LÄKEMEDELSVERKET
SWEDISH MEDICAL PRODUCTS AGENCY

Public Assessment Report
Scientific discussion

Mepivacaine Accord
(mepivacaine hydrochloride, mepivacaine)

SE/H/2551/001-002/DC

This module reflects the scientific discussion for the approval of Mepivacaine Accord. The Public Assessment Report was written in February 2020 by the previous RMS (DE) after initial procedure (DE/H/5960/01-02) and is attached at the end of this document. RMS transfer from DE to SE was completed 25 January 2024. For information on changes after this date please refer to the module 'Update'.

Postadress/Postal address: P.O. Box 26, SE-751 03 Uppsala, SWEDEN
Besöksadress/Visiting address: Dag Hammarskjölds väg 42, Uppsala
Telefon/Phone: +46 (0)18 17 46 00 Fax: +46 (0)18 54 85 66
Internet: www.lakemedelsverket.se E-mail: registrator@lakemedelsverket.se

LÄKEMEDELSVERKET
SWEDISH MEDICAL PRODUCTS AGENCY

Public Assessment Report – Update

Procedure number*	Scope	Product Information affected (Yes/No)	Date of end of procedure	Approval/ non approval	Summary/ Justification for refuse

*Only procedure qualifier, chronological number and grouping qualifier (when applicable)

Postadress/Postal address: P.O. Box 26, SE-751 03 Uppsala, SWEDEN
Besöksadress/Visiting address: Dag Hammarskjölds väg 42, Uppsala
Telefon/Phone: +46 (0)18 17 46 00 Fax: +46 (0)18 54 85 66
Internet: www.lakemedelsverket.se E-mail: registrator@lakemedelsverket.se

Decentralised Procedure

Public Assessment Report

Mepivacainhydrochlorid Accord 10 // 20 mg/ml Injektionslösung

Mepivacaine hydrochloride

DE/H/5960/001-002/DC

(formerly UK/H/6116/001-002/DC)

Applicant: Accord Healthcare Limited

Date: 27.02.2020

This module reflects the scientific discussion for the approval of "Mepivacainhydrochlorid Accord 10 // 20 mg/ml Injektionslösung". The procedure was finalised on 17th May 2016.

TABLE OF CONTENTS

ADMINISTRATIVE INFORMATION

Name of the medicinal product in the RMS:	Mepivacainhydrochlorid Accord 10 // 20 mg/ml Injektionslösung
Name of the drug substance (INN name):	Mepivacaine hydrochloride
Pharmaco-therapeutic group (ATC Code):	N01BB03

Pharmaceutical form(s) and strength(s):	Solution for injection; 10 // 20 mg/ml
Reference Number(s) for the Decentralised Procedure:	DE/H/5960/001-002/DC (formerly UK/H/6116/001002/DC)
Reference Member State:	DE (formerly UK)
Concerned Member States:	AT, BE, DK, FR, IT, SE, UK
Applicant (name and address):	Accord Healthcare Limited Sage House, 319, Pinner Road HA1 4HF NORTH HARROW, MIDDLESEX United Kingdom

I. INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the Member States considered that the applications for Mepivacaine hydrochloride solution for injection (PL 20075/0448-449; UK/H/6116/001-2/DC) could be approved. The products are prescription-only medicines (POM) and are indicated for local anaesthesia by infiltration of the fingers, toes, ears, nose and penis and in other cases where adrenaline is considered contraindicated; peripheral nerve block; caudal anaesthesia and non-obstetric epidural anaesthesia.

The applications were submitted using the Decentralised Procedure (DCP), with the UK as Reference Member State (RMS), and Austria, Belgium, Germany, Denmark, France, Italy, Poland and Sweden as Concerned Member States (CMS). The applications were submitted under Article 10(1) of Directive 2001/83/EC, as amended, as generic applications. The reference medicinal products for these applications are Carbocain 10 mg/ml and 20 mg/ml injektionsvätska, lösning (AstraZeneca AB) which were first authorised in Sweden to AstraZeneca AB (marketing authorisation numbers 59695970) on 11 December 1987.

Mepivacaine hydrochloride is a local anaesthetic of the amide type with rapid onset of effect and reversible blockade of vegetative, sensory and motor nerve fibres as well as cardiac conduction. It is assumed that its effect is due to the blocking of sodium channels in the nerve membrane. Mepivacaine hydrochloride solution has a pH of 5.5 to 6.5 and a pKa value of 7.6. The ratio of dissociated to lipid-soluble base is determined by the pH of the tissues.

The active substance is diffused initially by the nerve membrane to the nerve fibre in the alkaline form, but becomes effective as a mepivacaine cation only after reprotonation. Where pH values are low, e.g. in tissue with inflammatory changes, only small amounts are available in alkaline form, and so adequate anaesthesia cannot be achieved.

The motor blockade does not outlast the analgesia.

No new non-clinical studies were conducted, which is acceptable given that the applications were based on being generic medicinal products of originator products that have been licensed for over 10 years.
No new clinical data have been submitted and none are required for applications of this type. A bioequivalence study was not necessary to support these applications as both test and reference products are aqueous solutions at the time of administration.

The RMS has been assured that acceptable standards of Good Manufacturing Practice (GMP) are in place at all sites responsible for the manufacture, assembly and batch release of this product.
For manufacturing sites within the Community, the RMS has accepted copies of current manufacturer authorisations issued by inspection services of the competent authorities as certification that acceptable standards of GMP are in place at those sites.

For manufacturing sites outside the Community, the: RMS has accepted copies of current GMP Certificates of satisfactory inspection summary reports, issued by the inspection services of the competent authorities (or those countries with which the EEA has a Mutual Recognition Agreement for their own territories) as certification that acceptable standards of GMP are in place at those noncommunity sites.

The RMS and CMS considered that the application could be approved at the end of procedure (Day 210) on 17 May 2016. After a subsequent national phase, licences were granted in the UK on 06 June 2016 and in Germany on 18th August 2016.

After changing the RMS, Germany is the new RMS. The former procedure number was UK/H/6116/001-002/DC.

II. QUALITY ASPECTS

II.1 Introduction

Mepivacaine hydrochloride 10mg/ml solution/or injection:
Each ml contains 10 mg of the active ingredient mepivacaine hydrochloride.
Each 10 ml ampoule contains mepivacaine hydrochloride 100 mg. Each 20 ml vial contains mepivacaine hydrochloride 200 mg.

Mepivacaine hydrochloride 20mg/ml solution for injection
Each ml contains 20 mg the active ingredient mepivacaine hydrochloride.
Each 2 ml ampoule contains mepivacaine hydrochloride 40 mg.
Each 5 ml ampoule contains mepivacaine hydrochloride 100 mg.
Each 10 ml ampoule contains mepivacaine hydrochloride 200 mg. Each 20 ml vial contains mepivacaine hydrochloride 400 mg.

Other ingredients consist of the pharmaceutical excipients sodium chloride, sodium hydroxide (for pH adjustment), hydrochloric acid (for pH adjustment) and Water for injections. The finished product is packed into:
Mepivacaine hydrochloride 10mg/ml solution/or injection:

- 10 ml red band Type I glass ampoules, supplied in packs of 1 and 5 ampoules
- 20 ml Type I glass vials with chlorobutyl rubber stopper and mist grey flip-off seal, supplied in packs of 1, 5 and 10 vials.

Mepivacaine hydrochloride 20mg/ml solution for injection

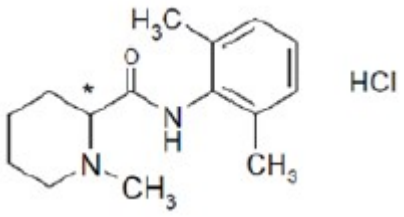
- 2 ml green band Type I glass ampoules, supplied in packs of 1 and 5 ampoules
- 5 ml red band Type I glass ampoules, supplied in packs of 1, 5, 10 and 50 ampoules
- 10 ml green band Type I glass ampoules, supplied in packs of 1 and 5 ampoules
- 20 ml Type I glass vials with chlorobutyl rubber stopper and lavender flip-off seal, supplied in packs of 1, 5 and 10 vials.

The ampoules are available as blister/tray packs. Not all packs may be marketed.
Satisfactory specifications and Certificates of Analysis have been provided for all packaging components.

II.2 Drug substance

INN name:	Mepivacaine hydrochloride
Chemical name:	(*RS*)-N-(2,6-dimethylphenyl)-1-methylpiperidine-2-carboxamide hydrochloride

Structural formula:



Molecular formula:	$(C_{15}H_{22}N_2O)$ HCl
Molecular mass:	282.8 g/mol
Appearance:	White or almost white, crystalline powder
Solubility:	Freely soluble in water and ethanol (96%), very slightly soluble in methylene chloride.

Mepivacaine hydrochloride is the subject of a European Pharmacopoeia monograph.

All aspects of the manufacture and control of the active substance, mepivacaine hydrochloride, are covered by the European Directorate for the Quality of Medicines and Health care (EDQM)
Certificate of Suitability.

II.3 Medicinal product

I.1.1.1.1.1 Pharmaceutical Development

The objective of the development programme was to formulate a safe, efficacious, solution for injection containing 10 mg or 20 mg mepivacaine hydrochloride per ml of solution that was comparable to the originator products Carbocain 10 mg/ml and 20 mg/ml injektionsvätska, lösning (AstraZeneca AB).
A satisfactory account of the pharmaceutical development has been provided.
All excipients comply with their respective European Pharmacopoeia monographs.
Satisfactory Certificates of Analysis have been provided for all excipients. Suitable batch analysis data have been provided for each excipient.
None of the excipients contain materials of animal or human origin.
No genetically modified organisms (GMO) have been used in the preparation of this product.

I.1.1.1.1.2 Manufacture of the product

Satisfactory batch formulae have been provided for the manufacture of the product, along with an appropriate account of the manufacturing process. The manufacturing process has been validated at commercial scale batch size and has shown satisfactory results. The process validation protocols to be followed for manufacture of a further commercial scale batch of each presentation of each strength are presented and are satisfactory.

I.1.1.1.1.3 Finished Product Specification

The finished product specification proposed is acceptable. Test methods have been described that have been adequately validated. Batch data have been provided that comply with the release specifications.
Certificates of Analysis have been provided for all working standards used.

I.1.1.1.1.4 Stability of the Product

Finished product stability studies were performed in accordance with current guidelines on batches of finished product in the packaging proposed for marketing. The data from these studies support a shelf-life of 2 years for the unopened via ampoule with no special storage conditions. Do not freeze. Suitable post approval stability commitments have been provided to continue stability testing on batches of finished product.

II.4 Discussion on chemical, pharmaceutical and biological aspects

There are no objections to the approval of these applications from a pharmaceutical viewpoint.

III. NON-CLINICAL ASPECTS

III.1 Introduction

As the pharmacodynamic, pharmacokinetic and toxicological properties of mepivacaine hydrochloride are well-known, no new non-clinical studies are required and none have been provided. An overview based on the literature review is, thus, appropriate.
The applicant's non-clinical expert report has been written by an appropriately qualified person and is satisfactory, providing an appropriate review of the relevant non-clinical pharmacology, pharmacokinetics and toxicology.

III.2 Pharmacology

Not applicable for this product type. Refer to section 'III.I; Introduction' detailed above.

III.3 Pharmacokinetics

Not applicable for this product type. Refer to section 'III.I; Introduction' detailed above.

III.4 Toxicology

Not applicable for this product type. Refer to section 'III.I; Introduction' detailed above.

III.5 Environmental Risk Assessment (ERA)

Since Mepivacaine hydrochloride solution for injection 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.6 Discussion on the non-clinical aspects

There are no objections to the approval of these applications from a non-clinical viewpoint.

IV. CLINICAL ASPECTS

IV.1 Introduction

No new efficacy or safety studies have been performed and none are required for this type of application. A comprehensive review of the published literature has been provided by the applicant, citing the well-established clinical pharmacology, efficacy and safety of mepivacaine hydrochloride. Based on the data provided, Mepivacaine hydrochloride solution for injection can be considered a generic of Carbocain 10 mg/ml and 20 mg/ml injektionsvätska, lösning (AstraZeneca AB).

IV.2 Pharmacokinetics

A bioequivalence study was not submitted as the products meet the criteria regarding parenteral solutions specified in the CHMP guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev. 1/Corr**). The test products are aqueous solutions at the time of administration and contains the same active substance in the same concentration as the reference products and the same excipients in similar amounts as the reference products.

IV.3 Pharmacodynamics
No new pharmacodynamic data were submitted and none were required for an application of this type.

IV.4 Clinical efficacy
No new efficacy data were submitted and none were required for an application of this type.

IV.5 Clinical safety
No new safety data were submitted and none were required for this application.

IV.6 Risk Management Plan
The marketing authorisation holder (MAH) has submitted a risk management plan (RMP), 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 Mepivacaine hydrochloride solution for injection.

A summary of safety concerns and planned risk minimisation activities, as approved in the RMP, is listed below:
Summary table of safety concerns:

Important identified risks	– Toxic reactions (cardiovascular or neurological) due to overdose or rapid intravenous injections – Allergic reactions
Important potential risks	– Foetotoxicity
Missing information / special patient population	– Use in children aged below 1 year

Routine pharmacovigilance and routine risk minimisation are proposed for all safety concerns.

IV.7 Discussion on the clinical aspects
The grant of marketing authorisations is recommended for these applications.

V. USER CONSULTATION
The package leaflet 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 PIL was English.
The results show that the package leaflet 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

I.1.2 RECOMMENDATION

The quality of the product is acceptable, and no new non-clinical or clinical safety concerns have been identified. Extensive clinical experience with mepivacaine hydrochloride is considered to have demonstrated the therapeutic value of the compound. The product is considered bioequivalent to the marketed reference product. The benefit-risk is, therefore, considered to be positive.

I.1.2.1.1 Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and Labels

In accordance with Directive 2010/84/EU the Summaries of Product Characteristics (SmPC) and Patient Information Leaflets (PIL) for products granted Marketing Authorisations at a national level are available on the MHRA website.

The application is approved. For intermediate amendments see current product information.