IPAR

Public Assessment Report for a
Medicinal Product for Human Use

Scientific Discussion

Aniva 25 mg film-coated tablets
Amitriptyline hydrochloride
PA22871/023/002

The Public Assessment Report reflects the scientific conclusion reached by the Health Products Regulatory Authority (HPRA) at the end of the evaluation process and provides a summary of the grounds for approval of a marketing authorisation for a specific medicinal product for human use. It is made available by the HPRA for information to the public, after deletion of commercially sensitive information. The legal basis for its creation and availability is contained in Article 21 of Directive 2001/83/EC, as amended. It is a concise document which highlights the main parts of the documentation submitted by the applicant and the scientific evaluation carried out by the HPRA leading to the approval of the medicinal product for marketing in Ireland.

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I. INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the HPRA has granted a marketing authorisation for Aniva 10 mg, 25 mg and 50 mg film-coated tablets, from Azure Pharmaceuticals Limited on 28th February 2025 for the following indications:

- 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.

Aniva 25 mg and 50 mg film-coated tablets are submitted as a generic application under Art.10 (1), while Aniva 10 mg film-coated tablets are submitted as hybrid application under Article 10(3).

The Summary of Product Characteristics for (SmPC) for this medicinal product is available on the HPRA's website at www.hpra.ie

Name of the product	Aniva 10 mg, 25 mg & 50 mg film-coated tablets
Name(s) of the active substance(s) (INN)	Amitriptyline hydrochloride
Pharmacotherapeutic classification (ATC Code)	N06AA09
Pharmaceutical form and strength(s)	10 mg, 25 mg & 50 mg film-coated tablets
Marketing Authorisation Number(s) in Ireland (PA)	PA22871/023/001-003
Marketing Authorisation Holder	Azure Pharmaceuticals Ltd. 12 Hamilton Drive The Rock Road Blackrock Co. Louth A91 T997 Ireland
MRP/DCP No.	IE/H/1142/001-003/DC
Reference Member State	IE
Concerned Member State(s)	MT

II. QUALITY ASPECTS

II.1. Introduction

This application is for Aniva (Amitriptyline) 10 mg, 25 mg and 50 mg film-coated tablets.

II.2 Drug substance

The active substance is Amitriptyline hydrochloride, an established active substance described in the European Pharmacopoeia, and is manufactured in accordance with the principles of Good Manufacturing Practice (GMP)

The active substance specification is considered adequate to control the quality and meets current pharmacopoeial requirements. Batch analytical data demonstrating compliance with this specification has been provided.

II.3 Medicinal product

P.1 Composition

The excipients in the medicinal product are listed in section 6.1 of the SmPC.
A visual description of the product is included in section 3 of the SmPC.

P.2 Pharmaceutical Development

The product is an established pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines.

P.3 Manufacture of the Product

The product is manufactured in accordance with the principles of good manufacturing practice (GMP) at suitably qualified manufacturing sites.

P.4 Control of Other Substances (Excipients)

All ingredients comply with Ph. Eur. or are adequately controlled by the manufacturer's specifications.

P.5 Control of Finished Product

The Finished Product Specification is based on the pharmacopoeial monograph for tablets, and the tests and control limits are considered appropriate for this type of product.

The analytical methods used are described in sufficient detail and are supported by validation data.

Batch analytical data for a number of batches from the proposed production site have been provided and demonstrate the ability of the manufacturer to produce batches of finished product of consistent quality.

P.7 Packaging material

The approved packaging for this product is described in section 6.5 of the SmPC.

Evidence has been provided that the packaging complies with EU legislation for use with foodstuffs requirements.

P.8 Stability of the Finished Product

Stability data on the finished product in the proposed packaging have been provided in accordance with EU guidelines and support the shelf-life and storage conditions listed in sections 6.3 and 6.4 of the SmPC.

II.4 Discussion on Chemical, Pharmaceutical and Biological Aspects

The important quality characteristics of the product are well-defined and controlled. Satisfactory chemical and pharmaceutical documentation has been provided, assuring consistent quality of Aniva 10 mg, 25 mg and 50 mg film-coated tablets.

III. NON-CLINICAL ASPECTS

III.1 Introduction

This active substance is a generic formulation of Laroxyl 50 mg and Amirol 25mg film-coated tablets on the European market. The 10 mg strength is a hybrid formulation. No new preclinical data have been submitted. This is acceptable for this type of application.

III.2 Pharmacology

N/A

III.3 Pharmacokinetics

N/A

III.4 Toxicology

N/A

III.5 Ecotoxicity/environmental risk assessment

Since Amitriptyline 10 mg, 25 mg, and 50 mg film-coated tablets are generic products, they will not lead to an increased exposure to the environment. Additional studies on environmental risk assessment are therefore not deemed necessary.

III.6 Discussion on the non-clinical aspects

Pharmacodynamic, pharmacokinetic and toxicological properties of amitriptyline hydrochloride are well known. As amitriptyline hydrochloride is a widely used, well-known active substance, the applicant has not provided additional nonclinical studies and further studies are not required. A nonclinical overview based on literature review was provided and is acceptable for this type of application. Non-clinical findings are adequately represented in the appropriate sections of the SmPC.

IV. CLINICAL ASPECTS

IV.1 Introduction

Amitriptyline hydrochloride is a well-known active substance with established efficacy and tolerability.

The content of the SmPC approved during the decentralised procedure is in accordance with that accepted for the reference product Laroxyl film-coated tablets, Teofarma S.R.L

For this application, the applicant has submitted one bioequivalence study in which the pharmacokinetic profile of the test product Aniva (Amitriptyline) 50 mg film-coated tablets is compared with the pharmacokinetic profile of the reference product Laroxyl 50 mg film-coated tablets.

A single-dose, randomised, two-period, two-treatment, two-sequence, crossover bioequivalence study was carried out. Aniva (Amitriptyline Hydrochloride) 50 mg film-coated tablets, was compared to the reference product Laroxyl 50 mg film-coated tablets. Based on the pharmacokinetic parameters of active substance, the reference Laroxyl 50 mg film-coated tablets marketed by Teofarma S.R.L and Aniva (Amitriptyline) 50 mg film-coated tablets are bioequivalent with extent to the rate and extent of absorption and fulfil the bioequivalence requirements outlined in the relevant CHMP Note for Guidance.

A biowaiver for the 10 mg and 25 mg strengths has been requested. The requirements of the 'Guideline on the investigation of bioequivalence, CPMP/EWP/QWP/1401/98 Rev. 1/Corr. **' for a biowaiver of additional strengths are met.

The HPRA has been assured that GCP standards were followed in an appropriate manner in the studies conducted.

IV.2 Pharmacokinetics

Absorption
Film-coated tablets
Oral administration of tablets results in maximum serum levels in about 4 hours.
(t_{max}= 3.89±1.87 hours; range 1.93-7.98 hours). After peroral administration of 50 mg the mean C_{max}= 30.95±9.61 ng/ml; range 10.85-45.70 ng/ml (111.57±34.64 nmol/l; range 39.06-164.52 nmol/l). The mean absolute oral bioavailability is 53% (F_{abs}= 0.527±0.123; range 0.219-0.756).

Distribution

The apparent volume of distribution $(Vd)_\beta$ estimated after intravenous administration is 1221 L ± 280 L; range 769-1702 L (16 ± 3 L/kg).

The plasma protein binding is about 95%.

Amitriptyline and the main metabolite nortriptyline pass across the placental barrier.

In nursing mothers amitriptyline and nortriptyline are excreted in small amounts with the breast milk. The ratio milk concentration/plasma concentration in women is around 1:1. The estimated daily infant exposure (amitriptyline + nortriptyline) averages 2% of the corresponding maternal weight related doses of amitriptyline (in mg/kg) (see section 4.6).

Biotransformation
In vitro the metabolism of amitriptyline proceeds mainly by demethylation (CYP2C19, CYP3A4) and hydroxylation (CYP2D6) followed by conjugation with glucuronic acid. Other isozymes involved are CYP1A2 and CYP2C9. The metabolism is subject to genetic polymorphism. The main active metabolite is the secondary amine, nortriptyline.

Nortriptyline is a more potent inhibitor of noradrenaline than of serotonin uptake, while amitriptyline inhibits the uptake of noradrenaline and serotonin equally well. Other metabolites such as cis- and trans-10-hydroxyamitriptyline and cis- and trans-10-hydroxynortriptyline have the same profile as nortriptyline but is considerably weaker. Demethylnortriptyline and amitriptyline N oxide are only present in plasma in minute amounts; the latter is almost inactive. All the metabolites are less anticholinergic than amitriptyline and nortriptyline. In plasma the amount of total 10-hydroxynortriptyline dominates but most of the metabolites are conjugated.

Elimination
The elimination half-life ($t_{½\beta}$) amitriptyline after peroral administration is about 25 hours (24.65 ± 6.31 hours; range 16.49-40.36 hours). The mean systemic clearance (Cls) is 39.24 ± 10.18 L/h, range 24.53-53.73 L/h.

The excretion proceeds mainly with urine. The renal elimination of unchanged amitriptyline is insignificant (about 2%).

Steady state plasma levels of amitriptyline + nortriptyline are reached within a week for most patients, and in steady state the plasma level comprises approximately equal parts of amitriptyline and nortriptyline around the clock following treatment with conventional tablets 3 times a day.

Elderly patients
Longer half-lives and decreased oral (Cl_o) clearance values due to a reduced rate of metabolism have been demonstrated in elderly patients.

Reduced hepatic function
Hepatic impairment may reduce hepatic extraction resulting in higher plasma levels and caution should be exercised when dosing these patients (see section 4.2).

Reduced renal function
Renal failure has no influence on the kinetics.

Polymorphism
The metabolism is subject to genetic polymorphism (CYP2D6 and CYP2C19) (see section 4.2).

Pharmacokinetic/pharmacodynamic relationship
Plasma concentrations of amitriptyline and nortriptyline vary very widely between individuals and no simple correlation with therapeutic response has been established.
The therapeutic plasma concentration in major depression is around 80 – 200 ng/ml (≈ 280 – 700 nmol/l) (for amitriptyline + nortriptyline). Levels above 300-400 ng/ml are associated with increased risk of disturbance in cardiac conduction in terms of prolonged QRS-complex or AV block.

IV.3 Pharmacodynamics

Amitriptyline is a tricyclic antidepressant and an analgesic. It has marked anticholinergic and sedative properties. It prevents the re-uptake, and hence the inactivation of noradrenaline and serotonin at nerve terminals. Reuptake prevention of these monoamine neurotransmitters potentiate their action in the brain. This appears to be associated with the antidepressant activity.

The mechanism of action also includes ion-channel blocking effects on sodium, potassium and NMDA channel at both central and spinal cord level. The noradrenaline, sodium and the NMDA effects are mechanisms known to be involved in the maintenance of neuropathic pain, chronic tension type headache prophylaxis and migraine prophylaxis. The pain reducing effect of amitriptyline is not linked to its anti- depressive properties.

Tricyclic antidepressants possess affinity for muscarinic and histamine H1 receptors to varying degrees

IV.4 Clinical Efficacy

Clinical efficacy and safety
The efficacy and safety of amitriptyline has been demonstrated in treatments of the following indications in adults:

- Major Depressive Disorder
- Neuropathic Pain
- Chronic tension type headache prophylaxis
- Migraine prophylaxis

The efficacy and safety of amitriptyline has been demonstrated for treatments of nocturnal enuresis in children aged 6 years and above (see section 4.1).

IV.5 Clinical Safety

The safety profile of amitriptyline is well-established.

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 10 mg, 25 mg and 50 mg Film-coated Tablets.

Safety specification

Summary of safety concerns	
Important identified risks	None
Important potential risks	None
Missing information	None

Pharmacovigilance Plan
Routine pharmacovigilance is suggested and no additional pharmacovigilance activities are proposed by the applicant, which is endorsed.

Risk minimisation measures
Routine risk minimisation is suggested and no additional risk minimisation activities are proposed by the applicant, which is endorsed.

Periodic Safety Update Report (PSUR)
With regard to PSUR submission, the MAH should take the following into account:

- PSURs shall be submitted in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal. Marketing authorisation holders shall continuously check the European medicines web-portal for the DLP and frequency of submission of the next PSUR.
- For medicinal products authorized under the legal basis of Article 10(1) or Article 10a of Directive 2001/83/EC, no routine PSURs need to be submitted, unless otherwise specified in the EURD list.

- In case the active substance will be removed in the future from the EURD list because the MAs have been withdrawn in all but one MS, the MAH shall contact that MS and propose DLP and frequency for further PSUR submissions together with a justification.

IV.6 Discussion on the clinical aspects

Amitriptyline hydrochloride is a well-known active substance with established efficacy and tolerability. With the exception of data from two bioequivalence studies, no new clinical data were provided or are required for this type of application.

As shown in the bioequivalence study, the reference Laroxyl 50 mg film-coated tablets marketed by Teofarma S.R.L and Aniva (Amitriptyline) 50 mg film-coated tablets are bioequivalent with extent to the rate and extent of absorption and fulfil the bioequivalence requirements outlined in the relevant CHMP Note for Guidance.

A biowaiver for the 10 mg and 25 mg strengths has been requested. The requirements of the 'Guideline on the investigation of bioequivalence, CPMP/EWP/QWP/1401/98 Rev. 1/Corr. **' for a biowaiver of additional strengths are met.

V. OVERALL CONCLUSIONS

Aniva (Amitriptyline) 10 mg, 25 mg and 50 mg film-coated tablets is a generic form of product Laroxyl film-coated tablets, Teofarma S.R.L. Laroxyl film-coated tablets, Teofarma S.R.L is a well-known medicinal product with a proven chemical-pharmaceutical quality and an established favourable efficacy and safety profile.

Bioequivalence has been shown to be in compliance with the CHMP guidance documents. The SmPC is consistent with that of the reference product.

The MAH has provided written confirmation that systems and services are in place to ensure compliance with their pharmacovigilance obligations.

The HPRA, on the basis of the data submitted considered that Aniva (Amitriptyline) 10 mg, 25 mg and 50 mg film-coated tablets demonstrated bioequivalence with the reference product as well as a satisfactory risk/benefit profile and therefore granted a marketing authorisation.

VI. REVISION DATE

23.12.2029