COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Imeros 3% w/v solution for injection (mepivacaine hydrochloride)

NL/H/5083/001/DC

Date: 22 November 2021

This module reflects the scientific discussion for the approval of Imeros 3% w/v solution for injection. The procedure was finalised at 8 July 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
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
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
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 Imeros 3% w/v solution for injection, from Intermed S.A.

Imeros 3% w/v Solution for injection is a local anaesthetic indicated for the local and loco-regional anaesthesia in dental surgery in adults, adolescents and children above 4 years of age (c.a. 20 kg of body weight).

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

This decentralised procedure concerns a hybrid application claiming essential similarity with the innovator product Scandonest 30 mg/ml solution for injection (NL RVG 09269) which has been registered in the Netherlands by Septodont NV-SA since 20 May 1990 by a full application procedure.

The concerned member states (CMS) involved in this procedure were Cyprus and Greece.

The marketing authorisation has been granted pursuant to Article 10(3) of Directive 2001/83/EC.

II. QUALITY ASPECTS

II.1 Introduction

Imeros is a clear, colourless, odourless solution for injection with a pH between 4.5 and 6.8 and osmolarity between 270 and 320 mOsmol/ kg. 1 ml solution for injection contains 30 mg of mepivacaine hydrochloride. Each cartridge of 1.7 ml of solution for injection contains 51 mg of mepivacaine hydrochloride.

The solution for injection is packed in clean, pre-sterilised, crimped, siliconised type I glass single dose cartridges, sealed with grey, sterile plunger stoppers made by bromobutyl rubber and a cap made of aluminium with a bromo butyl rubber membrane. These cartridges are stored in PVC/aluminium blisters and boxes.

The excipients are: sodium chloride, sodium hydroxide (for pH-adjustment) (E524) and water for injection.

II.2 Drug Substance

The active substance is mepivacaine hydrochloride, an established active substance described in the European Pharmacopoeia (Ph.Eur.). The active substance is a white or almost white crystalline powder, freely 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 drug substance specification is provided by the MAH, which is based on the Ph. Eur. monograph of mepivacaine hydrochloride. The additional test for residual solvent stated in the CEP is covered by the loss on drying test in the drug substance specification of the drug product manufacturer. Analytical methods and references to Ph. Eur. methods are adequate. Batch analytical results are provided for one batch, as the drug product manufacturer has tested only one batch. Reference to the CEP and commitment to provide more batch data as soon as available are accepted. An additional control for microbiological quality of the drug substance is included in the drug substance specification, suitability of the Ph. Eur. methods in presence of the drug substance has been demonstrated. The information about reference standards in use at the drug product manufacturing site is adequate.

Stability of drug substance
The active substance is stable for five years when stored under the stated conditions. Assessment thereof was part of granting the CEP and has been granted by the EDQM. Compliance to the limits for microbial quality has been demonstrated throughout the retest period of the drug substance.

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 properties of the drug substance and excipients are adequately discussed. As the chosen excipients are very simple and common ones, it is acceptable that no compatibility studies

with the drug substance are performed. No functionality related characteristics are relevant for these excipients. Essential similarity from a pharmaceutical point of view is demonstrated including in the study of three batches each of test and reference product. The only difference is in target pH of the two products, however an adequate justification is provided for this difference having no impact on efficacy and safety of the product. The manufacturing process development is not described in terms of trial batches and results, however sufficient justifications are provided for the chosen parameters. The MAH clarified that a theoretical risk of loss of sterility is present after freezing of the cartridges. A suitable warning about this has been included in the SmPC. An acceptable justification is provided for the choice of filtration and aseptic filling as sterilisation method for the drug product. Acceptable justification is provided for the choice of sterilisation method for the primary container components. The validation report of the sterilisation process has been provided. Upon request, an updated validation report and additional data from recent runs are provided. The sterilisation cycle for the empty cartridges is considered suitable.

Manufacturing process

The manufacturing process consists of dissolving the active substance in water, addition of sodium chloride, pH adjustment, aseptic filtration, aseptic filling, sealing and packaging. The manufacturing process and control of critical steps are described with sufficient details, regarding the finished product manufacture, the filtration steps and the sterilisation of cartridges. Total process holding time is minimized and clearly stated. Process validation data on the product have been presented for three commercial size batches in accordance with the relevant European guidelines.

Filter validation reports are provided, which confirm suitability of the chosen filters for the intended use. For the sterilisation processes of the cartridges sufficient validation data, as requested in the guideline on sterilisation, has been provided. The rubber stoppers are sterilised using a standard gamma irradiation process and an adequate ISO certificate is provided for the site, therefore no additional validation information is requested.

Control of excipients

The excipients comply with Ph. Eur. requirements. Sodium hydroxide is purchased as pellets and the 2.5 M solution is prepared at the drug product manufacturing site with water for injections. 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 includes tests for appearance, identification, assay, related substances, uniformity of dosage units (by mass variation), pH, osmolality, extractable volume, particulate contamination, sterility and bacterial endotoxins. Limits in the specification have been justified and are considered appropriate for adequate quality control of the product. The analytical methods are described with sufficient details and analytical method validation reports are provided. The methods are adequately validated and stability indicating nature is demonstrated by forced degradation studies, which showed degradation in oxidizing conditions.

Satisfactory validation data for the analytical methods have been provided.

Batch analytical data from three batches from the proposed production site have been provided, demonstrating compliance with the specification. Risk assessments about elemental impurities as per ICH Q3D is provided. It is adequately performed and the conclusion is that no risk is identified. An adequate risk evaluation concerning the presence of nitrosamine impurities in the finished product has been provided, no risk is identified.

Stability of drug product

Stability data on the product have been provided for three process validation batches stored at 25°C/60%RH (planned up to 36 months, results available up to 24 months) and 40°C/75%RH (study completed up to six months) in accordance with applicable ICH stability guidelines. The batches were packaged as proposed for commercial use. A photostability study in accordance with ICH recommendations is presented and the results confirm that the finished product is not sensitive to light. On basis of the data submitted, a shelf life was granted of 36 months. The labelled storage condition "Do not freeze" is agreed on based on available results.

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 Imeros 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 Imeros is intended for hybrid 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 hybrid formulation of Scandonest 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 member states agreed that no further non-clinical studies are required.

IV. CLINICAL ASPECTS

IV.1 Introduction

Mepivacaine hydrochloride 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 member states agreed that no further clinical studies are required.

IV.2 Pharmacokinetics

Imeros 3% w/v solution for injection is a parenteral formulation and therefore fulfils 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 authorized reference medicinal product (CPMP/EWP/QWP/1401/98 Rev. 1/ Corr). The quantitative composition of Imeros 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.

<u>Biowaiver</u>
The reasons provided by the MAH to justify a waiver for a bioequivalence study are in accordance with the principles mentioned in Appendix II of the Guideline on Bioequivalence for Parenteral solutions.

- Mepivacaine is a well-known active ingredient with a favourable efficacy and safety profile, available in clinical practice as solution for injection for more than 60 years.
- Both the reference and test products are of the same type, containing the exact same concentration in active substance.
- Both the reference and test products have the exact same method, means and route of administration, the exact same indications and posology.
- Both the reference and test products have the exact same qualitative composition in excipients.

- No excipients are presented in the test formulation that could interact with the drug substance and affect local residence time, in vivo solubility, in vivo stability of the active substance or alter the pharmacokinetic and pharmacodynamic profile of mepivacaine, as compared to the reference medicinal product.

The physical-chemical properties of the test and reference product were comparable. A concern was raised regarding the difference in pH between the Imeros and the reference product. Therefore, the MAH procured two additional batches of reference product and provided testing of additional physicochemical characteristics in three batches of reference product and three of proposed product. The results show adequate similarity of all parameters, including the release parameters, osmolality, density and viscosity.
The only significant difference observed is in the pH value. However, the lower pH value of Imeros is not expected to have any impact on safety and efficacy, as it is in line with that of several other similar products and of the USP monograph for mepivacaine HCl injections and it is demonstrated to have no negative effect on stability of the product.
Based on the additional results provided, the similarity of formulation with the reference product and the principles of the Guideline on Bioequivalence, Appendix II, the response was considered acceptable and the waiver of bioequivalence studies has been granted.

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 Imeros.

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

Important identified risks	• Toxic reactions (cardiovascular or neurological) due to overdose or rapid intravenous injections • Allergic reactions
Important potential risks	None
Missing information	None

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 product Scandonest. No new clinical studies were conducted. The MAH demonstrated that the pharmacokinetic profile of the product is similar to the pharmacokinetic profile of this reference product. Risk management is adequately addressed. This hybrid medicinal product can be used instead of the reference product.

V. USER CONSULTATION

The package leaflet (PL) has been evaluated via a user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC. The language used for the purpose of user testing the PL was English.
The test consisted of a pilot test with three participants, followed by two rounds with ten participants each. The questions covered the following areas sufficiently: traceability, comprehensibility and applicability.
The results show that the PL meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Since both the reference and current product are intended for parenteral use, no bioequivalence study is deemed necessary. A biowaiver has been granted.

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 Imeros with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 8 July 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