

Public Assessment Report

Scientific discussion

**ZENAVIL 5 mg, 10 mg and 20 mg,
film-coated tablets**

(tadalafil)

NL/H/3062/001-003/DC

Date: 28 September 2015

This module reflects the scientific discussion for the approval of ZENAVIL 5 mg, 10 mg and 20 mg, film-coated tablets. The procedure was finalised on 11 December 2014. For information on changes after this date please refer to the 'steps taken after finalisation' at the end of this PAR.

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for ZENAVIL 5 mg, 10 mg and 20 mg, film-coated tablets from Medochemie Limited.

The product is indicated for:

- Treatment of erectile dysfunction in adult males. In order for tadalafil to be effective for the treatment of erectile dysfunction, sexual stimulation is required.
- Treatment of pulmonary arterial hypertension (PAH) classified as WHO functional class II and III, to improve exercise capacity (see section 5.1 of the approved SmPC). Efficacy has been shown in idiopathic PAH (IPAH) and in PAH related to collagen vascular disease.
- Treatment of the signs and symptoms of benign prostatic hyperplasia in adult males.

A comprehensive description of the indications and posology is given in the SmPC.

This decentralised procedure concerns a generic application claiming essential similarity with the innovator product Cialis 5 mg, 10 mg and 20 mg tablets which has been registered in the EEA through centralised procedure EMEA/H/C/000436 by Eli Lilly Nederland B.V. since 12 November 2002.

The concerned member states (CMS) involved in this procedure were:

5 mg – Cyprus, Czech Republic, Estonia, Greece, Lithuania, Malta and Slovakia

10 mg – Croatia, Cyprus, Estonia, Greece and Malta

20 mg – Bulgaria, Croatia, Cyprus, Czech Republic, Estonia, Greece, Lithuania, Malta and Slovakia

The marketing authorisation has been granted pursuant to Article 10(1) of Directive 2001/83/EC.

Similarity assessment in view of the orphan drug legislation

The MAH applied for the indication Pulmonary Arterial Hypertension (PAH) for the 20 mg tablets. For this indication a number of orphan medicinal products are currently registered in the EU. In line with the orphan drug legislation, the MAH has submitted a similarity assessment against all products that hold an orphan designation and are authorised in the EU at the time of this application.

In the similarity report, reference is made to the similarity assessment of the reference product Adcirca to the orphan drugs with the PAH indication at the time of registration of Adcirca: sildenafil, bosentan, iloprost, sitaxentan and ambrisentan, which is acceptable.

Furthermore, a search was performed for orphan drugs with the indication PAH which received a marketing authorisation since the registration of the reference product Adcirca. In the initial application, a similarity report was submitted by the MAH, comparing the product to the active substance macitentan (Opsumit). A similarity assessment against macitentan was provided, concluding that tadalafil and macitentan are different active substances, with different principal molecular structural features that act via different mechanisms of action. Therefore, tadalafil is considered non similar to the authorised orphan medicinal product macitentan. This conclusion is supported.

At that time this was correct and the similarity report was acceptable. Since then, a new orphan drug received a marketing authorization in the indication PAH: the active substance riociguat (brandname Adempas). The MAH provided an additional similarity assessment against Adempas, concluding that tadalafil and riociguat are different active substances, with different principal molecular structural features that act via different mechanisms of action. Therefore, tadalafil is considered non similar to the authorised orphan medicinal product riociguat (based on two of the three criteria for similarity, i.e. molecular structure and mechanism of action). This conclusion is also supported by the member states.

Overall, the generic product tadalafil applied for is considered non similar to all orphan medicinal products with the indication PAH currently authorised in EU. Thus the application of Zenavil 20 mg film-coated tablets for marketing authorization for the indication PAH can be accepted in view of the orphan drug legislation.

II. QUALITY ASPECTS

II.1 Introduction

ZENAVIL 5 mg, is a brick-red, round, convex, film-coated tablet with a diameter of nucleus 6 mm.
ZENAVIL 10 mg is an orange-brown, round, convex, film-coated tablet with diameter of nucleus 8 mm.
ZENAVIL 20 mg is a yellow, round, convex film-coated tablet with diameter of nucleus 10.3 mm.

The film-coated tablets are packed in PVC/PE/PVDC-Alu or oPa-Al-PVC/Al blisters.

The excipients are:

Tablet core - lactose monohydrate, hydroxypropylcellulose, croscarmellose sodium, sodium laurilsulphate, cellulose microcrystalline, magnesium stearate

Film coating – Hypromellose, lactose monohydrate, triacetin, titanium dioxide (E171), talc, iron oxide yellow (E172)

The different product strengths are fully dose proportional with regard to their composition including their film-coating.

II.2 Drug Substance

The active substance is tadalafil, an established active substance described in the European Pharmacopoeia (Ph.Eur.). The active substance is a white or almost white powder, which is practically insoluble in water. Tadalafil has two asymmetric carbons and shows isomerism. Several polymorphic forms of tadalafil are described. The drug substance is supplied as polymorphic Form I. Tadalafil is supplied by four different suppliers. For two suppliers the ASMF procedure is followed. For the other two suppliers a CEP has been provided.

The main objective of the Active Substance Master File (ASMF) procedure, commonly known as the European Drug Master File (EDMF) procedure, is to allow valuable confidential intellectual property or 'know-how' of the manufacturer of the active substance (ASM) to be protected, while at the same time allowing the applicant or marketing authorisation holder (MAH) to take full responsibility for the medicinal product, the quality and quality control of the active substance. Competent Authorities/EMA thus have access to the complete information that is necessary to evaluate the suitability of the use of the active substance in the medicinal product.

The CEP procedure means that under the official Certification Procedures of the EDQM of the Council of Europe, manufacturers or suppliers of substances for pharmaceutical use can apply for a certificate of suitability concerning the control of the chemical purity and microbiological quality of their substance according to the corresponding specific monograph, or the evaluation of reduction of Transmissible Spongiform Encephalopathy (TSE) risk, according to the general monograph, or both. This procedure is meant to ensure that the quality of substances is guaranteed and that these substances comply with the European Pharmacopoeia.

Manufacturing process

For the two CEPs no details on the manufacturing process have been included, which is acceptable. At the first ASMF holder, the manufacturing process of tadalafil consists of three synthetic steps followed by a purification step. The second ASMF holder applies a synthesis of four synthetic steps. Neither of them uses any class 1 organic solvents or heavy metal catalysts or reagents in the manufacturing process. The active substance has been adequately characterized and acceptable specifications have been adopted for the starting materials, solvents and reagents.

Quality control of drug substance

The drug substance specification is in line with the Ph.Eur., with additional requirements for residual solvents. The specification is acceptable in view of the route of synthesis and the various European guidelines. Batch analytical data demonstrating compliance with the drug substance specification have been provided for batches of each supplier.

Stability of drug substance

For the first ASMF holder, stability data have been provided on three full-scaled batches of active substance that were stored at 25°C/60% RH (12 months) and 40°C/75% RH (6 months).

For the second ASMF holder, stability data have been provided on three pilot scale batches stored at 30°C/65% RH (36 months) and 40°C/75% RH (6 months) and on another four pilot scaled and one full scaled batch that were stored at 30°C/65% RH (9-18 months).

For one of the CEP holders, stability data have been provided on four batches stored at 25°C/60% RH (12-18 months) and 40°C/75% RH (6 months). The second CEP holder provided stability data on three batches that were stored at 25°C/60% RH (36 months) and 40°C/75% RH (6 months).

The stability data of each supplier show no trends or changes in any of the tested parameters.

The MAH applies a retest period of 24 months for the active substance from all four sources when stored at a temperature not exceeding 25°C and a relative humidity not exceeding 65%. The proposed retest period and storage conditions are acceptable based on the presented stability data and the information provided on the CEPs.

II.3 Medicinal Product

Pharmaceutical development

The development of the product has been described, the choice of excipients is justified and their functions explained. The main development studies performed were the optimization of the formulation to achieve comparable dissolution profiles with the reference product and the performance of comparative dissolution studies in support of the bioequivalence (BE) study and to support a biowaiver of the additional 5 mg and 10 mg strengths. The 20 mg test batch that was used in the BE study versus the 20 mg strength of reference product was manufactured according to the finalized composition and manufacturing process. *In vitro* dissolution data demonstrate similar dissolution between the 20 mg BE study test batch versus two tablets of 10 mg and four tablets of 5 mg in pH 1.2, pH 4.5 and pH 6.8 dissolution media (without a surfactant). The MAH adequately justified that the 1 tablet to 1 tablet comparison between the 20 mg BE test batch and the additional strengths no similarity could be obtained in pH 1.2, 4.5 and 6.8 media due to the fact that sink conditions were not achieved and this effect was strength related.

Similarity in dissolution between the BE study test and reference batch was demonstrated in pH 4.5 and pH 6.8 dissolution medium, but was not confirmed in pH 1.2 dissolution medium. This was sufficiently justified.

The pharmaceutical development of the product has been adequately performed and a biowaiver of the 5 mg and 10 mg strengths was justified based on *in vitro* dissolution studies.

Manufacturing process

The main steps in the manufacturing process are wet granulation and drying, blending, tableting and film-coating. For the manufacture of the drug product micronized tadalafil is used. The manufacturing process has been adequately validated according to relevant European guidelines. Process validation data on the product has been presented for three pilot-scale batches of common blend that were compressed into lab and pilot scale batches of each strength. The product is manufactured using conventional manufacturing techniques. Process validation for full-scale batches will be performed post authorisation.

Control of excipients

Except for iron oxide yellow all excipients comply and are tested in accordance with their European Pharmacopoeia monographs. Iron oxide yellow complies with the purity criteria of Regulation 231/2012. The specifications are acceptable.

Quality control of drug product

The product specification includes tests for appearance, average weight, hardness, disintegration, water content, identity, dissolution, uniformity of dosage units, related substances, chiral purity, assay and microbial quality. Except for water content, related substances and assay the release and shelf-life requirements are identical. The specification is acceptable. The analytical methods have been adequately described and validated. Batch analytical data from the proposed production sites have been provided on two laboratory scale and two pilot-scale batches per strength, demonstrating compliance with the release specification.

Stability of drug product

Stability data on the product have been provided on three laboratory scale batches and two pilot-scale batches per strength that were stored at 25°C/60% RH (up to 24 months), 30°C/75% RH (up to 24 months) and 40°C/75% RH (up to 6 months). The conditions used in the stability studies are according to the ICH stability guideline. The batches were stored in PVC-PE-PVdC/Al-blisters and Al/Al-blisters. No clear trends or changes were seen in any of the tested parameters. A photostability study was performed, demonstrating that the product is photostable. Based on the presented stability data the claimed shelf-life of 30 months without any special storage requirements is justified.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies

For lactose monohydrate compliance with the Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via medicinal products has been satisfactorily demonstrated as well as for magnesium stearate for which a CEP has been provided.

II.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the member states consider that ZENAVIL 5 mg, 10 mg and 20 mg, film-coated tablets have a proven chemical-pharmaceutical quality. Sufficient controls have been laid down for the active substance and finished product.

The following post-approval commitments were made:

- The MAH committed to perform comparative dissolution profiles of the first three production batches per strength versus the 20 mg batch utilised in the BE study. None of these batches will be marketed unless comparative dissolution profiles are completed.
- The MAH committed to perform process validation on the first three production-scale batches of each strength according to the process validation scheme.
- The on-going stability studies will be prolonged, according to the testing protocol, until the planned completion of all studies (up to 36 months for the real time stability studies).
- The MAH committed to place the first three production batches per strength of drug product on long-term stability studies through the proposed shelf-life and accelerated studies for 6 months.

III. NON-CLINICAL ASPECTS

III.1 Ecotoxicity/environmental risk assessment (ERA)

Since ZENAVIL is intended for generic substitution, this will not lead to an increased exposure to the environment. An environmental risk assessment is therefore not deemed necessary.

III.2 Discussion on the non-clinical aspects

This product is a generic formulation of Cialis, which is available on the European market. Reference is made to the preclinical data obtained with the innovator product. A non-clinical overview on the pharmacology, pharmacokinetics and toxicology has been provided, which is based on up-to-date and adequate scientific literature. The overview justifies why there is no need to generate additional non-clinical pharmacology, pharmacokinetics and toxicology data. Therefore, the member states agreed that no further non-clinical studies are required.

IV. CLINICAL ASPECTS

IV.1 Introduction

Tadalafil is a well-known active substance with established efficacy and tolerability. A clinical overview has been provided, which is based on scientific literature. The overview justifies why there is no need to generate additional clinical data. Therefore, the member states agreed that no further clinical studies are required. The indications for both the innovator products Cialis and Adcirca are approved for ZENAVIL.

For this generic application, the MAH has submitted a bioequivalence study, which is discussed below.

IV.2 Pharmacokinetics

The MAH conducted a bioequivalence study in which the pharmacokinetic profile of the test product ZENAVIL 20 mg (Medochemie Limited, Cyprus) is compared with the pharmacokinetic profile of the reference product Cialis 20 mg, film-coated tablets (Eli Lilly Nederland B.V., the Netherlands).

The choice of the reference product in the bioequivalence study is justified as the reference product was authorised in the EU through a centralized procedure.

The formula and preparation of the bioequivalence batch is identical to the formula proposed for marketing.

Biowaiver

The bioequivalence study has been conducted with the 20 mg strength. The following criteria for extrapolation to the lower strengths have been fulfilled:

- the formulations are dose proportional
- the formulations are manufactured by the same manufacturer and manufacturing process
- tadalafil shows linear pharmacokinetics over the therapeutic dose range of 2.5 – 20 mg
- comparable dissolution has been shown at pH 1.2, 4.5 and 6.8 using the same dose.

As such the results obtained in the bioequivalence study with the 20 mg can be extrapolated to the 5 and 10 mg tablet.

Bioequivalence studies

Design

A single-dose, randomised, two-period, two-treatment, two-sequence, crossover bioequivalence study was carried out under fasted conditions in 26 healthy male subjects, aged 19-36 years. Each subject received a single dose (20 mg) of one of the 2 tadalafil formulations. The tablet was orally administered with 240 ml water after an overnight fast. Fasting was continued for 4 hours after dosing. There were 2 dosing periods, separated by a washout period of 10 days.

Blood samples were collected pre-dose and at 0.167, 0.33, 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 6, 8, 12, 24, 48 and 72 hours after administration of the products.

A single dose, crossover study under fasting conditions to assess bioequivalence for tadalafil is considered adequate. Tadalafil can be taken with or without food.

Analytical/statistical methods

The analytical method has been adequately validated and is considered acceptable for analysis of the plasma samples. The methods used in this study for the pharmacokinetic calculations and statistical evaluation are considered acceptable.

Results

One subject dropped out before any study drug administration and another subject was withdrawn at admission in period II due to a positive result for the illicit drug tests. Twenty-four subjects completed the study and were included in the analysis.

Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean \pm SD, t_{max} (median, range)) of tadalafil under fasted conditions.

Treatment N=24	AUC _{0-t} ng.h/ml	AUC _{0-∞} ng.h/ml	C _{max} ng/ml	t _{max} h	t _{1/2} h
Test	6999 \pm 2647	8351 \pm 3091	293 \pm 62	1.75 (0.75 – 4.5)	22 \pm 6
Reference	6770 \pm 1816	8013 \pm 2311	278 \pm 54	2.0 (0.50 – 4.5)	22 \pm 6

*Ratio (90% CI)	0.99 (0.89 - 1.10)	--	1.05 (0.97 - 1.13)	--	--
CV (%)	21.3	--	14.7	--	--
AUC_{0-∞} area under the plasma concentration-time curve from time zero to infinity AUC_{0-t} area under the plasma concentration-time curve from time zero to t hours C_{max} maximum plasma concentration t_{max} time for maximum concentration t_{1/2} half-life CV coefficient of variation					

**In-transformed values*

Conclusion on bioequivalence study

The 90% confidence intervals calculated for AUC_{0-t} and C_{max} are within the bioequivalence acceptance range of 0.80–1.25. Based on the submitted bioequivalence study ZENAVIL 20 mg is considered bioequivalent with Cialis 20 mg, film-coated tablets.

The MEB has been assured that the bioequivalence study has been conducted in accordance with acceptable standards of Good Clinical Practice (GCP, see Directive 2005/28/EC) and Good Laboratory Practice (GLP, see Directives 2004/9/EC and 2004/10/EC).

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 ZENAVIL.

Summary of the RMP

Safety concern	Proposed pharmacovigilance activities (routine and additional)	Proposed risk minimisation activities (routine)
Important identified risks		
Priapism	Routine PV	SmPC section 4.4 and 4.8
Hypotension/Increased Hypotensive Effect	Routine PV	SmPC section 4.3, 4.4, 4.5 and 4.8
Important potential risks		
Nonarteritic Anterior Ischemic Optic Neuropathy (NAION)	Routine PV	SmPC section 4.3, 4.4 and 4.8
Sudden Hearing Loss	Routine PV	SmPC section 4.8
For women with PAH: Increased Uterine Bleeding (including menorrhagia, metrorrhagia, menometrorrhagia and vaginal haemorrhage)	Routine PV	SmPC section 4.8
Missing information (for Once-a-Day ED and BPH)		
Characterization of adverse events in elderly patients (≥65 years)	Routine PV	N.A.

The member states agreed that routine pharmacovigilance activities and routine risk minimisation measures are sufficient for the risks and areas of missing information.

IV.4 Discussion on the clinical aspects

For this authorisation, reference is made to the clinical studies and experience with the innovator product Cialis. The indications approved for ZENAVIL, listed on page 2 of this report, correspond to those of both Cialis and Adcirca. No new clinical studies were conducted. The MAH demonstrated through a bioequivalence study that the pharmacokinetic profile of the product is similar to the pharmacokinetic profile of this reference product. Risk management is adequately addressed. This generic medicinal product can be used instead of the reference product.

V. USER CONSULTATION

The package leaflet (PL) has been compared to the reference product Cialis, and for the indication Pulmonary Arterial Hypertension (PAH) to the reference product Adcirca. Both are centrally authorised products. The MAH has combined the two texts into one combined text covering the three strengths and the three indications into one PL.

The leaflet reflects the results of testing with patients to make sure it meets their needs and can enable the patient to use the medicinal product safely and effectively. The readability of the PIL has been assessed in an appropriate way, using methodology in line with the readability guideline. The RMS considers that the layout and design of this leaflet are acceptable.

Overall, the results of user testing 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

ZENAVIL 5 mg, 10 mg and 20 mg, film-coated tablets have a proven chemical-pharmaceutical quality and are generic forms of Cialis 5 mg, 10 mg and 20 mg tablets. Cialis is a well-known medicinal product with an established favourable efficacy and safety profile.

Bioequivalence has been shown to be in compliance with the requirements of European guidance documents.

The Board followed the advice of the assessors.

There was no discussion in the CMD(h). Agreement between member states was reached during a written procedure. The member states, on the basis of the data submitted, considered that essential similarity has been demonstrated for ZENAVIL 5 mg, 10 mg and 20 mg with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 11 December 2014.

STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

Scope	Procedure number	Type of modification	Date of start of the procedure	Date of end of the procedure	Approval/ non approval	Assessment report attached