COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Amitriptyline Expharma 10 mg film-coated tablets
(amitriptyline hydrochloride)

NL License RVG: 127134

Date: 28 November 2022

This module reflects the scientific discussion for the approval of Amitriptyline Expharma 10 mg film-coated tablets. The marketing authorisation was granted on 10 August 2022. 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
CMS	Concerned Member State
EDMF	European Drug Master File
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 medicinal 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 Expharma 10 mg film-coated tablets, from ExtractumPharma Ltd.

The product is indicated for:

- the treatment of major depressive disorder in adults,
- the treatment of neuropathic pain in adults,
- the prophylactic treatment of chronic tension type headache (CTTH) in adults,
- the 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 European Reference Product Saroten 10 mg film-coated tablets by H. Lundbeck A/S registered since 27-07-1961 (DK/H/2760/001/MR).

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

II. QUALITY ASPECTS

II.1 Introduction

Amitriptyline Expharma are light pink, round, biconvex film-coated tablets, plain on one side and “10” imprint on the other side and contain as active substance 10 mg amitriptyline, as 11,32 mg amitriptyline hydrochloride.

The tablets are packed in PVC/aluminium blisters, or white opaque high-density polyethylene tablet containers with a polypropylene cap.

The excipients are:
Tablet core – lactose monohydrate, maize starch, povidone (PVP K-25), magnesium stearate (E470b) and talc.

Tablet coating – polyvinyl alcohol (E1203), titanium dioxide (E171), macrogol 3350 (E1521), talc (E553b) and yellow and red iron oxide (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 a powder and is very soluble in water. The active substance is not chiral and does not show polymorphism.

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 active substance specification is considered adequate to control the quality and meets the requirements of the monograph in the Ph.Eur. and the CEP, with no additional requirements. Batch analytical data demonstrating compliance with this specification have been provided for three batches.

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 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. Solubility data have been provided in support of a BCS class I biowaiver. The quality control dissolution method has been sufficiently justified. The optimal composition and manufacturing process parameters have been adequately investigated. The pharmaceutical development of the product has been adequately performed.

Manufacturing process
The drug product is manufactured by a wet granulation process which consists of pre-homogenisation, granulation, drying, blending, tabletting 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 batches for both commercial scale batch sizes. The product is manufactured using conventional manufacturing techniques.

Control of excipients

The excipients comply with Ph.Eur. and in-house requirements. These specifications are acceptable and functionality related characteristics of several excipients are included in their specifications.

Quality control of drug product

The product specification includes tests for appearance, dimensions, average weight, uniformity of mass, disintegration time, water content, residual solvent, identification, assay, uniformity of dosage units, dissolution, degradation products and microbiological purity. Release and shelf-life limits are identical. The specifications are acceptable.

Satisfactory validation data for the analytical methods have been provided.

Batch analytical data from four commercial scale batches from the proposed production site have been provided, demonstrating compliance with the specification. An adequate risk evaluation concerning the presence of nitrosamine impurities in the drug product has been provided.

Stability of drug product

Stability data on the product has been provided on three commercial scale batches stored at 25°C/60% RH (60 months), 30°C/65% RH (12 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-Alu blisters, HDPE containers with PP cap and double polyethylene bags (bulk packaging). Photostability studies were performed in accordance with ICH recommendations and showed that the product is not stable when exposed to light. Open dish stability study shows that no in-use shelf life is necessary.

Out of specification results of total impurities are seen for the product packed in blisters under accelerated conditions. For the product packed in blisters, the accepted shelf-life is 5 years,with the storage conditions “store below 30°C” and “keep the blisters in the outer carton in order to protect from light”. For the product packed in HDPE containers, the proposed shelf-life of 5 years could be granted, with the storage conditions “keep the tablets in the original container in order to protect from light. This medicinal product does not require any special temperature storage conditions”.

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

Certificates of suitability issued by the EDQM have been provided for lactose, and compliance with the Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via medicinal products has been satisfactorily

demonstrated. The other excipients are not from animal origin, including magnesium stearate.

II.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the MEB considers that Amitriptyline Expharma 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 Expharma 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 Saroten 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 finds that no further non-clinical studies are required.

IV. CLINICAL ASPECTS

IV.1 Introduction

Amitriptyline hydrochloride 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 found that no further clinical studies were required.

IV.2 Pharmacokinetics

For a generic application such as this one, bioequivalence between the new product and the reference product should be demonstrated. According to the Committee for Medicinal Products for Human Use (CHMP)'s *Guideline on the Investigation of Bioequivalence*

(CPMP/EWP/QWP/1401/98 Rev. 1/ Corr **), a BCS (Biopharmaceutics Classification System)-based biowaiver may represent a surrogate for *in vivo* bioequivalence studies.

BCS-based class I biowaivers are applicable for an immediate release drug product if:

- the drug substance has been proven to exhibit high solubility and complete absorption (BCS-class I) and
- 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 and
- excipients that might affect bioavailability are qualitatively and quantitatively the same. In general, the use of the same excipients in similar amounts is preferred.

For this generic application, the MAH has shown:

- Amitriptyline hydrochloride 10 mg dissolved completely in the required media (pH 1.0, 4.5 and 6.8 at 37 ± 0.5 °C). The pKa of amitriptyline, a weak base, is in the range of 9.2-9.8. The pKa of amitriptyline is not included in the range 1.0-6.8, so no additional testing at that level (pH = pKa) is required.
- Amitriptyline has a (near) complete absorption. It can be concluded that amitriptyline is a BSC-class I drug (high solubility and high permeability), in line with the existing marketing authorisation for Amitriptyline Expharma 25 mg film-coated tablets.
- The qualitative composition of the test and reference product is not identical, but a comparative dissolution test showed that test and reference product both dissolved very rapidly (≥85% in 15 minutes). For BCS-class I drugs, qualitative differences in formulation are permitted. The MAH also justified that the difference in excipients does not affect absorption.
- Amitriptyline does not belong to the class of narrow therapeutic drugs.

Based on the submitted data for this biowaiver, the justification can be accepted. Therefore, Amitriptyline Expharma 10 mg tablets is considered bioequivalent with Saroten 10 mg tablets.

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 Expharma.

Table 1. Summary of safety concerns as approved in RMP

Important identified risks	None
Important potential risks	None
Missing information	None

The MEB finds 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 Saroten. No new clinical studies were conducted. The MAH demonstrated that a BCS-based biowaiver is applicable. Risk management is adequately addressed. This generic medicinal product can be used instead of the reference product.

V. USER CONSULTATION

A user consultation with target patient groups on the package leaflet (PL) has been performed on the basis of a bridging report making reference to Amitriptyline Expharma 25 mg film-coated tablets (National procedure in NL, RVG 117611) for design/layout/format and making reference to Saroten 10 mg, 25 mg film-coated tablets (DK/H/2760/001-002/MR, EMEA/H/A-30/1430) or Amitriptyline BB 10 mg, 25 mg, 50 mg film-coated tablets (NL/H/1967/001-003/DC) for the key safety messages. The bridging report submitted by the MAH has been found acceptable; bridging is justified for both content and layout of the leaflet.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Amitriptyline Expharma 10 mg film-coated tablets has a proven chemical-pharmaceutical quality and is a generic form of Saroten 10 mg film-coated tablets. Saroten is a well-known medicinal product with an established favourable efficacy and safety profile. There were no post-approval commitments made during the procedure and a BCS class I biowaiver was granted in compliance with the requirements of European guidance documents.

The Board followed the advice of the assessors.

The MEB, on the basis of the data submitted, considered that essential similarity has been demonstrated for Amitriptyline Expharma with the reference product, and have therefore granted a marketing authorisation. Amitriptyline Expharma was authorised in the Netherlands on 10 August 2022.

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
N/A	N/A	N/A	N/A	N/A	N/A