CBG MEB

Public Assessment Report

Scientific discussion

Gerocilan 2.5 mg, 5 mg, 10 mg and 20 mg film-coated tablets

(tadalafil)

NL/H/3670/001-004/DC

Date: 10 April 2017

This module reflects the scientific discussion for the approval of Gerocilan 2.5 mg, 5 mg, 10 mg and 20 mg film-coated tablets. The procedure was finalised on 2 November 2016. For information on changes after this date please refer to the 'steps taken after finalisation' at the end of this PAR.

List of abbreviations

CEP	Certificate of Suitability to the monographs of the European Pharmacopoeia
CMD(h)	Coordination group for Mutual recognition and Decentralised procedure for human medicinal products
CMS	Concerned Member State
EDQM	European Directorate for the Quality of Medicines
EEA	European Economic Area
ERA	Environmental Risk Assessment
ICH	International Conference of Harmonisation
MAH	Marketing Authorisation Holder
Ph.Eur.	European Pharmacopoeia
PL	Package Leaflet
RH	Relative Humidity
RMP	Risk Management Plan
SmPC	Summary of Product Characteristics
TSE	Transmissible Spongiform Encephalopathy

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for Gerocilan 2.5 mg, 5 mg, 10 mg and 20 mg film-coated tablets from G.L. Pharma GmbH.

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 the signs and symptoms of benign prostatic hyperplasia in adult males (only the 5 mg strength).

Gerocilan is not indicated for use by women.

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 2.5 mg, 5 mg, 10 mg and 20 mg film-coated 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 Austria, Bulgaria, Czech Republic, Hungary, Romania and Slovakia.

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

II. QUALITY ASPECTS

II.1 Introduction

Gerocilan is a biconvex, film-coated tablet in four strengths:
- The 2.5 mg strength is yellow-orange coloured, caplet shaped, debossed with “T 2” on one side and plain on the other side.
- The 5 mg strength is yellow coloured, caplet shaped, debossed with “T 5” on one side and plain on the other side.
- The 10 mg strength is yellow coloured, caplet shaped, debossed with “T 10” on one side and plain on the other side.
- The 20 mg strength is yellow coloured, caplet shaped, debossed with “T 20” on one side and plain on the other side.

Each film-coated tablet contains 2.5 mg, 5 mg, 10 mg or 20 mg tadalafil.

The film-coated tablets are packed in PVC/PVDC/Aluminium blisters.

The excipients are:
Tablet core: anhydrous lactose, croscarmellose sodium, sodium laurilsulfate, hydroxylpropylcellulose (E463), polysorbate 80 and magnesium stearate.
Tablet coating: hypromellose 2910 (E464), lactose monohydrate, titanium dioxide (E171), triacetin, talc (E553b), iron oxide yellow (E172), iron oxide red (E172) (only the 2.5 mg strength) and iron oxide black (E172) (only the 10 mg strength).

The 5 mg and 10 mg tablet cores are fully dose proportional with the 20 mg product.

II.2 Drug Substance

The active substance is tadalafil, an established active substance described in the European Pharmacopoeia (Ph.Eur.). Tadalafil is a white or almost white powder. It is practically insoluble in water, freely soluble in dimethyl sulfoxide and slightly soluble in methylene chloride. Tadalafil exhibits polymorphism. The manufacturer consistently produces the crystalline form 1.

The CEP procedure is used for the active substance. 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 Ph.Eur.

Manufacturing process
A CEP has been submitted; therefore no details on the manufacturing process have been included.

Quality control of drug substance
The active substance specification is considered adequate to control the quality. It meets the requirements of the monograph in the Ph.Eur. and additional requirements of the CEP, including a test for particle size. Batch analytical data demonstrating compliance with this specification have been provided for three batches.

Stability of drug substance
The active substance is stable for 60 months when stored under the stated conditions. Assessment thereof was part of granting the CEP and has been granted by the EDQM.

II.3 Medicinal Product

Pharmaceutical development
The product is an established pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines. The choice of excipients is justified and their functions explained. The main development studies were the characterisation of the reference product, optimisation of the excipient levels in the formulation and the performance of comparative in vitro dissolution studies complementary to the in vivo bioequivalence studies and in order to justify a biowaiver for the 5 mg and 10 mg product strengths. The choices of the packaging and manufacturing are justified. The pharmaceutical development of the product has been adequately performed.

Bioequivalence studies under fed and fasted conditions have been performed with the 2.5 mg strength as well as the 20 mg strength versus the respective reference product strengths. The batches used in the bioequivalence studies were manufactured according to the finalised formulation and manufacturing process. Similarity in dissolution was confirmed between the 20 mg test and reference batch in pH 1.2, 4.5 and 6.8 media and also between the 2.5 mg test and reference batch in pH 1.2 and pH 4.5 media. Similarity between the 2.5 mg batches in pH 6.8 could not be confirmed. In this case the results of the *in vivo* studies prevail.

The biowaiver for the 5 mg and 10 mg strengths is supported by the results of comparative *in vitro* dissolution studies. Although similarity in dissolution could not be confirmed in pH 1.2, 4.5 and 6.8 dissolution media when comparing the 5 mg or 10 mg strength with the bioequivalence study test strengths, the MAH has sufficiently demonstrated that this discrepancy was due to poor dissolution of the active substance and was not drug product related. Similarity was then adequately demonstrated by comparing the 5 mg and 10 mg strengths with the 20 mg bioequivalence study test batch at similar dose levels.

Manufacturing process
The main steps of the manufacturing process are dry mixing, wet mixing/granulation, drying, sizing, blending, lubrication, compression and film-coating. The manufacturing process has been adequately validated according to relevant European guidelines. Process validation data on the product has been presented for three pilot scaled batches per strength. The product is manufactured using conventional

manufacturing techniques. Process validation for full scaled batches will be performed post authorisation.

Control of excipients
The excipients comply with their Ph.Eur. monographs or in-house specification. These specifications are acceptable.

Quality control of drug product
The finished product specifications are adequate to control the relevant parameters for the dosage form. The specification includes tests for appearance, identification, water content, average weight, disintegration, dissolution, uniformity of dosage units, assay, related substances, residual acetone and microbiological quality. Except for water content and total impurities, the release and shelf-life requirements are identical. Limits in the specification have been justified and are considered appropriate for adequate quality control of the product.
Satisfactory validation data for the analytical methods have been provided. Batch analytical data from three pilot scale batches per strength from the proposed production site have been provided, demonstrating compliance with the specification.

Stability of drug product
Stability data on the product has been provided on three pilot scale batches per strength stored at 25°C/60% RH (18 months) and 40°C/75% RH (6 months). The conditions used in the stability studies are according to the ICH stability guideline. The batches were stored in the proposed packaging. All parameters remained within the set limits. Results of a formal photostability study showed that the drug product was not sensitive to light exposure when directly exposed. Based on the presented stability data, the proposed shelf-life of 30 months without any special storage requirements is justified.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies
Anhydrous lactose and lactose monohydrate are the only materials of animal origin included in the drug product. Scientific data and/or certificates of suitability issued by the EDQM have been provided and compliance with the Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via medicinal products has been satisfactorily demonstrated.

II.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the member states consider that Gerocilan has a proven chemical-pharmaceutical quality. Sufficient controls have been laid down for the active substance and finished product.

No post-approval commitments were made.

III. NON-CLINICAL ASPECTS

III.1 Ecotoxicity/environmental risk assessment (ERA)

Since Gerocilan 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.

For this generic application, the MAH has submitted four bioequivalence studies, which are discussed below.

IV.2 Pharmacokinetics

Bioequivalence studies
The MAH conducted four bioequivalence studies in which the pharmacokinetic profile of the test product Gerocilan (G.L. Pharma GmbH, Austria) is compared with the pharmacokinetic profile of the reference product Cialis (Eli Lilly, UK):

- A single dose bioequivalence study with the 2.5 mg tablet under fasting conditions.
- A single dose bioequivalence study with the 2.5 mg tablet under fed conditions.
- A single dose bioequivalence study with the 20 mg tablet under fasting conditions.
- A single dose bioequivalence study with the 20 mg tablet under fed conditions.

The choice of the reference product
The choice of the reference product in the bioequivalence studies has been justified. The formula and preparation of the bioequivalence batches are identical to the formulas proposed for marketing.

Biowaiver
The following criteria for extrapolation of the results obtained in the bioequivalence studies for the 20 mg to the 5 mg and 10 mg tablets have been fulfilled:

- The formulations are manufactured by the same manufacturer and manufacturing process.
- The 5 mg, 10 mg and 20 mg formulations are dose-proportional.
- Tadalafil shows linear pharmacokinetics over the therapeutic dose range of 2.5 - 20 mg
- Sink conditions could not be reached, as tadalafil is a low solubility drug. Dissolution data comparing the 5 mg tablet against the 5 mg Cialis tablet and the 10 mg tablet against the 10 mg Cialis tablet, showed comparable dissolution (f_2>50). In addition, dissolution data without the use of sodium dodecyl sulphate (SLS) at a pH 1.2, 4.5 and 6.8 have been provided showing comparable dissolution using the same dose (4x 5mg vs. 2x 10mg vs. 1x 20mg). This is acceptable.

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

Bioequivalence study 1: single dose study with the 2.5 mg tablet under fasting conditions
Design
An open-label, balanced, randomised, single-dose, two-treatment, two-sequence, two-period, crossover bioequivalence study was carried out under fasted conditions in 38 healthy male subjects, aged 20-44 years. Each subject received a single dose (2.5 mg) of one of the 2 tadalafil formulations. The tablet was orally administered with 240 ml water after an overnight fast. There were 2 dosing periods, separated by a washout period of 21 days.

Blood samples were collected pre-dose and at 0.33, 0.67, 1, 1.33, 1.67, 2, 2.33, 2.67, 3, 3.33, 3.67, 4, 4.5, 5, 6, 8, 10, 12, 16, 24, 36, 48 and 72 hours after administration of the products.

The design of the study is acceptable. Tadalafil can be taken with or without food, according to the SmPC.

Results
One subject withdrew consent of his own accord before check-in of period II due to a personal problem. Therefore, 37 subjects were eligible for pharmacokinetic analysis.

Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of 2.5 mg tadalafil under fasted conditions.

Treatment N=37	AUC_{0-t} ng.h/ml	C_{max} ng/ml	t_{max} h	$t_{1/2}$ h
Test	1718 ± 624	76 ± 19	1.67 (0.67 – 6.0)	35 ± 13
Reference	1683 ± 469	79 ± 17	1.67 (0.33 – 5.0)	34 ± 16
***Ratio (90% CI)**	0.99 (0.91 - 1.06)	0.95 (0.90 - 1.00)	--	--
CV (%)	17.7	13.9	--	--

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

**ln-transformed values*

Two subjects did not report for the 72 hour ambulatory sample in period I and four subjects did not report for the 72 hour ambulatory sample in period II. For these subjects, the primary pharmacokinetic parameter AUC_{0-72h} could not be estimated precisely due to the missed 72 hour blood draw. These subjects were identified before bio-analysis and their data was excluded from the statistical analysis of AUC_{0-72h}. However, these subjects were included in the statistical calculations of C_{max}. This is considered acceptable.

Bioequivalence study 2: single dose study with the 2.5 mg tablet under fed conditions
Design
An open-label, balanced, randomised, single-dose, two-treatment, two-sequence, two-period, crossover bioequivalence study was carried out under fed conditions in 38 healthy male subjects, aged 18-41 years. Each subject received a single dose (2.5 mg) of one of the 2 tadalafil formulations. The tablet was orally administered with 240 ml water 30 minutes after the start of intake of a high fat, high caloric breakfast. There were 2 dosing periods, separated by a washout period of 21 days.

Blood samples were collected pre-dose and at 0.33, 0.67, 1, 1.33, 1.67, 2, 2.33, 2.67, 3, 3.33, 3.67, 4, 4.5, 5, 6, 8, 10, 12, 16, 24, 36, 48 and 72 hours after administration of the products.

The design of the study is acceptable. Tadalafil can be taken with or without food, according to the SmPC.

Results
One subject was withdrawn due to an adverse event and three subjects did not report for check-in for period II. Therefore, 34 subjects were eligible for pharmacokinetic analysis.

Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of 2.5 mg tadalafil under fed conditions.

Treatment N=34	AUC_{0-t} ng.h/ml	C_{max} ng/ml	t_{max} h	$t_{1/2}$ h
Test	1574 ± 558	61 ± 11	3.0 (1.0 – 5.0)	33 ± 15
Reference	1486 ± 478	59 ± 15	3.5 (1.0 – 5.0)	32 ± 12

***Ratio (90% CI)**	1.05 (0.99 - 1.12)	1.06 (1.00 - 1.13)	--	--
CV (%)	14.6	14.8	--	--

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

**ln-transformed values*

Bioequivalence study 3: single dose study with the 20 mg tablet under fasting conditions

Design

An open-label, balanced, randomised, single-dose, two-treatment, two-sequence, two-period, crossover, oral bioequivalence study was carried out under fasting conditions in 38 healthy male subjects, aged 19-43 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. There were 2 dosing periods, separated by a washout period of 21 days.

Blood samples were collected pre-dose and at 0.33, 0.67, 1, 1.33, 1.67, 2, 2.33, 2.67, 3, 3.33, 3.67, 4, 4.5, 5, 6, 8, 10, 12, 16, 24, 36, 48 and 72 hours after administration of the products.

The design of the study is acceptable. Tadalafil can be taken with or without food, according to the SmPC.

Results

One subject was withdrawn due to an adverse event in period I. Therefore, 37 subjects were eligible for pharmacokinetic analysis.

Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of 20 mg tadalafil under fasting conditions.

Treatment N=37	**AUC_{0-t}** ng.h/ml	**C_{max}** ng/ml	**t_{max}** h	**$t_{1/2}$** h
Test	11584 ± 3979	358 ± 91	3.0 (0.67 – 24.0)	35 ± 19
Reference	10848 ± 3122	391 ± 104	2.67 (0.67 – 4.5)	35 ± 19
***Ratio (90% CI)**	1.06 (0.96 - 1.17)	0.92 (0.83 - 1.01)	--	--
CV (%)	22.4	25.6	--	--

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

**ln-transformed values*

Eight subjects did not report for the 72 hour ambulatory sample in period I and two subjects did not report for the 72 hour ambulatory sample in period II. For these subjects, the primary pharmacokinetic parameter AUC_{0-72h} could not be estimated precisely due to the missed 72 hour blood draw. These subjects were identified before bio-analysis and their data was excluded from the statistical analysis of AUC_{0-72h}. However, these subjects were included in the statistical calculations of C_{max}. This is considered acceptable.

Bioequivalence study 4: single dose study with the 20 mg tablet under fed conditions

Design

An open-label, balanced, randomised, single-dose, two-treatment, two-sequence, two-period, crossover bioequivalence study was carried out under fed conditions in 38 healthy male subjects,

aged 19-42 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 30 minutes after the start of intake of a high fat, high caloric breakfast. There were 2 dosing periods, separated by a washout period of 21 days.

Blood samples were collected pre-dose and at 0.33, 0.67, 1, 1.33, 1.67, 2, 2.33, 2.67, 3, 3.33, 3.67, 4, 4.5, 5, 6, 8, 10, 12, 16, 24, 36, 48 and 72 hours after administration of the products.

The design of the study is acceptable. Tadalafil can be taken with or without food, according to the SmPC.

Results
One subject was withdrawn due to an adverse event and two subjects did not report for check-in for period II. Therefore, 35 subjects were eligible for pharmacokinetic analysis.

Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of 20 mg tadalafil under fed conditions.

Treatment N=35	**AUC_{0-t}** ng.h/ml	**C_{max}** ng/ml	**t_{max}** h	**$t_{1/2}$** h
Test	11914 ± 2968	448 ± 102	4.0 (1.67 – 5.0)	28 ± 13
Reference	12232 ± 3384	457 ± 86	3.67 (1.67 – 8.0)	29 ± 13
***Ratio (90% CI)**	0.98 (0.91 - 1.06)	0.97 (0.92 - 1.04)	--	--
CV (%)	15.6	15.5	--	--

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

**ln-transformed values*

Nine subjects did not report for the 72 hour ambulatory sample in period I and two subjects did not report for the 72 hour ambulatory sample in period II. For these subjects, the primary pharmacokinetic parameter AUC_{0-72h} could not be estimated precisely due to the missed 72 hour blood draw. These subjects were identified before bio-analysis and their data was excluded from the statistical analysis of AUC_{0-72h}. However, these subjects were included in the statistical calculations of C_{max}. This is considered acceptable.

Conclusion on bioequivalence studies
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 studies Gerocilan is considered bioequivalent with Cialis.

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 Gerocilan.

Summary table of safety concerns as approved in RMP:

Important identified risks	• Priapism • Hypotension, increased hypotensive

	effect
Important potential risks	• Non-arteritic anterior ischaemic optic neuropathy (NAION) • Sudden hearing loss
Missing information	• Use in older patients (≥65 years)

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. No new clinical studies were conducted. The MAH demonstrated through bioequivalence studies 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) of the 5 mg strength 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 test consisted of: a pilot test with two participants, followed by two rounds with ten participants each. The questions covered the following areas sufficiently: traceability, comprehensibility and applicability. The results show that the PL meets the criteria for readability as set out in the Guideline on the readability of the label and PL of medicinal products for human use.

The 5 mg strength has an additional indication (benign prostatic hyperplasia) in comparison to the other strengths. Bridging for content is acceptable, since the differences in the strengths are related to the additional indication for the 5 mg strength. The MAH demonstrated that the design and lay-out of daughter PLs for the 2.5 mg and 20 mg strengths is identical to that of the PL of the 5 mg strength tested. The MAH also provided a bridging report showing that the content, design and layout of the PL of the 10 mg strength is identical to the PL of the 20 mg strength, other than the differences in strength.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Gerocilan 2.5 mg, 5 mg, 10 mg and 20 mg film-coated tablets have a proven chemical-pharmaceutical quality and are generic forms of Cialis 2.5 mg, 5 mg, 10 mg and 20 mg film-coated 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 Gerocilan with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 2 November 2016.

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