IPAR

Public Assessment Report for a
Medicinal Product for Human Use

Scientific discussion

Amoxicillin 125 mg/5 ml and 250 mg/5 ml powder for oral suspension
AMOXICILLIN TRIHYDRATE
PA0126/282/003-004

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.

CONTENTS

I INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the HPRA has granted a marketing authorisation for Amoxicillin 125 mg/5 ml and 250 mg/5 ml powder for oral suspension from Clonmel Healthcare Ltd on 26th August 2016, indicated for the treatment of the following infections in adults and children:

- Acute bacterial sinusitis
- Acute otitis media
- Acute streptococcal tonsillitis and pharyngitis
- Acute exacerbations of chronic bronchitis
- Community acquired pneumonia
- Acute cystitis
- Asymptomatic bacteriuria in pregnancy
- Acute pyelonephritis
- Typhoid and paratyphoid fever
- Dental abscess with spreading cellulitis
- Prosthetic joint infections
- *Helicobacter pylori* eradication
- Lyme disease

Amoxicillin is also indicated for the prophylaxis of endocarditis.

This application for a marketing authorisation was submitted in accordance with Article 10c of Directive 2001/83/EC and is referred to as an 'informed consent' application. This means that the Marketing Authorisation Holder for Pinamox (Amoxicillin Oral suspension BP) 125mg/5ml and 250mg/5ml (PAs 298/10/1&2), which are authorised medicinal products in Ireland, has permitted the applicant to refer to their dossier to obtain an authorisation for Amoxicillin 125 mg/5 ml and 250 mg/5 ml powder for oral suspension respectively. Amoxicillin 125 mg/5 ml and 250 mg/5 ml Oral Suspensions have the same qualitative and quantitative composition in terms of actives substances and the same pharmaceutical form as Pinamox (Amoxicillin Oral Suspension BP) 125mg/5ml and 250mg/5ml Oral Suspension from Athlone Laboratories Limited.

These products are subject to prescription, are for supply in pharmacies only and are for promotion to healthcare professionals only.

The Summary of Product Characteristics for (SmPC) for these medicinal products are available on the HPRA's website at www.hpra.ie

Name of the product	Amoxicillin powder for oral suspension
Name(s) of the active substance(s) (INN)	AMOXICILLIN TRIHYDRATE
Pharmacotherapeutic classification (ATC code)	J01CA04
Pharmaceutical form and strength(s)	125 mg/5 ml and 250 mg/5 ml
Marketing Authorisation Number(s) in Ireland (PA)	PA0126/282/003-004
Marketing Authorisation Holder	Clonmel Healthcare Ltd

II QUALITY ASPECTS

II.1. Introduction

This application is for 125 mg/5ml and 250 mg/5ml powder for oral suspension.

II.2 Drug substance

The active substance is amoxicillin trihydrate, 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

Amoxicillin 125 mg/5ml and 250 mg/5ml powder for oral suspension contains amoxicillin trihydrate equivalent to 125mg or 250mg of amoxicillin per 5 ml on reconstitution.

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.

The manufacturing process has been validated according to relevant European/ICH guidelines and the process is considered to be sufficiently validated.

P.4 Control of Other Substances (Excipients/*Ancillary Substances*)

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 Liquid Preparations for Oral Use, 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(s) have been provided, and demonstrate the ability of the manufacturer to produce batches of finished product of consistent quality.

P.6 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 Ph. Eur. /EU legislation for use with foodstuffs.

P.7 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 Amoxicillin 125mg/5ml and 250mg/5ml powder for oral suspension.

III NON-CLINICAL ASPECTS

III.1 Introduction

This active substance is the same as that present in Pinamox (Amoxicillin Oral suspension BP) 125mg/5ml and 250mg/5ml (PAs 298/10/1&2) on the Irish market. No new non-clinical data have been submitted. As such, no non-clinical assessment has been made on the application. This is acceptable for this type of application.

III.2 Pharmacology

See clinical section

III.3 Pharmacokinetics

See clinical section

III.4 Toxicology

Not applicable as this is an informed consent application.

III.5 Ecotoxicity/environmental risk assessment

Not applicable as this is an informed consent application.

III.6 Discussion on the non-clinical aspects

As this is an informed consent application, additional non-clinical data is not necessary for this application. The active substance amoxicillin is well known and its preclinical effects are well documented. Relevant preclinical aspects are mentioned in section 5.3 of the SmPCs.

IV CLINICAL ASPECTS

IV.1 Introduction

Amoxicillin is a well-known active substance with established efficacy and tolerability. These medicinal products are the same as Pinamox (Amoxicillin Oral Suspension BP) 125mg/5ml and 250mg/5ml on the Irish market.

The content of the SmPCs approved during the national procedure are in accordance with that accepted for the reference products Pinamox (Amoxicillin Oral Suspension BP) 125mg/5ml and 250mg/5ml marketed in Ireland by Athlone Laboratories Limited.

IV.2 Pharmacokinetics

Absorption
Amoxicillin is stable to gastric acid and 50 – 90% of a dose is absorbed after oral administration.

Blood concentration
After an oral dose of 500mg, peak serum concentration of 3 to 20 ug/ml are attained in 1 to 2 hours, detectable concentrations are present after 8 hours. Peak concentrations occur earlier in children and infants, but later in neonates.

Half-life
Serum half-life, is 1 hour which may be increased to 15 hours in renal failure.

Distribution
Enters most tissues and fluid but is not detectable in the cerebrospinal fluid even when meninges are inflamed; crosses the placenta and small amounts are secreted in the milk; volume of distribution at steady-state serum concentrations, about 0.3 litres/kilogram body weight; protein binding, 15 – 25% bound to plasma protein.

Excretion
35 – 45% is excreted in the urine after an oral dose; urinary excretion is delayed by probenecid and it also occurs more slowly in the newborn; small amounts are excreted in the bile.
In preterm infants with gestational age 26-33 weeks, the total body clearance after intravenous dosing of amoxicillin, day 3 of life, ranged between 0.75-2ml/min, very similar to the inulin clearance (GFR) in this population. Following oral administration, the absorption pattern and the bioavailability of amoxicillin in small children may be different to that of adults. Consequently, due to the decreased clearance, the exposure is expected to be elevated in this group of patients, although this increase in exposure may in part be diminished by decreased bioavailability when given orally.

IV.3 Pharmacodynamics

Amoxicillin is a semisynthetic penicillin, which is acid resistant and has a similar antibacterial spectrum to ampicillin. It acts by inhibiting bacterial cell-wall synthesis.

IV.4 and 5 Clinical Efficacy and Safety

As this is an informed consent application no new clinical efficacy or safety data has been submitted. Efficacy and safety is expected to be similar to the reference products Pinamox (Amoxicillin Oral suspension BP) 125mg/5ml and 250mg/5ml.

The marketing authorisation holder (MAH) has submitted a summary of the Pharmacovigilance System, including confirmation of the availability of an EU Qualified Person for Pharmacovigilance (EU-QPPV) and the means for notification of adverse reaction reports in the EU or from a Third Country.

The MAH has submitted a Risk Management Plan.

Risk Management Plan Version 1.1 (Dated 25/5/2016) is acceptable.

Summary of safety concerns

Important identified risks

- Hypersensitivity and anaphylaxis
- Hepatic and Cholestatic Jaundice
- Severe neutropenia or agranulocytosis
- Prolongation of prothrombin time
- Overgrowth of non-susceptible organisms with prolonged use
- Antibiotic associated colitis
- Drug interaction with probenecid

- Allergic skin reactions with concomitant allopurinol
- Erythematous rash in patients with Glandular fever
- Severe skin reactions
- Impaired renal function

Important potential risks

- None

Missing information

- None

Based on consideration of the identified risks, the potential risks and the need for additional information on the medicinal product, it is concluded that routine pharmacovigilance and risk minimisation measures are sufficient.

Periodic Safety Update Report (PSUR)
The next PSUR should be submitted in accordance with the requirements set out in the list of Union reference dates (EURD list) provided under Article 107c (7) of Directive 2001/83/EC and published on the European medicines web-portal.

IV.6 Discussion on the clinical aspects

Amoxicillin is a well-known substance and has been widely marketed. As this is an informed consent application no new efficacy or safety data have been submitted. Efficacy and safety is expected to be similar to the reference products Pinamox (Amoxicillin Oral suspension BP) 125mg/5ml and 250mg/5ml.

The product information SmPCs and patient leaflets are identical to those of the reference products.

V OVERALL CONCLUSIONS

Amoxicillin 125 mg/5 ml and 250 mg/5 ml powder for oral suspension are the same as Pinamox (Amoxicillin Oral Suspension BP) 125mg/5ml and 250mg/5ml Oral Suspension on the Irish market. Amoxicillin is a well-known medicinal product with a proven chemical-pharmaceutical quality and an established favourable efficacy and safety profile.

The HPRA, on the basis of the data submitted considered that Amoxicillin 125 mg/5 ml and 250 mg/5 ml powder for oral suspension are the same as the reference products and therefore granted a marketing authorisation to both of these products.

VI REVISION DATE

VII UPDATES

This section reflects the significant changes following finalisation of the initial procedure.

SCOPE	PROCEDURE NUMBER	PRODUCT INFORMATION AFFECTED	DATE OF START OF PROCEDURE	DATE OF END OF PROCEDURE