:	(6*R*,12a*R*)-6-(1,3-Benzodioxol-5-yl)-2-methyl-2,3,6,7,12,12a-hexahydropyrazino[1′,2′:1,6]-pyrido[3,4-*b*]indole-1,4-dione.
CAS-No:	[171596-29-5]

Structure:

Molecular formula:	$C_{22}H_{19}N_3O_4$
Molecular weight:	389.4

Structural formula:



General Properties:

White or almost white powder, practically insoluble in water, freely soluble in dimethyl sulfoxide, slightly soluble in methylene chloride.

Manufacture, process controls and characterisation

As CEP procedure is used, information on manufacture, process controls and characterisation of the active substance has been assessed by EDQM.

Specification, analytical procedures, batch analysis

Active substance specifications are in accordance with Ph. Eur. monograph and additional relevant tests are included.

Container closure system

As CEP procedure is used, information on packaging material of active substance has been assessed by EDQM.

Stability

Re-test period is included in the CEP. Stability studies have been assessed by EDQM.

II.3 Medicinal Product

Description of the product

Tadalafil Farmalter 5 mg orodispersible tablets: White to off-white, flat, unscored tablets, about 7 mm of diameter. Each orodispersible tablet contains 5 mg of tadalafil. Other ingredients are lactose monohydrate, microcrystalline cellulose, hydroxypropylcellulose, croscarmellose sodium, sodium laurilsulfate, aspartame (E-951), ethyl vanillin and magnesium stearate.
The orodispersible tablets are contained in blisters.

Tadalafil Farmalter 10 mg orodispersible tablets: White to off-white, round, biconvex tablets with no functional score on one side, about 8 mm of diameter. Each orodispersible tablet contains 10 mg of tadalafil. Other ingredients are lactose monohydrate, microcrystalline cellulose, hydroxypropylcellulose, croscarmellose sodium, sodium laurilsulfate, aspartame (E-951), ethyl vanillin and magnesium stearate.
The orodispersible tablets are contained in blisters.

Tadalafil Farmalter 20 mg orodispersible tablets: White to off-white, round, biconvex, unscored tablets, about 11 mm of diameter. Each orodispersible tablet contains 20 mg of tadalafil. Other ingredients are lactose monohydrate, microcrystalline cellulose, hydroxypropylcellulose, croscarmellose sodium, sodium laurilsulfate, aspartame (E-951), ethyl vanillin and magnesium stearate.
The orodispersible tablets are contained in blisters.

Pharmaceutical Development

The development of the product has been described, the choice of excipients is justified and their functions explained.
The physicochemical characteristics of the active substance that may affect the pharmaceutical form are identified and their control strategy is justified.
The choice of dissolution method is considered appropriate. The information presented supports the proposed quality control dissolution method.

Manufacture of the product

The manufacturing process is fully described and in-process controls are appropriate considering the nature of the product and the manufacturing process. The industrial batch size is well-defined.

Sufficient validation data are provided.

Excipients

Excipients used are well known and of appropriate quality.

Lactose monohydrate is the only excipient of animal origin. Declaration of absence of risk of BSE/TSE for each of the components in the formulation are presented.

Product specification, analytical procedures, batch analysis

The finished product specifications are adequate to control the finished product. Provided description and validation data for the analytical methods are adequate. Batch analysis data have been submitted and the results show that the finished product meets the proposed release specification.

Container closure system

The finished product is packaged in PCTFE/PVC-Aluminium blisters. The choice of the container closure system is justified considering the nature of the finished product. Compliance with the relevant requirements and/or regulations is confirmed.

Stability

Stability studies have been performed in accordance with current guidelines. The proposed protocol is considered adequate. The packaging material is the same as that intended for marketing. Proposed shelf-life and storage conditions are properly established.

Shelf-life: 27 months.

Storage conditions: Do not store above 30°C.

In-use shelf life: Not applicable.

III. NON-CLINICAL ASPECTS

III.1 Critical evaluation of the Non-Clinical Overview

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.

III.2 Environmental Risk Assessment (ERA)

Since Tadalafil Farmalter 5 mg, 10 mg and 20 mg orodispersible tablets is a generic product, it will not lead to an increased exposure to the environment. Therefore, additional ERA studies are not deemed necessary.

IV. CLINICAL ASPECTS

IV.1 Introduction

Tadalafil is a well-known active substance with established efficacy and safety. A clinical overview has been provided, which is based on scientific literature. The clinical overview justifies that there no need to generate additional clinical data.

For this generic application of an immediate release formulation, the MAH has submitted two bioequivalence studies with the 20 mg strength according to the Guideline on the investigation of bioequivalence and the Tadalafil Product-Specific Bioequivalence Guidance, which are discussed below.

IV.2 Pharmacokinetics

Biowaiver

This application concerns three strengths, i.e., 5 mg, 10 mg and 20 mg orodispersible tablets and the bioequivalence study has been carried out with the 20 mg strength.
The criteria according to the Guideline on the Investigation of Bioequivalence for waiving the 5 and 10 mg tablets are fulfilled as:

- All the strengths are manufactured with the same process.
- The qualitative composition of all strengths is the same.
- The composition of the strengths is quantitatively proportional.
- Appropriate dissolution profiles between the different strengths have confirmed to be similar.

Bioequivalence studies

GCP compliance
The studies were conducted in accordance with Good Clinical Practice (GCP) standards. Monitoring reports and certificates of audits carried out by the Quality Assurance Unit are presented. The sites have been previously inspected by EU regulatory authorities.

Clinical and analytical facilities:
Clinical site: Clinical Trials Unit, Hospital Universitario de la Princesa. C/ Diego de León, nº 62 (Madrid) Spain.
Analytical centre: Anapharm Europe, S.L.U. Encuny 22, 2nd floor, 08038 Barcelona, Spain.

Study code

UECHUP-TADODT/22-1; EUDRA-CT: 2022-000374-26

Design.
A randomised, single-dose, two-treatment, two-period, two sequence, crossover bioequivalence study was carried out under fasted conditions in 36 healthy male subjects, aged 28 – 42 years. Each subject received a single dose (20 mg orodispersible tablet) of one of the two active substance formulations. The tablet was orally administered with 240 mL of water for the reference product and just with 20 mL of water in the case of the test product to moisten the mouth, after an overnight fast of at least ten hours. There were two dosing periods, separated by a washout period of 7 days.

Analytical and statistical methods
The analytical method has been adequately validated and is considered acceptable for analysis of the plasma samples.
The 90% confidence interval (90% CI) of the ratio of the test formulation to the reference formulation for the log-transformed values of Cmax and AUC was calculated using an ANOVA model. This model included the covariates sequence, period, formulation and subject nested to sequence. Bioequivalence was defined when the 90% CI of the ratios (test/reference) for Cmax and AUC was in the range 80.00 -125.00%.
The methods used in this study for the pharmacokinetic calculations and statistical evaluation are considered acceptable.

Results
36 subjects, were included in the study. 36 subjects were treated, 34 subjects completed the study and 33 were used in the statistical analysis according to the protocol.
The inclusion and exclusion criteria are considered acceptable for a bioequivalence study.

Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, tmax median, range)

Treatment	**AUC_{0-t}** ng/ml/h	**$AUC_{0-\infty}$** ng/ml/h	**C_{max}** ng/ml	**t_{max}** h
Test	8578.01± 2575.35	10006.19 ±3733.03	312.69 ±57.78	3.00 (0.67- 6.00)
Reference	8250.63± 2182.72	9745.78 ± 3382.63	291.63 ± 64.40	3.50 (0.83 - 6.00)
***Ratio (90% CI)**	102.92 (98.42 – 107.62)	101.79 (96.80 – 107.03)	108.35 (101.15 – 116.06)	-

AUC_{0-t} Area under the plasma concentration curve from administration to last observed concentration at time t.
AUC_{0-72h} can be reported instead of AUC_{0-t}, in studies with sampling period of 72 h, and where the concentration at 72 h is quantifiable. Only for immediate release products
$AUC_{0-\infty}$ Area under the plasma concentration curve extrapolated to infinite time.
$AUC_{0-\infty}$ does not need to be reported when AUC_{0-72h} is reported instead of AUC_{0-t}
C_{max} Maximum plasma concentration
t_{max} Time until Cmax is reached

Study code

UECHUP-TADODT/22-2; EUDRA-CT: 2022-000357-81

Design.
A randomised, single-dose, two-treatment, two-period, two sequence, crossover bioequivalence study was carried out under fed conditions in 36 healthy male subjects, aged 28 – 42 years. Each subject received a single dose (20 mg orodispersible tablet) of one of the two active substance formulations. The medication was administered 30 minutes after the beginning of the breakfast (high fat, high calorie). For the reference product the volunteers had 240 mL of water and just with 20 mL of water in the case of the test product to moisten the mouth. The subjects had been fasting for 10 hours before dosing and until 5 hours after dose administration. There were two dosing periods, separated by a washout period of 8 days.

Analytical and statistical methods
The analytical method has been adequately validated and is considered acceptable for analysis of the plasma samples.
The 90% confidence interval (90% CI) of the ratio of the test formulation to the reference formulation for the log-transformed values of Cmax and AUC was calculated using an ANOVA

model. This model included the covariates sequence, period, formulation and subject nested to sequence. Bioequivalence was defined when the 90% CI of the ratios (test/reference) for Cmax and AUC was in the range 80.00 -125.00%.
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Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, tmax median, range)

Treatment	**AUC_{0-t}** ng/ml/h	**$AUC_{0-\infty}$** ng/ml/h	**C_{max}** ng/ml	**t_{max}** h
Test	8759.05 ± 3149.95	10062.61 ±4256.83	328.54 ±91.06	4.00 (0.83- 6.00)
Reference	8917.92 ± 2936.68	10316.48 ± 4019.58	313.12 ± 99.13	4.00 (1.33 - 10.00)
***Ratio (90% CI)**	97.34 (93.63 – 101.19)	96.55 (92.66 – 103.61)	95.69 (88.10 – 103.93)	-

AUC_{0-t} Area under the plasma concentration curve from administration to last observed concentration at time t.
AUC_{0-72h} can be reported instead of AUC_{0-t}, in studies with sampling period of 72 h, and where the concentration at 72 h is quantifiable. Only for immediate release products
$AUC_{0-\infty}$ Area under the plasma concentration curve extrapolated to infinite time.
$AUC_{0-\infty}$ does not need to be reported when AUC_{0-72h} is reported instead of AUC_{0-t}
C_{max} Maximum plasma concentration
t_{max} Time until Cmax is reached

Conclusion on bioequivalence studies:
Based on the submitted bioequivalence studies Tadalafil Farmalter 20 mg orodispersible tablets is considered bioequivalent with Cialis® 20 mg film-coated tablets.

If applicable,
The results of studies UECHUP-TADODT/22-1 and UECHUP-TADODT/22-2 with 20 mg formulation can be extrapolated to 5 mg and 10 mg strengths, according to conditions in Guideline on the Investigation of Bioequivalence CPMP/EWP/QWP/1401/98 Rev. 1/Corr*, section 4.1.6.

IV.3 Pharmacodynamics

NA

IV.4 Clinical efficacy

NA

IV.5 Clinical safety

NA

IV.6 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 Farmalter 5 mg, 10 mg, 20 mg orodispersible tablets.
There are neither proposed additional pharmacovigilance activities nor proposed additional risk minimisation measures planned for Tadalafil Farmalter 5 mg, 10 mg, 20 mg orodispersible tablets.

IV.7 Discussion on the clinical aspects

The clinical efficacy and safety of tadalafil are sufficiently known, since tadalafil-containing medicinal products have been marketed in several countries for several years for the proposed indications. Proposed information on the PI for Tadalafil Farmalter is aligned with the information contained in the PI of the reference medicinal product Cialis® 5 mg, 10 mg and 20 mg film coated tablets.

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 Cialis® 5 / 10 / 20 mg film-coated tablets, EMEA/H/C/000436. The bridging report submitted by the applicant has been found acceptable.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

The quality of the generic products Tadalafil Farmalter 5 mg, 10 mg and 20 mg orodispersible tablets are found adequate. There are no objections to the approval of Tadalafil Farmalter 5 mg, 10 mg and 20 mg orodispersible tablets 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 benefit/risk is considered positive, and the application is therefore recommended for approval.

The results of the studies) with the 20 mg strength can be extrapolated to the 5 mg and 10 mg strengths, according to conditions in Guideline on the Investigation of Bioequivalence CPMP/EWP/QWP/1401/98 Rev. 1/Corr*, section 4.1.6.