COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Amoxicilline Prolepha, powder for solution for injection/infusion 250 mg, 500 mg, 1 g and 2 g (amoxicillin sodium)

NL/H/5810/001-004/DC

Date: 9 March 2026

This module reflects the scientific discussion for the approval of Amoxicilline Prolepha, powder for solution for injection/infusion 250 mg, 500 mg, 1 g and 2 g. The procedure was finalised on 18 July 2024. 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
EDMF	European Drug Master File
EDQM	European Directorate for the Quality of Medicines
EEA	European Economic Area
EMA	European Medicines Agency
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
RMS	Reference Member State
SmPC	Summary of Product Characteristics
TSE	Transmissible Spongiform Encephalopathy

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for Amoxicilline Prolepha, powder for solution for injection/infusion 250 mg, 500 mg, 1 g and 2 g, from Prolepha Research B.V.

The product is indicated for the treatment of the following infections in adults and children:

- Severe infections of the ear, nose and throat (such as mastoiditis, peritonsillar infections, epiglottitis, and sinusitis when accompanied by severe systemic signs and symptoms)
- Acute exacerbations of chronic bronchitis
- Community acquired pneumonia
- Acute cystitis
- Acute pyelonephritis
- Severe dental abscess with spreading cellulitis
- Prosthetic joint infections
- Lyme disease
- Bacterial meningitis
- Bacteremia that occurs in association with, or is suspected to be associated with, any of the infections listed above

The product is also indicated for the treatment and prophylaxis of endocarditis.

A comprehensive description of the up-to-date indications and posology is given in the SmPC.

The marketing authorisation has been granted pursuant to Article 10(1) of Directive 2001/83/EC, which concerns a generic application.

In this decentralised procedure, essential similarity is proven between the new product and two European Reference Products (ERPs), Clamoxyl 250 mg, powder for solution for injection/infusion (GlaxoSmithKline) and Xyllomac 500 mg, 1 g, 2 g, powder for solution for injection/infusion (Laboratoires Delbert, FR/H/0790/001-003), which have been registered in since 27 September 1982 and 27 September 1984, respectively.

The concerned member states (CMS) involved in this procedure was Cyprus.

II. QUALITY ASPECTS

II.1 Introduction

Amoxicilline Prolepha is a powder for solution for injection/infusion. The vial contains a sterile white to almost white powder.

Each vial contains as active substance amoxicillin sodium equivalent to 250 mg, 500 mg, 1 g or 2 g amoxicillin.

Besides the protective gas (nitrogen) there are no excipients.

The powder for solution for injection/infusion is packed in clear type III glass vials of nominal capacity 8 ml (250 mg) or 20 ml (500 mg, 1 g and 2 g strength) sealed with a chlorobutyl rubber stopper of 20 mm diameter and an aluminium overcap (with or without plastic flip-off seal), with a leaflet, in card cartons.

II.2 Drug Substance

The active substance is amoxicillin sodium, an established active substance described in the European Pharmacopoeia (Ph.Eur.). It is a semi-synthetic product derived from a fermentation product. The active substance is a white or almost white, very hygroscopic powder and is very soluble in water.

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 Ph.Eur.

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 is in line with the CEP, with additional requirements for sterility and particulate matters. The specification is acceptable in view of the various European guidelines. Batch analytical data demonstrating compliance with this specification have been provided for three batches.

Stability of drug substance

The active substance is stable for 36 months 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 drug product, a powder for solution for infusion, was based on previous experience of the MAH in the manufacturing of the same dosage form. The amount of the active ingredient is

equivalent to the amount in the reference products. The compatibility of the product with different intravenous (IV)/intramuscular (IM) diluents has been adequately studied for all of the diluents compatible with the reference products.

Manufacturing process

The manufacturing process has been validated according to relevant European/ICH guidelines. Process validation data on the product have been presented for twelve full scale batches (three for each strength) in accordance with the relevant European guidelines.

Control of excipients

Nitrogen gas is used as protective gas in the glass vials. The excipient complies with Ph.Eur. requirements. These specifications are acceptable.

Microbiological attributes

The microbiological tests included in the specifications applied consist of the sterility test, the particulate matter test and the bacterial endotoxins test. All these tests are performed according to the general methods described in the current edition of the Ph.Eur. and the BP monograph for Amoxicillin Injection. The tests are in line with ICH Q8 the integrity of the container closure system as it relates to preventing microbial contamination is evaluated. This is acceptable.

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 description, identification, constituted solution, reconstitution time, colour, clarity of solution, alkalinity, water content, related substances, assay, uniformity of dosage units, sterility, bacterial endotoxins and particulate contamination sub visible particles. Limits in the specification have been justified and are considered appropriate for adequate quality control of the product. An adequate nitrosamines risk evaluation report has been provided. No risk for presence of nitrosamines in the drug product was identified.

Satisfactory validation data for the analytical methods have been provided.

Batch analytical data from for twelve full scale batches (three for each strength) from the proposed production site have been provided, demonstrating compliance with the specification.

Stability of drug product

Stability data on the product have been provided from three full scaled batches per strength (twelve batches in total) stored at 25°C/60% RH (36 months), 30°C/75 RH (36 months) and 40°C/75% RH (6 months) in accordance with applicable European guidelines. In line with *EMA guideline on Stability Testing: Stability testing of existing active substances and related finished product*s, photostability testing was conducted on at least one primary batch of each strength of the finished product. The light conditions are in line with ICH Q1B. This is acceptable. Based on the results of photostability studies, it can be concluded that the product is not photo-labile. On basis of the data submitted, a shelf life was granted of 36 months. No specific storage conditions needed to be included in the SmPC or on the label.

In-use stability studies show that for IV use the product is stable in the same diluents as those mentioned in the SmPC of the reference products. For IM use the drug product must be used immediately after reconstitution, as after 30 min the product is no longer compliant with the drug product specification.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies
There are no substances of ruminant animal origin present in the product nor have any been used in the manufacturing of this product, so a theoretical risk of transmitting TSE can be excluded.

II.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the member states consider that Amoxicilline Prolepha 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 Amoxicilline Prolepha is intended for generic substitution, this will not lead to an increased exposure to the environment. An environmental risk assessment was therefore not deemed necessary.

III.2 Discussion on the non-clinical aspects

This product is a generic formulation of Clamoxyl and Xyllomac which are available on the European market. Reference was made to the preclinical data obtained with the innovator products. A non-clinical overview on the pharmacology, pharmacokinetics and toxicology has been provided, which was 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 member states agreed that no further non-clinical studies are required.

IV. CLINICAL ASPECTS

IV.1 Introduction

Amoxicillin sodium is a well-known active substance with established efficacy and tolerability. A clinical overview has been provided, which is based on scientific literature. The member states agreed that no further clinical studies are required.

IV.2 Pharmacokinetics

Amoxicilline Prolepha, powder for solution for injection/infusion 250 mg, 500 mg, 1 g and 2 g are parenteral formulations and therefore fulfil the exemption mentioned in the Note for Guidance on bioequivalence "5.1.6 parenteral solutions", which states that a bioequivalence study is not required if the product is administered as an aqueous intravenous solution containing the same active substance in the same concentration as the currently authorised reference medicinal product (NfG CPMP/EWP/QWP 1401/98). The quantitative composition of Amoxicilline Prolepha is entirely the same as the originator. Therefore, it may be considered as therapeutic equivalent, with the same efficacy/safety profile as known for the active substance of the reference medicinal product. The current product can be used instead of its reference product.

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 Amoxicilline Prolepha. At the time of approval, the most recent version of the RMP was version 0.1 dated 3 March 2023.

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

Important identified risks	• Hypersensitivity reactions (anaphylactoid) • Convulsions • Acute generalised exanthemous pustulosis (AGEP) • Hepatic events • Antibiotic-associated colitis
Important potential risks	Prolongation of prothrombin time due to concomitant use with oral anticoagulants
Missing information	• Exposure during pregnancy • Exposure through human milk

The member states 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 products Clamoxyl and Xyllomac. No new clinical studies were conducted. 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 Amoxil and associated names (amoxicillin) powder for solution for injection or infusion, FR/H/0649 (for key safety messages) and to Aktiprol (amisulpride) tabletten, DK/H/2877 (for design/layout). 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

Amoxicilline Prolepha, powder for solution for injection/infusion 250 mg, 500 mg, 1 g and 2 g have a proven chemical-pharmaceutical quality and are generic forms of Clamoxyl 250 mg, powder for solution for injection/infusion and Xyllomac 500 mg, 1 g, 2 g, powder for solution for injection/infusion. Clamoxyl and Xyllomac are well-known medicinal products with an established favourable efficacy and safety profile.

Since both the reference and current products are intended for parenteral use, no bioequivalence study is deemed necessary.

The Board followed the advice of the assessors.

There was no discussion in the CMD(h). Agreement between member states was reached during a written procedure. The member states, on the basis of the data submitted, considered that essential similarity has been demonstrated for Amoxicilline Prolepha with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 18 July 2024.

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
NL/H/5810/001-004/IB/001/G	Replacement or addition of a manufacturing site for part or all of the manufacturing process of the finished product - Site where any manufacturing operation(s) take place, except batch release, batch control, and secondary packaging, for sterile medicinal products (including those that are aseptically manufactured) manufactured using an aseptic method excluding biological/ immunological medicinal products. Replacement or addition of a manufacturing site for part or all of the manufacturing process of the finished product - Secondary packaging site. Change to importer, batch release arrangements and quality control testing	No No No	17-2-2025	Approved	N.A.

	of the finished product - Replacement or addition of a site where batch control/testing takes place. Change in the batch size (including batch size ranges) of the finished product - Up to 10-fold compared to the originally approved batch size. Change in the manufacturing process of the finished product , including an intermediate used in the manufacture of the finished product - Minor change in the manufacturing process.	No No			
NL/H/5810/001-004/IB/002	Change in the batch size (including batch size ranges) of the finished product - Up to 10-fold compared to the originally approved batch size.	No	17-2-2025	Approved	N.A.
NL/H/5810/001-004/IB/003	Submission of a new or updated Ph. Eur. certificate of suitability or deletion of Ph. Eur. certificate of suitability: For an active substance, For a starting	No	25-2-2025	Approved	N.A.

	material/reagent /intermediate used in the manufacturing process of the active substance, For an excipient - European Pharmacopoeial Certificate of Suitability to the relevant Ph. Eur. Monograph - New certificate from a new manufacturer (replacement or addition).				
NL/H/5810/001 -004/IB/004	Change in the batch size (including batch size ranges) of the finished product - Up to 10-fold compared to the originally approved batch size.	No	3-9-2025	Approved	N.A.
NL/H/5810/001 -004/IB/005	Changes (Safety/Efficacy) to Human and Veterinary Medicinal Products - Other variation.	Yes	29-11-2025	Approved	N.A.
NL/H/5810/001 -004/IA/006	Submission of a new or updated Ph. Eur. certificate of suitability or deletion of Ph. Eur. certificate of suitability: For an active substance, For a starting material/reagent /intermediate used in the manufacturing process of the active	No	22-10-2025	Approved	N.A.

	substance, For an excipient - European Pharmacopoeial Certificate of Suitability to the relevant Ph. Eur. Monograph - Updated certificate from an already approved manufacturer.				