CBG MEB

Public Assessment Report

Scientific discussion

Amitriptyline PhP 25 mg film-coated tablets

(amitriptyline hydrochloride)

NL License RVG: 117611

Date: 12 July 2018

This module reflects the scientific discussion for the approval of Amitriptyline PhP 25 mg film-coated tablets. The marketing authorisation was granted on 12 September 2017. For information on changes after this date please refer to the 'steps taken after finalisation' at the end of this PAR.

List of abbreviations

BCS	Biopharmaceutics Classification System
CEP	Certificate of Suitability to the monographs of the European Pharmacopoeia
EDQM	European Directorate for the Quality of Medicines
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 Medicines Evaluation Board (MEB) of the Netherlands has granted a marketing authorisation for Amitriptyline PhP 25 mg film-coated tablets, from Pharmaplant Kft.

The product is indicated for:
- treatment of major depressive disorder in adults
- treatment of neuropathic pain in adults
- prophylactic treatment of chronic tension-type headache (CTTH) in adults
- prophylactic treatment of migraine in adults
- the treatment of nocturnal enuresis in children aged 6 years and above when organic pathology, including spina bifida and related disorders, have been excluded and no response has been achieved to all other non-drug and drug treatments, including antispasmodics and vasopressin-related products. This medicinal product should only be prescribed by a healthcare professional with expertise in the management of persistent enuresis.

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

This national procedure concerns a generic application claiming essential similarity with the innovator product Laroxyl 25 mg film-coated tablets, which has been registered in France by Teofarma S.R.L. since 1991 (original product). In the Netherlands, the innovator product Laroxyl Roche 25 mg was authorised in 1969, but withdrawn in 1971.

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

Withdrawal of 10 mg and 50 mg strengths
Initially the application included two more strengths: Amitriptyline PhP 10 mg and 50 mg film-coated tablets. The 50 mg strength was withdrawn from the application after the first round of assessment.
The application for the 10 mg strength was made as a hybrid application according to Article 10(3), as no 10 mg reference product is registered. This strength was considered not approvable. Bioequivalence was not demonstrated by means of an *in vivo* study. The BCS-based biowaiver applied for could not be granted for this strength. The company MAH withdrew Amitriptyline PhP 10 mg from the application before finalisation of the procedure.

II. QUALITY ASPECTS

II.1 Introduction

Amitriptyline PhP 25 mg is a pink, round, biconvex film-coated tablet, plain on both sides. Each tablet contains 25 mg amitriptyline, corresponding to 28.3 mg amitriptyline hydrochloride.

The film-coated tablets are packed in PVC/Alu blisters or in a HDPE container with a PP cap.

The excipients are:
tablet core - lactose monohydrate, maize starch, povidone (PVP K-25), magnesium stearate and talc
film-coating - polyvinyl alcohol, titanium dioxide (E171), macrogol, talc, iron oxide red (E172) and iron oxide yellow (E172).

II.2 Drug Substance

The active substance is amitriptyline hydrochloride, an established active substance described in the European Pharmacopoeia (Ph. Eur.). The active substance is very soluble in water, in ethanol (96%), in methylene chloride, in methanol and in chloroform. It is insoluble in ether. The drug substance is a white crystalline powder or can consist of small crystals. No polymorphs exist. The molecule does not contain asymmetric carbon atoms and does not have any enantiomers.

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 European Pharmacopoeia.

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

Quality control of drug substance
The drug substance specification is in line with the Ph. Eur. and requirements of the CEP. The specification is acceptable in view of the route of synthesis and the various European guidelines.
Batch analysis data from the drug substance manufacturer and from the MAH have been provided on three batches. All data for all batches comply with the specifications.

Stability of drug substance
The active substance is stable for 5 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 development of the product has been described, the choice of excipients has been justified and their functions explained. During development it was targeted to develop tablets with composition and physico-chemical properties equivalent with Laroxyl film-coated tablets. Development studies were performed on granulation and tabletting, the best product was obtained after wet granulation. The test product formulation has similar pharmaceutical quality and physic-chemical properties compared to the reference product. However, the excipient composition differs, as in the test product povidone is used as binder material while in the reference product copovidone is applied.
No *in vivo* demonstration of bioequivalence was deemed necessary by the MAH. Instead a Biopharmaceutics Classification System (BCS)-based biowaiver was requested. The dissolution profiles obtained for the 25 mg test product and the Laroxyl 25 mg reference product are similar in pH 1.0 pH 4.5 and pH 6.8 medium (i.e. > 85% in 15 minutes).

Manufacturing process
The manufacturing process is common and involves homogenization, wet-granulation, pre-drying, particle size setting, drying, regranulation, blending and tabletting. The manufacturing process has been adequately validated according to relevant European guidelines. Process validation data on the product has been presented for the first three consecutive pilot size batches. Process validation for full scaled batches will be performed post authorisation.

Control of excipients
The specifications of the excipients are set according to the Ph. Eur. These specifications are acceptable.

Quality control of drug product
The product specification includes tests for appearance, average weight, uniformity of mass, disintegration time, water content, residual solvents, identification (drug substance and colour reaction), assay, uniformity of dosage units, dissolution, degradation products and microbiological purity. The release and shelf-life requirements are identical and acceptable. The analytical methods have been adequately described and validated. Batch analytical data from the proposed production site have been provided on three pilot scaled batches, demonstrating compliance with the release specification.

Stability of drug product
Stability data has been presented on three pilot size batches stored at long-term conditions (25°C/60%RH, up to 36 months), intermediate conditions (30°C/65%RH, up to 12 months) and

accelerated conditions (40°C/75%RH, up to 6 months). The product was stored in PVC/Alu blister or HDPE container. The conditions used in the stability studies are according to the ICH stability guideline.
Amitriptyline tablets stored at accelerated conditions in the proposed PVC/Alu blister primary packaging did not meet their specification criteria. All samples of Amitriptyline 25 mg film-coated tablets stored at intermediate and long term conditions stayed within specification, and no specific up or downward trends were observed.
The tablets stored in the HDPE containers met their specification criteria under long-term, intermediate and accelerated conditions.
A photostability study on the tablets stored in accordance with the ICH Q1B conditions has been done. Tablets stored outside of the immediate pack or in the proposed PVC/Alu blister primary packaging materials were sensitive to light. Samples stored corresponding to the final marketing pack for blisters and HDPE containers were photostable.
The MAH provided stability results of unpacked tablets, where it was demonstrated that the tablets are stable for up to 6 months in open air. Therefore a separate in-use storage period is not deemed necessary.
Based on the provided stability data, the claimed shelf-life and storage conditions for PVC/Alu blister (36 months, store below 30°C, keep in the original package in order to protect from light) and HDPE container (36 months, no specific storage conditions) are justified.

Specific measures for the prevention of the transmission of animal spongiform encephalopathies
Lactose monohydrate is the only excipient of animal origin. 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 MEB considers that Amitriptyline PhP 25 mg film-coated tablets 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 Amitriptyline PhP 25 mg 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 Laroxyl, 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 MEB agreed that no further non-clinical studies are required.

IV. CLINICAL ASPECTS

IV.1 Introduction

Amitriptyline 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 MEB agrees that no further clinical studies are required.

For this generic application, a Biopharmaceutics Classification System (BCS)-based biowaiver was requested.

IV.2 Pharmacokinetics

BCS-based biowaiver
In order for the applicant to apply for a BCS class I biowaiver for an immediate release drug product the following criteria have to be fulfilled taken from the EMA guidance 2010 Appendix III:

- the drug substance has been proven to exhibit high solubility and complete absorption (BCS class I)
- either very rapid (> 85% within 15 min) or similarly rapid (85% within 30 min) *in vitro* dissolution characteristics of the test and reference product has been demonstrated considering specific requirements
- excipients that might affect bioavailability are qualitatively and quantitatively the same. In general, the use of the same excipients in similar amounts is preferred.

Solubility
The Note for Guidance on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev.01/ Corr) provides that an active substance can be considered “highly soluble” if the highest single dose administered as immediate release formulation(s) is completely dissolved in 250 ml of buffers within the range of pH 1.2-6.8 at 37 ± 1 °C.
Experiments were performed in three buffers (at pH 1.2, 4.5 and 6.8), by using 3 parallel weightings under all experimental conditions. The SmPC recommends that a highest single dose of amitriptyline of 150 mg can be used. In solubility experiments, a double of this dose (i.e. 300 mg of amitriptyline, corresponding to 340 mg of amitriptyline hydrochloride) was used, dissolved in 250 ml of buffers.
The in-house dissolution studies performed by MAH demonstrated that the drug substance exhibits high solubility in all of the three investigated media.

Permeability - absorption
The MAH provided sufficient data to demonstrate that the extent of absorption of amitriptyline hydrochloride is ≥ 85% and thus amitriptyline (hydrochloride) can be classified as a BCS class I drug substance.

In vitro dissolution comparison
In vitro dissolution comparison studies on three batches of Amitriptyline PhP 25 mg and two batches of Laroxyl 25 mg in 900 ml of buffers with pH 1.0, 4.5 and 6.8, at 37°C ± 0.5° C, using a Ph. Eur. basket apparatus at a stirring rate of 100 rpm (n=12 each) showed that in all cases more than 85% was dissolved within 10 minutes and that the dissolution can be considered as very rapid. Samples were collected for 45 minutes, taken at 5, 10, 15, 20, 30 and 45 minutes from each dissolution vessel.
Therefore, it can be concluded that *in vitro* dissolution has been shown to be similar between Amitriptyline PhP 25 mg and Laroxyl 25 mg film-coated tablets.

Drug product excipients
The qualitative composition of the test product has been compared to the reference product Laroxyl 25 mg. There are minor differences in excipient composition between the test and reference product with respect to the binder material (povidone versus copovidone), of which it is not clear whether the chemical properties are the same. However, *in vitro* dissolution experiments show similar dissolution for the test and reference product, as for both products more than 85% of amitriptyline hydrochloride was dissolved within 10 minutes at all dissolution conditions.
Coatings of Laroxyl and Amitriptyline PhP film-coated tablets contain different film-former materials. Laroxyl cores are coated with hypromellose and Amitriptyline PhP is coated with polyvinyl alcohol (PA). Amitriptyline hydrochloride as hygroscopic material needs protection against humidity. Results of comparative dissolution studies indicate that the difference in film-forming materials has no impact on the dissolution behavior of test and reference film-coated tablets.

Therapeutic index
Amitriptyline is not considered a narrow therapeutic index drug.

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 Amitriptyline PhP 25 mg film-coated tablets.

- Summary table of safety concerns as approved in RMP

Important identified risks	Suicide/suicidal thoughts or clinical worsening Withdrawal symptoms (including neonatal ones) Cardiovascular disorders (myocardial infarction, cardiac arrhythmias and stroke) Serotonergic syndrome in concomitant use with MAO-inhibitors Increased risk of bone fractures (in elderly)
Important potential risks	None
Missing information	None

The MEB 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 Laroxyl. No new clinical studies were conducted and no bioequivalence study was performed to support the application. Instead a BCS-based biowaiver was requested and granted. Dissolution is rapid and similar between test and reference product, and a difference in bioavailability is not expected. Risk management is adequately addressed. This generic medicinal product can be used instead of the reference product.
The MAH initially proposed to include the indication ‘chronic pain’. In accordance with the indications approved for the reference product Laroxyl, authorised in France, this indicated has been replaced with ‘neuropathic pain’.

V. USER CONSULTATION

The package leaflet 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 2 participants, followed by two rounds with 10 participants each. The questions covered the following areas sufficiently: traceability, comprehensibility and applicability.
The results 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

Amitriptyline PhP 25 mg film-coated tablets has a proven chemical-pharmaceutical quality and is a generic form of Laroxyl 25 mg film-coated tablets. Laroxyl is a well-known medicinal product with an established favourable efficacy and safety profile.

For this generic application, the MAH submitted an argumentation for not performing a bioequivalence study. The MAH applied for a BCS (class I)-based biowaiver, based on criteria according to the Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98).

In the Board meetings of 26 November 2015 and 30 March 2017 the application was discussed. The Board concluded that the application for the Amitriptyline PhP 25 mg strength was approvable since the BCS biowaiver was sufficiently justified.

The MEB, on the basis of the data submitted, considered that essential similarity has been demonstrated for this medicinal product with the reference product, and have therefore granted a marketing authorisation. Amitriptyline PhP 25 mg film-coated tablets was authorised in the Netherlands on 12 September 2017.

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
Type Iain: C.I.8.a	Introduction of a summary of pharmacovigilance system, changes in QPPV (including contact details) and/or changes in the Pharmacovigilance System Master File (PSMF) location	-	01-05-2018	Approved	-
Type IB: A.2.b	Change in the (invented) name of the medicinal product; for Nationally Authorised Products	Y	01-06-2018	Approved	-