COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Amitriptyline Expharma 50 mg, film-coated tablets
(amitriptyline (as hydrochloride))

NL License RVG: 127449

Date: 29 March 2023

This module reflects the scientific discussion for the approval of Amitriptyline Expharma 50 mg, film-coated tablets. The marketing authorisation was granted on 15 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
CMD(h)	Coordination group for Mutual recognition and Decentralised procedure for human medicinal products
CMS	Concerned Member State
CTTH	Chronic tension type headache
EDMF	European Drug Master File
EDQM	European Directorate for the Quality of Medicines
EEA	European Economic Area
EEG	Electroencephalogram
ERA	Environmental Risk Assessment
HDPE	High density polyethylene
ICH	International Conference of Harmonisation
MAH	Marketing Authorisation Holder
Ph.Eur.	European Pharmacopoeia
PL	Package Leaflet
PP	Polypropylene
RCT	Randomized controlled trial
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 Expharma 50 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.

An indication for use in paediatric patients was sought. The pharmacokinetics in children was insufficiently supported and the MAH has withdrawn this indication.

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

This national procedure concerns a bibliographical application based on well-established medicinal use of amitriptyline hydrochloride. For this type of application, the applicant needs to demonstrate that the active substance of the medicinal product has been in well-established medicinal use within the Community for at least ten years in the specific therapeutic use. The results of non-clinical and clinical trials are replaced by detailed references to published scientific literature.

Amitriptyline hydrochloride has been in use for the indications mentioned above for over ten years. Its recommended use for prophylaxis of migraine/CTTH has been documented in the Netherlands for at least 20 years. The use for major depressive disorder and neuropathic pain is described in European (and Canadian) guidelines for at least 15 years.

The MAH submitted a justification for bridging between their product and the product used in the literature based on comparable composition of the two formulations. The product used in literature is Saroten 25 mg film-coated tablets by H. Lundbeck A/S (EMEA/H/A-30/1430) licensed since 2015.

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

II. QUALITY ASPECTS

II.1 Introduction

Amitriptyline Expharma 50 mg film-coated tablets are brownish pink, round, biconvex, film-coated tablets, smooth on both sides. Each tablet contains 50 mg amitriptyline, equivalent to 56.60 mg amitriptyline hydrochloride.

The tablets are packaged in clear, colourless PVC/Aluminium blisters or opaque white HDPE (high density polyethylene) containers with a polypropylene cap.

The excipients are:
Tablet core – lactose monohydrate, maize starch, povidone (PVP K-25), magnesium stearate (E470b) and talc (E553b).
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 CEP and of the monograph in the Ph.Eur. Batch analytical data demonstrating compliance with this specification have been provided for three commercial scale 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. The quality control (QC) 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 including justification for a bridge between the products mentioned in the literature references and the new product. The bridge justification included several formulations (from literature and/or registered products) and information was provided on their differences in formulation and dissolution.

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 finished product specifications are adequate to control the relevant parameters for the dosage form. The 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. Limits in the specification have been justified and are considered appropriate for adequate quality control of the product. Release and shelf-life limits are identical. An adequate risk evaluation concerning the presence of nitrosamine impurities in the drug product has been provided.

Satisfactory validation data for the analytical methods have been provided.

Batch analytical data from three commercial scale batches from the production site have been provided, demonstrating compliance with the specification.

Stability of drug product

Stability data on the product have 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 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 restriction is necessary.

Out of specification results for appearance are seen for the product packed in blisters under accelerated conditions. For the product packed in blisters, the proposed shelf-life of 60 months and storage condition “store below 30°C” and “keep the blisters in the original package in order to protect from light” are necessary. For the product packed in HDPE

containers, the shelf-life of 60 months can be granted under the 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 50 mg 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 Pharmacology & pharmacokinetics

The pharmacological properties of amitriptyline are well known. The provided overview based on literature regarding the primary and secondary pharmacology, safety pharmacology and pharmacodynamic interactions is considered sufficient for this application. The pharmacokinetic properties of amitriptyline are well known. The route of absorption, distribution, metabolism and excretion have been adequately discussed, as well as pharmacokinetic drug interaction studies (*in vitro* and *in vivo)* from literature. The provided overview based on literature is considered sufficient for this application.

III.2 Toxicology

The toxicological properties of amitriptyline are well known. Conflicting data are available regarding genotoxic potential of amitriptyline. Although amitriptyline does not appear to be mutagenic, a potential for induction of chromosome aberrations cannot be ruled out. As with other amitriptyline products, this has no negative impact on the benefit risk assessment, and is adequately reflected in the SmPC. No carcinogenicity studies have been conducted with amitriptyline, but the MAH has discussed a meta-analysis of human data indicating no tumour-promoting effect of antidepressant treatments including amitriptyline. This is considered sufficient.

III.3 Ecotoxicity/environmental risk assessment (ERA)

Since Amitriptyline Expharma 50 mg film-coated tablets is intended for substitution for other products already on the marked, this will not lead to an increased exposure to the environment. An environmental risk assessment is therefore not deemed necessary.

III.4 Discussion on the non-clinical aspects

This product has been granted a market authorisation for well-established use. 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 hydrochloride is a well-known active substance with an 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 agreed that no further clinical studies are required.

IV.2 Pharmacokinetics

An overview has been provided considering the pharmacokinetics of amitriptyline, wherein the absorption, distribution, metabolism and elimination of amitriptyline is sufficiently supported by literature. Additionally, the MAH has demonstrated that amitriptyline is a BCS-class I drug substance, as the absorption of amitriptyline is complete. Dose-proportionality of the pharmacokinetics of amitriptyline in the range of 10 mg to 150 mg has been shown.

The MAH has withdrawn the indication in paediatric patients; the pharmacokinetics in children was insufficiently supported in the clinical overview.

Bridging

The MAH provided information regarding the formulations used in the submitted literature and regarding differences in composition and physico-chemical characteristics, including dissolution of products used in the literature and products used as reference products in the EU. Similarity in dissolution profile was shown between Amitriptyline Expharma 50 mg tablets and the main reference product used in literature (2x Saroten 25 mg film-coated tablets).

To establish a bridge in the well-established use (article 10a) application, the MAH adequately demonstrated the requirements for a BCS-class I biowaiver have been met. In

accordance with ICH M9, the bridging can be considered acceptable for the following reasons:

- Solubility studies demonstrated that 340 mg amitriptyline hydrochloride is soluble in 250 mL medium at pH 1.0, 4.5 and 6.8. The highest recommended dose is 150 mg/day, divided over 2 doses. Because this is completely soluble in 250 mL, then lower amounts can be considered to be completely soluble in the same volume of medium as well.
- Literature showed that the absorption of amitriptyline can be considered nearly complete. The absolute bioavailability of amitriptyline after oral intake is around 40%, but first-pass metabolism is around 60%. A publication regarding permeability in Caco-2 cells in which amitriptyline was found to be highly permeable, was supportive for this conclusion.
- The excipients in the investigated products are all commonly used excipients. These excipients are not known to influence absorption. All core excipients in Amitriptyline Expharma are also used in Laroxyl, Tryptizol and/or Saroten, except talc. Talc is not known to affect absorption.
- The dissolution profiles of Amitriptyline Expharma are within the spectrum of dissolution profiles of the investigated products in literature. Comparative *in vitro* dissolution testing has demonstrated a dissolution of >85% within the first 15 minutes for the tablets of both Amitriptyline Expharma 50 mg and Saroten 2 x 25 mg.

In conclusion, the pharmacokinetics of Amitriptyline Expharma have been adequately described and the bridge to literature is sufficiently supported.

IV.3 Pharmacodynamics

A general overview has been provided on the primary and secondary pharmacology of amitriptyline. Although the exact mechanism is unknown, mechanisms thought to underly the pharmacodynamic effects of amitriptyline for the sought indications have been adequately described.

A thorough discussion has been provided on the relationship between plasma concentrations and effect in depression. It is agreed that no simple relationship between plasma concentrations of amitriptyline and/or nortriptyline and therapeutic response has been established. Summed plasma concentrations of amitriptyline + nortriptyline of 50 – 200 ng/mL are associated with a better clinical response. In the range of 80 – 200 ng/mL the mean response rate was 51%. It is noted that only 9% of the variability in clinical response could be explained by regression analyses. Concentrations above 350-450 ng/mL are associated with electroencephalogram (EEG) changes and a risk of delirium.

Amitriptyline is not considered a drug with a narrow therapeutic window, as per prior decision by the CMDh in 2015. Relevant pharmacodynamic drug-drug interactions have been discussed by the MAH and are included in section 4.5 of the SmPC, which is aligned with other national registrations of amitriptyline.

IV.4 Clinical efficacy

Bibliographic data was submitted by the MAH to support the efficacy of Amitriptyline Expharma for the treatment of depression, neuropathic pain, prophylaxis for migraine and prophylaxis for CTTH. The dosing regime is in accordance with the Saroten 25 mg tablets reference product.

Depression

Two meta-analyses were considered pivotal: Barbui & Hotopf (2001) and Leucht et al. (2012), as most of the studies discussed by the MAH were included in these publications. Both meta-analyses contained various trials in which amitriptyline was evaluated either against placebo or an active comparator. In major depressive disorder, comparisons between an antidepressant and reference substances are difficult to interpret since there is a high and variable placebo response in depression. Therefore the EMA guideline for medicinal products for depression recommends either a placebo-controlled study or a three arm parallel group study with active comparator and placebo. The meta-analysis by Barbui & Hotopf includes active comparator studies, and the meta-analysis by Leucht et al. includes placebo-controlled studies. This information taken together sufficiently supports the conclusion that amitriptyline is an efficacious anti-depressant drug.

Neuropathic pain

According to the EMA guideline for medicinal products for pain (EMA/CHMP/970057/2011), efficacy should be shown in at least two different pain models before a general indication of neuropathic pain can be claimed. To support the broad indication, the MAH discusses 23 trials conducted in postherpetic neuralgia, diabetic neuropathy and neuropathic pain following breast cancer. The literature is a mixture of randomised controlled trials (RCT's) in which either placebo and/or an active comparator evaluated amitriptyline in various neuropathic pain conditions. A few cross-over studies were also provided. The studies in literature are of limited value in their support of the efficacy of amitriptyline in this indication. In several of the studies, amitriptyline was likely used as standard-of-care comparator against a novel treatment in neuropathic pain. There was a lack of comparison against a placebo or an approved treatment for neuropathic pain. This complicates the interpretation of the effect of amitriptyline. In addition, several of the studies were limited in aspects such as the sample size.

The MAH refers to the Saroten referral procedure (EMA/255467/2017), in which most of the literature was discussed. This was an Article 30 referral to harmonise the SmPC's of Saroten and associated names across the EU. In this procedure, scientific literature was discussed that supported the efficacy and harmonisation of the following indications: major depressive disorder, neuropathic pain, migraine prophylaxis, chronic tension type headache prophylaxis and enuresis nocturnal in children. During the referral, the evidence provided was considered sufficient by the CHMP to support an indication of amitriptyline in neuropathic pain. The limited literature studies discussed above, together with the conclusions of the CHMP in the Saroten referral, was considered by the MEB to be sufficient to support this indication.

Migraine prophylaxis

Studies from the literature were discussed by the MAH to substantiate the efficacy of amitriptyline in migraine prophylaxis.

The study by Couch et al. from 2011 is considered supportive, as only one aspect of migraine (frequency) showed a significant improvement with amitriptyline treatment when compared to placebo. The Keskinbora & Aydinli study (2008) was an active comparator trial against topiramate, which is a drug approved for migraine prophylaxis. The results of the study indicate no difference between topiramate and amitriptyline with regard to migraine specific endpoints. In the statistical analyses, an additional study arm was included which combined amitriptyline with topiramate. This, together with the small sample size (20 per study arm) hampers the interpretation and generalisability.

Taken together, although the studies by Couch et al. (2011) and Keskinbora & Aydinli (2008) have their limitations, the results provide some support of efficacy. Moreover, all studies put forward by the MAH have been discussed previously in the Saroten article 30 referral, and found to be indicative of efficacy. This conclusion is followed by the MEB.

CTTH prophylaxis

To support the efficacy of amitriptyline in CTTH, literature was provided that consisted of randomised control trials and open-label studies, which evaluated amitriptyline either against placebo or an active comparator. There were two studies in which amitriptyline was evaluated head-to-head with placebo (Göbel et al., 1994; Agius et al., 2013) and three studies where both a placebo and an active comparator arm were included (Pfaffenrath et al., 1994; Bendtsen et al., 1996; Holroyd, 2001).

Prevention of CTTH was an indication which was discussed during the Saroten referral, including most of the submitted literature. Issues were raised by the CHMP in terms of shortcomings of the studies (e.g. issues with active comparator, or not consistently showing statistical significance), which were recognised in this application as well. In the referral it was concluded that the combination of the provided literature with clinical treatment guidelines across the EU would support an indication of amitriptyline in CTTH. Those treatment guidelines are discussed in the rationale for well-established use. While the shortcomings of the studies are acknowledged, the conclusions of the CHMP can be followed in this respect.

IV.5 Clinical safety

The MAH substantiated the safety of Amitriptyline Expharma with bibliographic data. Adverse events were not recorded systematically across the studies. However, the information provided in the literature supports the well-known safety profile of amitriptyline. The adverse events are dose-related and usually reversible when therapy is discontinued. The most common effects occurring with relatively small doses are visual disturbances, reduced bronchial secretion, dry mouth, constipation, reflux, flushing, difficulty in micturition and dryness of the skin. Transient bradycardia may develop, followed by tachycardia with palpitations and arrhythmias. These events are well known to be associated with amitriptyline.

Serious adverse events were infrequent. Specific safety concerns are discussed in more detail by the MAH, including those regarding the cardiovascular system, mood, convulsions, serotonin syndrome, hyponatraemia, psychosis, ileus, weight increase, self-poisoning/ suicide and bone fractures. The significant concerns are highlighted in the Amitriptyline SmPC (either in section 4.4 warnings and precautions for use or section 4.5 drug-drug interactions). The MAH's discussion regarding laboratory findings and vital signs is focused on what is reported in the published literature. Section 4.8 of the SmPC also lists several laboratory findings/changes in vital signs as common events, e.g. QT prolongation and palpitations. These effects have been sufficiently discussed.

Safety in special populations is discussed by the MAH, including pregnancy, lactation, fertility, children, elderly, patients with hepatic or renal impairment, effect on the ability to drive cars and operate machines and overdose. All of these special populations are adequately described in the SmPC of Amitriptyline Expharma, with the exception of paediatric patients, as this indication was dropped.

IV.6 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 50 mg.

Table 1. Summary table of safety concerns as approved in RMP

Important identified risks	None
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.7 Discussion on the clinical aspects

For this authorisation, reference is made to the literature and experience with established products. No new data or clinical studies have been submitted, which is acceptable for this bibliographic application. The MAH has adequately substantiated bridging between their product and the product(s) used in the literature, based on comparable composition of the two formulations. The pharmacodynamics of amitriptyline are well-established by literature. The efficacy of amitriptyline for each indication and associated posology has been sufficiently substantiated with literature and the article 30 Saroten referral procedure. The provided literature describing the safe use of amitriptyline in the indications and posologies is limited, but the indications and posologies are in line with the SmPCs of other amitriptyline products currently registered in the EU. The use of amitriptyline in the indications can be considered well-established. The safety profile of amitriptyline is well

known and overall acceptable. Risk management is adequately addressed. This medicinal product is considered well-established.

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 (RVG 117611) for design/layout of the leaflet, and Saroten 10 mg and 25 mg film-coated tablets (DK/H/2760/001-002/MR and 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 content. 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 50 mg, film-coated tablets has a proven chemical-pharmaceutical quality. The documentation in relation to this product is of sufficiently high quality in view of the European regulatory requirements.

From a clinical point of view, the indications are in line with current amitriptyline recommendations. The active substance has been registered in Europe for over ten years. Based upon clinical data and the longstanding clinical experience, the use of amitriptyline in the indications can be considered well-established with demonstrated efficacy and acceptable safety.

The Board followed the advice of the assessors.

The MEB, on the basis of the data submitted, considered that well-established use has been shown, and has therefore granted a marketing authorisation. The national procedure was finalised with a positive outcome on 15 August 2022.

LITERATURE REFERENCES

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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 IB: B.II.d.2.d	Change in test procedure for the finished product - Other changes to a test procedure (including replacement or addition)	No	14-12-2022	Approved	N/A