COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Extencin 1.200.000 and 2.400.000 IU, powder and solvent for suspension, for injection (benzylpenicillin benzathine)

NL License RVG: 124965 & 124966

Date: 12 October 2021

This module reflects the scientific discussion for the approval of Extencin. The marketing authorisation was granted on 7 January 2021. 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
CSF	Cerebrospinal fluid
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
CSF	Cerebrospinal fluid
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
OOS	Out of specification
Ph.Eur.	European Pharmacopoeia
PL	Package Leaflet
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 Extencin 1.200.000 and 2.400.000 IU, powder and solvent for suspension, for injection from Nordic Group B.V.

The product is indicated for intramuscular injection in adults, adolescents, children and neonates for the treatment and prophylaxis of the following infections caused by pathogens sensitive to penicillin:

Treatment

- Erysipelas;
- Syphilis: early syphilis (primary and secondary);
- Latent syphilis (except for neurosyphilis and presence of pathological cerebrospinal fluid (CSF) findings);
- Yaws;
- Pinta.

Prophylaxis

- Rheumatic fever (chorea, rheumatic carditis);
- Poststreptococcal glomerulonephritis;
- Erysipelas.

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 reference product Extencilline 1.2 MIU and 2.4 MIU powder and solvent for suspension for injection which has been registered by Sanofi Aventis France since 1983 (original product). The marketing authorisation holder (MAH) has purchased the dossier of the reference product from the manufacturer, this means the dossier of this national procedure is a duplication of the reference product. This was considered acceptable.

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

II. QUALITY ASPECTS

II.1 Introduction

Extencin is a white to almost-white powder with solvent and contains as active substance either 1.200.000 or 2.400.000 IU benzylpenicillin benzathine.

The powder is packed in a glass injection vial with a rubber stopper and aluminium cap. A glass ampoule of 5 ml which contains the solvent for injection is also supplied alongside the injection vial.

The excipients are soy lecithin, polysorbate 80, carmellose sodium, sodium citrate – anhydrous, povidone and water for injection (solvent).

The used excipients are well known and safe in the proposed concentrations. All excipients comply with the requirements in the relevant Ph.Eur. monographs.

II.2 Drug Substance

The active substance is benzylpenicillin benzathine, an established active substance described in the European Pharmacopoeia (Ph.Eur.). Benzylpenicillin benzathine is a white to almost-white powder which is very slightly soluble in water, freely soluble in dimethylformamide and formamide and slightly soluble in ethanol. The active substance is slightly hygroscopic and does not have any polymorphic forms.

The Active Substance Master File (ASMF) procedure is used for the active substance. The main objective of the ASMF procedure, commonly known as the European Drug Master File (EDMF) procedure, is to allow valuable confidential intellectual property or 'know-how' of the manufacturer of the active substance (ASM) to be protected, while at the same time allowing the applicant or MAH to take full responsibility for the medicinal product, the quality and quality control of the active substance. Competent Authorities/EMA thus have access to the complete information that is necessary to evaluate the suitability of the use of the active substance in the medicinal product.

Manufacturing process

The manufacturing process of the drug substance is a closed process, three starting materials are utilized. The process consists of the following steps: dissolution, filtration, crystallization, washing, draining, drying and spraying. Process validation is conducted on three consecutive batches.

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. Batch analytical data demonstrating compliance with this specification have been provided for three batches.

Stability of drug substance

The drug substance is not isolated. As a consequence, stability studies were not performed on the drug substance as a retest period does not have to be determined for the drug substance. Since the manufacturing process is continuous until the manufacture of the intermediate bulk powder, stability studies were performed on the intermediate product.

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 composition is the same as for Extencilline Sanofi, the originator product; since Sanofi has ceased production and marketing of Extencilline, Laboratoires Delbert have taken over the MAA. The formula is identical, therefore pharmaceutical development is not detailed. However, the manufacturers of active substance, bulk intermediate, and finished product, as well as the manufacturing process, are different. It is not possible to demonstrate that the manufacturing process provides product with the same quality as Extencilline Sanofi; therefore a comparison of Delbert product with Extencilline Sandoz, a product of different composition containing benzylbenzathine penicillin is provided. The physico-chemical comparison shows that assay, impurity content, pH, particle size before and after reconstitution are comparable.

Manufacturing process

The manufacturing process has been validated according to relevant European/ICH guidelines. The manufacturing process consists of the following steps: washing, sterilization, dosing, sealing and air blowing. As for the water for injection, the manufacturing process consists of tank filling, filtration, washing/depyrogenation, sealing and sterilization. Process validation data for the filling process of the product have been presented for seven batches in accordance with the relevant European guidelines. Process validation data for the process of the water for injection have been presented for three batches in accordance with the relevant European guidelines.

Control of excipients

The excipients comply with Ph. Eur. Requirements and in-house monographs. These specifications are acceptable.

Quality control of drug product

The finished product specifications are adequate to control the relevant parameters for the dosage form. The specification is based on monographs from the Ph.Eur. and includes tests for characterization, identification, pH, uniformity of mass, test for impurities, assay and microbiological tests. Limits in the specification have been justified and are considered appropriate for adequate quality control of the product.

Satisfactory validation data for the analytical methods have been provided.

Batch analytical data five batches from the proposed production sites have been provided, demonstrating compliance with the specification.

Stability of drug product

Stability data on the product have been provided for six batches (25°C/60% relative humidity (RH)) in accordance with applicable European guidelines demonstrating the stability of the product for three years. Tests at accelerated (40°C/75% RH) conditions were performed as

well. Stability studies have also been performed for two batches of premix intermediate product. Results of long term storage at 25°C±2°C /60%±5% RH are within the proposed specification limits. The sterile mixture is stable after a period of 12 months. Results of accelerated storage at 40°C±2°C/75%±5% RH are within the proposed specification limits with the exception for the content of benzathine which were marginally out of specification (OOS) at month one and month three. This OOS result has been attributed to the methodology. Nevertheless, the storage temperature is restricted to below 25°C.

For the water for injection three production scaled batches are included and tested under long term storage condition (25°C/60% RH), intermediate storage conditions (30°C/65% RH) and accelerated conditions (40°C/75% RH). The parameters included in the specification are all tested, acceptance criteria are identical to those at batch release. On basis of the data submitted, a shelf life was granted of three years for both the drug product as the water for injection without special precautions or storage conditions.

While results support storage of the reconstituted product (with water for injections) for up to 24 hours, the “Shelf-life after reconstitution” statement in the product information advises to use the reconstituted product immediately.

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 MEB considers that Extencin has a proven chemical-pharmaceutical quality. Sufficient controls have been laid down for the active substance and finished product. The following post-approval commitment was made:

1. Full process validation data for three additional batches of monosodium citrate (bioburden + dose mapping+ sterility result) will be presented.

III. NON-CLINICAL ASPECTS

III.1 Ecotoxicity/environmental risk assessment (ERA)

Since Extencin 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 Extencilline 1.2 MIU and 2.4 MIU powder and solvent for suspension for injection 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 agreed that no further non-clinical studies are required.

IV. CLINICAL ASPECTS

IV.1 Introduction

Extencin 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 agrees that no further clinical studies are required.

For this generic application, the MAH has not submitted any bioequivalence studies which is discussed below.

As the dossier from the drug product was purchased from the reference product manufacturer Delbert and is thus identical to this reference product, no bioequivalence studies have been performed. A statement from the MAH that confirms that these products are identical has been provided. Furthermore, a statement from the reference product manufacturer that confirms this as well has been submitted too. The absence of bioequivalence studies is justified and therefore acceptable.

IV.2 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 Extencin.

Summary table of safety concerns as approved in RMP

Important identified risks	• Jarisch-Herxheimer reaction (Syphilis) • Hypersensitivity including severe immediate hypersensitivity to benzathine benzylpenicillin, other penicillins, to another betalactam agent, or to any of the excipients • Antibiotic associated pseudomembranous colitis • Hoigne syndrome

	• Tissue damage and increased local vascularization
Important potential risks	• Lack of efficacy due to resistance
Missing information	• Use in haemodialysis patients

The MEB agreed that routine pharmacovigilance activities and routine risk minimisation measures are sufficient for the risks and areas of missing information.

IV.3 Discussion on the clinical aspects

For this authorisation, reference is made to the experience with the innovator product Extencilline 1.2 MIU and 2.4 MIU powder and solvent for suspension for injection. 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

No user consultation studies have been performed and no bridging report was provided. This is considered acceptable.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Extencin 1.200.000 and 2.400.000 IU, powder and solvent for suspension, for injection has a proven chemical-pharmaceutical quality and is a generic form of insert name of reference Extencilline 1.2 MIU and 2.4 MIU powder and solvent for suspension for injection. Extencilline 1.2 MIU and 2.4 MIU powder and solvent for suspension for injection is a well-known medicinal product with an established favourable efficacy and safety profile

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 Extencin with the reference product, and have therefore granted a marketing authorisation. Extencin was authorised in the Netherlands on 7 January 2021.

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 II: B.I.a.1.b	Change in the manufacturer of a starting material/ reagent/intermediate used in the manufacturing process of the active substance or change in the manufacturer (including where relevant quality control testing sites) of the active substance, where no Ph. Eur. Certificate of Suitability is part of the approved dossier. *Introduction of a manufacturer of the active substance supported by an ASMF*	None	20-7-2021	Approval	--