Public Assessment Report

Decentralised Procedure

Mepivacaine hydrochloride 10mg/ml solution for injection
Mepivacaine hydrochloride 20mg/ml solution for injection
(Mepivacaine hydrochloride)

Procedure No: UK/H/6116/001-2/DC

UK Licence No: PL 20075/0448-449

Accord Healthcare Limited
LAY SUMMARY

Mepivacaine hydrochloride 10mg/ml solution for injection

Mepivacaine hydrochloride 20mg/ml solution for injection

(Mepivacaine hydrochloride, solution for injection, 10mg/ml and 20mg/ml)

This is a summary of the Public Assessment Report (PAR) for Mepivacaine hydrochloride 10mg/ml solution for injection (PL 20075/0448; UK/H/6116/001/DC) and Mepivacaine hydrochloride 20mg/ml solution for injection (PL 20075/0449; UK/H/6116/002/DC). It explains how Mepivacaine hydrochloride 10mg/ml and 20mg/ml solution for injection were assessed and their authorisation recommended, as well as their conditions of use. It is not intended to provide practical advice on how to use Mepivacaine hydrochloride 10mg/ml and 20mg/ml solution for injection.

For practical information about using Mepivacaine hydrochloride 10mg/ml and 20mg/ml solution for injection, patients should read the package leaflet or contact their doctor or pharmacist.

The products will be collectively referred to as Mepivacaine hydrochloride solution for injection throughout the remainder of this public assessment report.

What is Mepivacaine hydrochloride solution for injection and what is it used for?
Mepivacaine hydrochloride solution for injection is a ‘generic medicine’. This means that Mepivacaine hydrochloride solution for injection is similar to a ‘reference medicine’ already authorised in the European Union (EU) called Carbocain 10 mg/ml and 20 mg/ml injektionsvätska,lösning (AstraZeneca AB).

This medicine is used for the temporary localised elimination of pain sensation by local infiltration and regional nerve block injection.

How does Mepivacaine hydrochloride solution for injection work?
Mepivacaine hydrochloride solution for injection contains the active substance mepivacaine hydrochloride which belongs to a group of medicines called ‘local anaesthetics’ (numbing medicines), which work by blocking the nerve impulses that send signals to the brain.

How is Mepivacaine hydrochloride solution for injection used?
The pharmaceutical form of this medicine is a solution for injection. The route of administration of this medicine is by injection in one of the following places:

- Into the skin (infiltration)
- Under the skin near a nerve (regional, plexus or nerve blockade)
- Around the spinal cord (thoracic or lumbar epidural or caudal anaesthesia).

The part of the body where that patient will be injected will depend on why the patient is being prescribed this medicine.

Mepivacaine hydrochloride solution for injection will be given to the patient by a doctor. The patient’s doctor will know the correct way to give them this medicine.
The recommended dose that the patient’s doctor gives them will depend on the type of pain relief that they need and the part of their body that the medicine will be injected into. It will also depend on the patient’s body weight, age and physical condition.

Mepivacaine hydrochloride solution for injection should be given as a slow injection. The maximum recommended dose for single administration is:

- **ENT region**: 200 mg mepivacaine hydrochloride (3 mg/kg body weight),
- **Intercostal blockade**: 300 mg mepivacaine hydrochloride (4 mg/kg body weight),
- **Epidural anaesthesia and peripheral blockades**: 400 mg mepivacaine hydrochloride (6 mg/kg body weight),
- **Plexus anaesthesia**: 500 mg mepivacaine hydrochloride (7 mg/kg body weight).
- **For caudal anaesthesia in children**: 5 mg/kg body weight. Individual differences are possible; please see section 3 of the package leaflet for further information.

Please read section 3 of the package leaflet for detailed information on dosing recommendations, the route of administration, and the duration of treatment.

This medicine can only be obtained with a prescription.

**What benefits of Mepivacaine hydrochloride solution for injection have been shown in studies?**

No additional studies were needed as Mepivacaine hydrochloride solution for injection is a generic medicine that is given as an injection and contains the same active substance as the reference medicine, Carbocain 10 mg/ml and 20 mg/ml injektionsvätska, lösning (AstraZeneca AB).

**What are the possible side effects of Mepivacaine hydrochloride solution for injection?**

Because Mepivacaine hydrochloride solution for injection is a generic medicine, its benefits and possible side effects are taken as being the same as the reference medicine.

For the full list of restrictions, see the package leaflet.

For the full list of all side effects reported with Mepivacaine hydrochloride solution for injection, see section 4 of the package leaflet available on the MHRA website.

**Why was Mepivacaine hydrochloride solution for injection approved?**

It was concluded that, in accordance with EU requirements, Mepivacaine hydrochloride solution for injection has been shown to have comparable quality and to be comparable to Carbocain 10 mg/ml and 20 mg/ml injektionsvätska, lösning (AstraZeneca AB). Therefore, the MHRA decided that, as for Carbocain 10 mg/ml and 20 mg/ml injektionsvätska, lösning (AstraZeneca AB), the benefits are greater than its risk and recommended that it can be approved for use.

**What measures are being taken to ensure the safe and effective use of Mepivacaine hydrochloride solution for injection?**

A risk management plan (RMP) has been developed to ensure that Mepivacaine hydrochloride solution for injection is used as safely as possible. Based on this plan, safety information has been included in the Summary of Product Characteristics and the package leaflet for Mepivacaine hydrochloride solution for injection including the appropriate precautions to be followed by healthcare professionals and patients.

Known side effects are continuously monitored. Furthermore new safety signals reported by patients/healthcare professionals will be monitored/reviewed continuously.
Other information about Mepivacaine hydrochloride solution for injection
Austria, Belgium, Germany, Denmark, France, Italy, Poland, Sweden and the UK agreed to grant Marketing Authorisations for Mepivacaine hydrochloride solution for injection on 17 May 2016. Marketing Authorisations were granted in the UK on 06 June 2016.

The full PAR for Mepivacaine hydrochloride solution for injection follows this summary.

For more information about treatment with Mepivacaine hydrochloride solution for injection, read the package leaflet, or contact your doctor or pharmacist.

This summary was last updated in July 2016.
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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 5969-5970) 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 non-Community 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.
II QUALITY ASPECTS

II.1 Introduction
Mepivacaine hydrochloride 10mg/ml solution for 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 for 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: Mepivacaine hydrochloride
Chemical name: \((RS)-N-(2,6\text{-dimethylphenyl})\text{-1-methylpiperidine-2-carboxamide}\) hydrochloride

Structural formula:

![Structural formula of Mepivacaine hydrochloride]

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 Healthcare (EDQM) Certificate of Suitability.

II.3. **Medicinal Product**

**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.

**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.

**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.

**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 vial/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.1; Introduction’ detailed above.

III.3 Pharmacokinetics
Not applicable for this product type. Refer to section ‘III.1; Introduction’ detailed above.

III.4 Toxicology
Not applicable for this product type. Refer to section ‘III.1; Introduction’ detailed above.

III.5 Ecotoxicity/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 (RMP)
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, are 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 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.
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 approved labelling for this medicine is presented below:
Mepivacaine hydrochloride 10mg/ml and 20mg/ml solution for injection

Mepivacaine Hydrochloride
For Perineural use,
Epidural use and Infiltration
Read the package leaflet before use.

accord

100 %
un-winding direction

200 mg/10 ml

Mepivacaine hydrochloride 20mg/ml solution for injection

Mepivacaine Hydrochloride
For Perineural use,
Epidural use and Infiltration
Read the package leaflet before use.

accord

200 %
Mepivacaine hydrochloride 20mg/ml solution for injection

Mepivacaine Hydrochloride

Each ml contains Mepivacaine hydrochloride 20 mg.
Each 10 ml ampoule of solution contains 200 mg Mepivacaine hydrochloride.

Excipients: sodium chloride, sodium hydroxide, hydrochloric acid, water for injections.
Contains sodium
See leaflet for further information

For single use only.

5 x 10 ml ampoule

5 x 10 ml ampoule