COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

# Public Assessment Report

# Scientific discussion

# Lafaval 20 mg film-coated tablets

# (tadalafil)

# NL/H/5573/001/DC

# Date: 30 July 2024

**This module reflects the scientific discussion for the approval of Lafaval 20 mg film-coated tablets. The procedure was finalised on 12 July 2023. For information on changes after this date please refer to the 'steps taken after finalisation' at the end of this PAR.**

# List of abbreviations

| | |
|---|---|
| ASMF | Active Substance Master File |
| CEP | Certificate of Suitability to the monographs of the European Pharmacopoeia |
| CHMP | Committee for Medicinal Products for Human Use |
| CMD(h) | Coordination group for Mutual recognition and Decentralised procedure for human medicinal products |
| CMS | Concerned Member State |
| EDMF | European Drug Master File |
| EDQM | European Directorate for the Quality of Medicines |
| EEA | European Economic Area |
| EMA | European Medicines Agency |
| 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 |
| RMS | Reference Member State |
| 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 Lafaval 20 mg film-coated tablets, from Genepharm S.A.

The product is indicated in adults for the treatment of pulmonary arterial hyper-tension (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 up-to-date indications and posology is given in the SmPC.

The marketing authorisation has been granted pursuant to Article 10(1) of Directive 2001/83/EC, which concerns a generic application.

In this decentralised procedure, essential similarity is proven between the new product and the innovator product Adcirca 20 mg film-coated tablets (EU/1/08/476) which is centrally registered since 1 October 2008. The first marketing authorisation for tadalafil in the European Union was granted on 12 November 2002 via the centralised procedure for the treatment of erectile dysfunction in adult males; the authorisation was granted under the brand name Cialis 20 mg film-coated tablets by Eli Lilly Nederland B.V. On 1 October 2008, a new centralised marketing authorisation was granted, under the brand name Tadalafil Lilly 20 mg film-coated tablets, as an informed consent application of Cialis 20 mg film-coated tablets. Tadalafil Lilly 20 mg film-coated tablets was then renamed to Adcirca 20 mg film-coated tablets and also a variation was submitted for changing the therapeutic indication of Adcirca from erectile dysfunction to the treatment of pulmonary arterial hypertension (PAH).

The concerned member state (CMS) involved in this procedure was Greece.

Similarity assessment

Having considered the arguments presented by the MAH and with reference to Article 8 of Regulation (EC) No 141/2000, Lafaval is considered not similar (as defined in Article 3 of Commission Regulation (EC) No. 847/2000) to Opsumit or Adempas. During this procedure the marketing exclusivity of Adempas expired.

Therefore, with reference to Article 8 of Regulation (EC) No. 141/2000, the existence of any market exclusivity for Opsumit in the treatment of pulmonary arterial hypertension does not prevent the granting of the marketing authorisation of Lafaval.

# II. QUALITY ASPECTS

## II.1 Introduction

Lafaval is a yellow coloured, caplet shaped, biconvex, film-coated tablet, debossed with “T 20” on one side and plain on the other side. Each film-coated tablet contains 20 tadalafil.

The excipients are:
*Tablet core* – lactose, croscarmellose sodium (E468), sodium laurilsulfate (E487), hydroxypropylcellulose (E463), polysorbate 80 (E433) and magnesium stearate.
*Coating* - hypromellose 2910 (E464), lactose monohydrate, titanium dioxide (E171), triacetin (E1518), talc (E553b) and yellow iron oxide E172).

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

## 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 and practically insoluble in water, freely soluble in dimethyl and sulfoxide and slightly soluble in methylene chloride. Tadalafil shows polymorphism; the form used in the drug product is 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 and meets the requirements of the monograph in the Ph.Eur. and additional requirements for the CEP, with an additional test for particle size. The specification is acceptable in view of the route of synthesis and the various European guidelines. 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. The choices of the packaging and manufacturing are justified.
Two bioequivalence studies have been performed: one under fasted and one under fed conditions. The 20 mg test batch used in the studies was manufactured according to the finalised formulation and manufacturing process. The pharmaceutical development of the product has been adequately performed.

Manufacturing process
The manufacturing process consists of dry mixing, wet mixing/granulation, drying, sizing, blending, lubrication, compression and film-coating. The process has been validated according to relevant European guidelines. Process validation data on the product have been presented for three pilot scaled batches in accordance with the relevant European guidelines. The product is manufactured using conventional manufacturing techniques. Process validation for full-scale batches will be performed post authorisation.

Control of excipients
The excipients comply with their Ph.Eur. monographs or in-house specification in case of the film-coating material. 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, length, width, water content, average weight, disintegration, dissolution, uniformity of dosage units, assay, related substances, residual acetone and microbiological quality. Except for water content, 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. Appropriate tests for nitrosamine presence are performed on the final product. Satisfactory validation data for the analytical methods have been provided. Batch analytical data from three pilot scaled batches from the proposed production site have been provided, demonstrating compliance with the specification.

Stability of drug product
Stability data on the product have been provided for three pilot scaled batches stored at 25°C/ 60% RH (36 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 PVC-PVdC/Al-blisters. Except for an increase in water content at both storage conditions, no clear trends were observed from the stability data. 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. On basis of the data submitted, a shelf life was granted of 36 months without any special storage requirements.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies
Lactose and lactose monohydrate (as a component of the coating agents) are the only materials of animal origin included in the drug product. The milk used for the production of

these excipients has been sourced form healthy cows in the same conditions as milk collected for human consumption. The lactose has been prepared without the use of other ruminant material than calf rennet, according to the description as published in Public Statement EMEA/CPMP/571/02 of 27 February 2002. The bovine spongiform encephalopathy risk is therefore negligible.

### II.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the member states consider that Lafaval 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 Lafaval is intended for generic substitution, this will not lead to an increased exposure to the environment. An environmental risk assessment was therefore not deemed necessary.

### III.2 Discussion on the non-clinical aspects

This product is a generic formulation of Adcirca which is available on the European market. Reference was made to the preclinical data obtained with the innovator product. A non-clinical overview on the pharmacology, pharmacokinetics and toxicology has been provided, which was 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 member states agreed that no further clinical studies are required, besides the 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 Lafaval 20 mg film-coated tablets (Genepharm S.A., Greece) was 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 has been justified by comparison of dissolution study results and composition. The formula and preparation of the bioequivalence batch was identical to the formula proposed for marketing.

Biowaiver

The MAH claims a biowaiver of the reference product Cialis with Adcirca (20 mg tadalafil tablet). The clamed biowaiver versus the Adcirca reference product is acceptable based on bioequivalence versus the Cialis 20 mg film coated EU reference product, similarity in quality between Adcirca and Cialis 20 mg film-coated tablets and similarity in dissolution profiles at three different pH covering a range of 1.2 to 6.8 and QC medium between the generic and Adcirca and Cialis reference products (see Quality assessment report). Also Adcirca and Cialis are the same product and as a consequence, quality, safety and efficacy of Adcirca are identical to the up-to-date quality, safety and efficacy profile of Cialis.

Bioequivalence studies

*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.

*Design*

The design of the studies is acceptable. In the Bioequivalence Guideline (CHMP/QWP/EWP/1401/98 Rev. 1 section 4.1.4 Fasting or fed conditions) it is stated that both fasted and fed studies are required for products with specific formulation characteristics. The Tadalafil Product-Specific Bioequivalence Guidance states that the reference product has specific formulation characteristics and thus that both fasted and fed studies should be performed. This is because for Cialis, the MAH showed that due to a difference in manufacturing process (co-precipitation or micronisation) a difference in bioavailability may be expected under fed conditions. As such, the submission of a bioequivalence study under fasting conditions and a bioequivalence study under fed conditions under fed conditions is in accordance with these guidelines.

***Bioequivalence study 1 – 20 mg under fasting conditions***

A single-dose, randomised, two-period, two-treatment, two-sequence, crossover bioequivalence study was carried out under fasted conditions in 38 healthy male subjects, aged 19-43 years. Each subject received a single dose (20 mg) of one of the two tadalafil formulations. The tablet was orally administered with 240 ml water after an overnight fast. There were two 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.

*Results*
One subject was withdrawn due to an adverse event (vomiting). Therefore, 37 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=37 | $AUC_{0-72h}$ (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 | -- | -- |

**$AUC_{0-72h}$** 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 2 – 20 mg under fed conditions***
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 19-42 years. Each subject received a single dose (20 mg) of one of the two tadalafil formulations. The tablet was orally administered with 240 ml water 30 minutes after start of intake of a high fat, high caloric breakfast. There were two 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.

*Results*
One subject was withdrawn due to an adverse event (vomiting) in period I. Two subjects did not report for period II. Therefore, 35 subjects were eligible for pharmacokinetic analysis.

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

| Treatment N=35 | $AUC_{0-72h}$ (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 | -- | -- |
| **$AUC_{0-72h}$** area under the plasma concentration-time curve from time zero to t hours<br>**$C_{max}$** maximum plasma concentration<br>**$t_{max}$** time for maximum concentration<br>**$t_{1/2}$** half-life<br>**CV** coefficient of variation | | | | |

**ln-transformed values*

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 Lafaval 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 Lafaval.

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

| | |
|---|---|
| Important identified risks | • Priapism<br>• Hypotension/increased hypotensive effect |
| Important potential risks | • Non-arteritic anterior ischemic optic neuropathy (NAION)<br>• Sudden hearing loss<br>• Increased uterine bleeding |
| Missing information | none |

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 Adcirca. 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) 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, followed by two rounds with 10 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 package leaflet of medicinal products for human use.

# VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Lafaval 20 mg film-coated tablets has a proven chemical-pharmaceutical quality and is a generic form of Adcirca 20 mg film-coated tablets. Adcirca 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 Lafaval with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 12 July 2023.

## 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 |
|---|---|---|---|---|---|
| NL/H/5573/1/II /001 | Submission of additional clinical and non-clinical studies, including BE-studies | No | 7-6-2024 | Approved | NA |
| NL/H/5573/IA/ /002/G | - Replacement or addition of a manufacturing site for part or all of the manufacturing process of the finished product<br>- Replacement or addition of a manufacturer responsible for importation and/or batch release | No | 6-6-2024 | Approved | NA |

# ANNEX I – TYPE II Variation C.I.13

## I. RECOMMENDATION

Based on the review of the submission of new bioequivalence studies, following Article 31 Referral EMEA/H/A-31/1529 (Synapse)provided by the MAH, the RMS considers that the variation for Lafaval 20 mg film-coated tablets, indicated in adults for:

- The treatment of pulmonary arterial hyper-tension (PAH) classified as WHO functional class II and III, to improve exercise capacity.

Is acceptable.

## II. SCOPE OF THE VARIATION

On 7 March 2024 a variation procedure was started applied for by the MAH Genepharm S.A. of Lafaval 20 mg film-coated tablets. It is considered a C.I.13 variation: Submission of additional clinical and non-clinical studies, including bioequivalence-studies (CMDh Recommendation for classification of unforeseen variations according to Article 5 of Commission Regulation (EC) No 1234/2008) following a Article 31 Referral EMEA/H/A-31/1529 (Synapse - referral).

## III. SCIENTIFIC DISCUSSION

### III.1 Introduction

In 2015, Tadalafil 20 mg tablets were proven bioequivalent to the EU innovator Cialis 20 mg tablets through two bioequivalence studies (study protocols 14-073 under fasting conditions and 14-074 under fed conditions) conducted at a contract research organisation (CRO). However, following an Article 31 Referral initiated by AEMPS, concerns arose regarding the benefit-risk balance of the bioequivalence studies performed at this facility.
Consequently, the bioequivalence studies were repeated at a different CRO (study protocol 0350-23 (fast) and 0351-23 (fed)). The results were submitted in the current single type II variation application.

## IV. QUALITY ASPECTS

Comparative dissolution data complementary to the bioequivalence studies have been provided, showing similar dissolution. Similar dissolution was also demonstrated versus Adcirca 20 mg film-coated tablets and three additional test product batches in four media. The dissolution limit was tightened in accordance with the Reflection paper on the dissolution specification for generic solid oral immediate release products with systemic action. The same limit was applied at release and shelf-life. Compliance with the revised dissolution limit was demonstrated for three stability batches, at the end of their shelf-lives, both at long-term and

accelerated conditions. The relevant dossier sections have been updated accordingly. No concerns are identified from a quality point of view.

# V. CLINICAL ASPECTS

## V.1 Pharmacokinetics

The MAH conducted two bioequivalence studies in which the pharmacokinetic profile of the test product Lafaval 20 mg film-coated tablets (Genepharm S.A., Greece) was 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 has been justified by comparison of dissolution study results and composition. The formula and preparation of the bioequivalence batch was identical to the formula proposed for marketing.

*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.

*Design*
The design of the studies is acceptable. In the Bioequivalence Guideline (CHMP/QWP/EWP/1401/98 Rev. 1 section 4.1.4 Fasting or fed conditions) it is stated that both fasted and fed studies are required for products with specific formulation characteristics. The Tadalafil Product-Specific Bioequivalence Guidance states that the reference product has specific formulation characteristics and thus that both fasted and fed studies should be performed. This is because for Cialis, the MAH showed that due to a difference in manufacturing process (co-precipitation or micronisation) a difference in bioavailability may be expected under fed conditions. As such, the submission of a bioequivalence study under fasting conditions and a bioequivalence study under fed conditions under fed conditions is in accordance with these guidelines.

***Bioequivalence study 1 – 20 mg under fasting conditions***
A single-dose, randomised, two-period, two-treatment, two-sequence, crossover bioequivalence study was carried out under fasted conditions in 68 healthy male subjects, aged 18-44 years. Each subject received a single dose (20 mg) of one of the two tadalafil formulations. The tablet was orally administered with 240 ml water after an overnight fast. There were two dosing periods, separated by a washout period of 20 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.

*Results*

Three subjects were withdrawn due to an adverse event and five subjects withdrew from the study before the second period. Therefore, 60 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=60 | $AUC_{0-72h}$ (ng.h/ml) | $C_{max}$ (ng/ml) | $t_{max}$ (h) |
|---|---|---|---|
| **Test** | 10908 ± 3852 | 354 ± 100 | 4.50 (0.67 – 5.00) |
| **Reference** | 12130 ± 4975 | 420 ± 134 | 4.25 (0.67 – 10.0) |
| ***Ratio (90% CI)** | 0.91 (0.86 – 0.96) | 0.85 (0.81 – 0.90) | -- |
| **CV (%)** | 19.1 | 17.7 | -- |

**$AUC_{0-72h}$** area under the plasma concentration-time curve from time zero to t hours
**$C_{max}$** maximum plasma concentration
**$t_{max}$** time for maximum concentration
**CV** coefficient of variation

**ln-transformed values*

***Bioequivalence study 2 – 20 mg under fed conditions***

A single-dose, randomised, two-period, two-treatment, two-sequence, crossover bioequivalence study was carried out under fed conditions in 40 healthy male subjects, aged 18-45- years. Each subject received a single dose (20 mg) of one of the two tadalafil formulations. The tablet was orally administered with 240 ml water 30 minutes after start of intake of a high fat, high caloric breakfast. There were two dosing periods, separated by a washout period of 20 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.

*Results*

Two subject were withdrawn due to an adverse event. Therefore, 38 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=38 | $AUC_{0-72h}$ (ng.h/ml) | $C_{max}$ (ng/ml) | $t_{max}$ (h) |
|---|---|---|---|
| **Test** | 13377 ± 3681 | 470 ± 96 | 5.00 (2.33 – 6.00) |
| **Reference** | 13073 ± 3316 | 456 ± 93 | 5.00 (1.67 – 24.00) |

| | | | |
|---|---|---|---|
| ***Ratio (90% CI)** | 1.02 (0.98 – 1.06) | 1.03 (0.98 – 1.08) | -- |
| **CV (%)** | 10.8 | 12.6 | -- |

**$AUC_{0-72h}$** area under the plasma concentration-time curve from time zero to t hours
**$C_{max}$** maximum plasma concentration
**$t_{max}$** time for maximum concentration
**CV** coefficient of variation

**ln-transformed values*

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 Lafaval 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).

# VI. OVERALL CONCLUSION AND BENEFIT/RISK ASSESSMENT

Based on the submitted bioequivalence studies, the Lafaval 20 mg film-coated tablets is considered bioequivalent with the Cialis 20 mg film-coated tablets, under fasting conditions as well as under fed conditions.

No concerns are identified regarding the bioequivalence studies from a pharmacokinetic point of view.