COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Ligion 5 mg, 10 mg, and 20 mg, soft capsules

(tadalafil)

NL/H/4293/001-003/DC

Date: 20 August 2019

This module reflects the scientific discussion for the approval of Ligion 5 mg, 10 mg, and 20 mg, soft capsules. The procedure was finalised at 10 April 2019. 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
PAH	Pulmonary Arterial Hypertension
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 Ligion 5 mg, 10 mg, and 20 mg, soft capsules from GAP S.A.

Ligion 5 mg, 10 mg and 20 mg 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.

Ligion 5 mg is indicated for treatment of the signs and symptoms of benign prostatic hyperplasia in adult males.

Ligion 20 mg is indicated for treatment of pulmonary arterial hypertension (PAH) classified as WHO functional class II and III, to improve exercise capacity (see SmPC section 5.1). Efficacy has been shown in idiopathic PAH (IPAH) and in PAH related to collagen vascular disease.

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 state (CMS) involved in this procedure was Greece.

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 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 submitted a similarity assessment against all products that hold an orphan designation and have a marketing authorisation in the EU, and that currently benefit from market exclusivity. The conclusion that tadalafil is not similar to the authorised orphan medicinal product Opsumit and Adempas, is endorsed

II. QUALITY ASPECTS

II.1 Introduction

Ligion is a white/yellow oval soft capsule in three strengths.

Each soft capsule contains 5 mg, 10 mg or 20 mg tadalafil.

The soft capsules are packed in PVC/PE/PVdC-Aluminium blisters.

The excipients are:
Capsule filling - soya-bean oil refined, glycerol monocaprylocaprate, macrogolglycerol ricinoleate, lauroyl macrogolglycerides, poloxamers, butylhydroxyanisole
Capsule shell – gelatin, glycerol, titanium dioxide (E171)

The three strengths are dose proportional.

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, slightly soluble in methylene chloride and is slightly hygroscopic. Tadalafil has different polymorphs and has two chiral centres. Tadalafil produced by manufacturer corresponds to polymorphic form I (form A) and to isomer R,R (cis isomer). The trans isomer (S,R) can occur too.

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 and meets the requirements of the monograph in the Ph.Eur. The specification also includes tests for microbiological purity and particle size distribution. Batch analytical data demonstrating compliance with this specification have been provided for three full scale batches.

Stability of drug substance

The active substance is stable for three years 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. In the formulation development studies the following items have been investigated: particle size and solubility in oils of drug substance, the dissolution profile of tadalafil in different excipients combinations, the choice of the oil components of the capsule fill and their proportions, the surfactant properties of the chosen mixture, the need and quantity of antioxidant and thickener additives. The MAH also performed a study to substantiate the needed quantity of antioxidant and discussed the safety of the chosen antioxidant. Since the chosen antioxidant is in the minimal quantity needed, it does not pone any safety concern in view of the EFSA acceptable daily intake and is diffusely used in the food industry, the argumentation is acceptable. The MAH further discussed the general advantages of soft capsules for patients.
Adequate information about manufacturing process development has been provided, including rationale for the chosen parameters and their criticality.
The development of the test method for the routine QC-dissolution test and its discriminatory power has been adequately discussed.
The dissolution acceptance limit used at release and in stability studies is adequate, based on the dissolution profile of the biobatch in the proposed test conditions.

The results of two bioequivalence studies have been submitted. The similarity of the dissolution profile of the biobatches used in the bioequivalence studies and with a batch of each of the other two strengths (in view of a biowaiver of strengths) has been investigated in line with the guideline on investigation of Bioequivalence, Annex III. This was performed only against one of the two batches of reference product used in the bioequivalence studies, because the other was expired. As the results of the bioequivalence studies *in vivo* prevail, this is acceptable and this comparison is considered adequate. The comparisons supportive to the biowaiver of strength are adequately performed and in all cases the f2 value is above 50. The biowaiver of strengths is acceptable from a pharmaceutical point of view.

Manufacturing process

Sufficient details about the manufacturing process, process controls and intermediates are provided. The manufacturing process consists of mixing ingredients up to the internal fill mix, preparation of gelatin mass, encapsulation, and packaging. The fill mix and the bulk capsules are identified as intermediates. Holding times are adequately substantiated. The expiry date will be calculated in line with the Note for guidance on start of shelf-life of the finished dosage form.
A complete process validation protocol has been proposed, which addresses critical quality attributes of each step of the manufacture. The validation results for eleven batches over

the three proposed strengths and the minimal and maximal commercial batch size are presented. The MAH commits to perform further process validation up to three maximal commercial size batches of 5 mg and 20 mg. For the 10 mg strength a bracketing approach is applied and only one maximal size batch will be validated. The bracketing approach is acceptable and the above described validation approach is acceptable.

Control of excipients

For all the excipients reference is made to the Ph.Eur. monograph for analysis methods, specifications, justifications and validation. Sufficient documentation is enclosed for each excipient. 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, uniformity of mass of content and of the whole capsule, uniformity of dosage units, assay, disintegration, dissolution, related substances, and microbial purity. 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 eleven full scale batches of the different strengths from the proposed production site have been provided, demonstrating compliance with the specification.

Stability of drug product

Results are available up to 24 months at long term and intermediate conditions and up to 6 months at accelerated conditions for at least one batch per strength. For the batches produced at the maximal proposed commercial batch size results up to 12 months are available. The available results comply with the proposed specification and show no significant trend. Since the results of the accelerated studies showed no significant change, a temperature storage condition is not needed. A photostability study has been performed in line with requirements in the Note for Guidance on the photostability testing of new active substances and medicinal products (ICH Q1B). No significant change has been observed, except for a slight increase in disintegration time for the directly exposed capsules, which is most likely due to exposure to moisture.
On basis of the data submitted, a shelf life was granted of 36 months. The labelled storage conditions are “Store in the original blister in order to protect from moisture”.

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

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 Ligion 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 Ligion 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 two bioequivalence studies, which are discussed below.

IV.2 Pharmacokinetics

The MAH conducted two bioequivalence studies in which the pharmacokinetic profile of the test product Ligion 20 mg soft capsules (GAP S.A., Greece) 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 studies has been justified. The formula and preparation of the bioequivalence batch is identical to the formula proposed for marketing.

The basis of the bioequivalence studies is justified because Cialis and Ligion have the same qualitative and quantitative composition in active substances and both products are oral products for immediate release (Cialis is a film-coated tablet and Ligion is a soft capsule).

Biowaiver

The MAH investigated the 20 mg capsule in the bioequivalence studies and was granted a biowaiver for the lower strengths 5 mg and 10 mg, by fulfilling the following conditions:

- The pharmaceutical products are manufactured by the same manufacturing process
- The qualitative composition of the different strengths is the same
- The composition of the strengths are quantitatively proportional, i.e. the ratio between the amount of each excipient to the amount of active substance is the same for all strengths
- Appropriate *in vitro* dissolution data confirm the adequacy of waiving additional in vivo bioequivalence testing

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.

Bioequivalence studies

Bioequivalence study under fasted conditions

Design

A single-dose, randomised, two-period, two-treatment, two-sequence, crossover bioequivalence study was carried out under fasted conditions in 43 healthy male subjects, aged 19-47 years. Each subject received a single dose (20 mg) of one of the two tadalafil formulations. The tablet was orally administered after an overnight fast of at least ten hours. There were two dosing periods, separated by a washout period of 13 days.

Blood samples were collected at 0:10, 0:20, 0:30, 1:00, 1:30, 2:00, 2:30, 3:00, 3:30, 4:00, 4:30, 5:00, 8:00, 12:00, 24:00, 48:00 and 72:00 hours after administration of the products.

The design of the study is acceptable. The wash-out of 13 days is long enough considering the elimination half-life. The sampling period is long enough and the sampling scheme is adequate to estimate relevant parameters. Studies were performed under both fasted and fed conditions, which is appropriate.

Results
32 subjects were eligible for pharmacokinetic analysis.

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

Treatment N=32	**AUC_{0-t}** (ng.h/ml)	**C_{max}** (ng/ml)	**t_{max}** (h)
Test	7482 ± 2393	319.7 ± 75.1	2 (0.5 - 4.5)
Reference	7540 ± 2284	340.8 ± 68.9	2 (0.5 - 5)
***Ratio (90% CI)**	0.99 (0.94 - 1.04)	0.93 (0.87 - 0.99)	--
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			

**ln-transformed values*

Bioequivalence study under fed conditions
Design
A single-dose, randomised, two-period, two-treatment, two-sequence, crossover bioequivalence study was carried out under fed conditions in 38 healthy male subjects, aged 21-53 years. Each subject received a single dose (20 mg) of one of the two tadalafil formulations. The tablet was orally administered 30 minutes after the start of a standard high-fat breakfast. There were two dosing periods, separated by a washout period of 10 days.

Blood samples were collected at 0:10, 0:20, 0:30, 1:00, 1:30, 2:00, 2:30, 3:00, 3:30, 4:00, 4:30, 5:00, 8:00, 12:00, 24:00, 48:00 and 72:00 hours after administration of the products.

The design of the study is acceptable. The wash-out of 10 days is long enough. Also the sampling period is long enough and the sampling scheme is adequate to estimate relevant parameters. Studies were performed under both fasted and fed conditions, which is appropriate.

Results
32 subjects were eligible for pharmacokinetic analysis.

Table 2. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of tadalafil under fed conditions.

Treatment N=32	**AUC_{0-t} (ng.h/ml)**	**C_{max} (ng/ml)**	**t_{max} (h)**
Test	9422 ± 4353	465.0 ± 119.7	1.5 (1.0 - 4.5)
Reference	9054 ± 3054	413.8 ± 97.3	2.5 (1.0 - 12.0)
***Ratio (90% CI)**	1.01 0.95 - 1.06	1.12 1.06 - 1.19	--
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			

**ln-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 studies Ligion is considered bioequivalent with Cialis.

The MEB has been assured that the bioequivalence studies have 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 Ligion.

Table 3. Summary table of safety concerns as approved in RMP

Important identified risks	• Prolonged and painful erection (priapism(• Low blood pressure (hypotension/ increased hypotensive effect) • Serious cardiovascular events
Important potential risks	• Non-arteritic anterior ischaemic optic neuropathy (NAION) • Sudden hearing loss • Increased uterine bleeding
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 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 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 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.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Ligion 5 mg, 10 mg, and 20 mg soft capsules has a proven chemical-pharmaceutical quality and is a generic form of Cialis 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 Ligion with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 10 April 2019.

STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

Procedure number*	Scope	Product Information affected	Date of end of procedure	Approval/ non approval	Summary/ Justification for refuse