COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Mepicart 30 mg/ml solution for injection (mepivacaine hydrochloride)

NL/H/5377/001/DC

Date: 12 September 2023

This module reflects the scientific discussion for the approval of Mepicart 30 mg/ml solution for injection. The procedure was finalised on 5 July 2022. 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
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 Mepicart 30 mg/ml solution for injection, from Inibsa Dental S.L.U. (Spain).

The product is 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.

The marketing authorisation has been granted pursuant to Article 10a of Directive 2001/83/EC, a so-called bibliographic application based on the well-established medicinal use of mepivacaine hydrochloride. This type of application does not require submission of the results of pre-clinical tests or clinical trials if it can be demonstrated that the active substance of the medicinal product has been in well-established medicinal use within the community for at least ten years, with recognised efficacy and an acceptable level of safety.

The concerned member states (CMS) involved in this procedure were Belgium, Bulgaria, Cyprus, Denmark, Estonia, Finland, Latvia, Lithuania, Luxembourg and Poland.

II. QUALITY ASPECTS

II.1 Introduction

Mepicart is a colourless and clear solution for injection, free from particles, with a pH of 5.5-6.5 and an osmolality of 272-300 mOsm/kg. 1 mL solution for injection contains 30 mg of mepivacaine hydrochloride as active substance. The solution is packaged in neutral colourless glass (type I) cartridges for single use. The cartridges are provided with a bromobutyl plunger on one side and an aluminium cap with a central orifice with a bromobutyl disc on the other side. Two types of cartridges are used for this product: cartridges with a flat plunger for self-aspiration and cartridges with a plunger with a cavity for manual aspiration. Each cartridge contains 1.8 mL of solution for injection of 54 mg mepivacaine hydrochloride. The cartridges are packed in a PVC/medical-grade paper, PET-PE/PET or PET-PE/PVC blisters.

The excipients are sodium chloride, sodium hydroxide (E524) (for pH-adjustment), hydrochloric acid (E507) (for pH-adjustment) 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.). Mepivacaine hydrochloride is a white or almost white crystalline powder, freely soluble in water and alcohol. The polymorphic form and

particle size distribution are not considered critical parameters as the drug substance is completely dissolved in the drug product.

The Certificate of Suitability to the monographs of the European (CEP) procedure is used for the active substance. Two suppliers are proposed for the active substance, for each a valid CEP was submitted. 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 meets the requirements of the Ph.Eur. which includes testing for: appearance, solubility, identification, appearance of solution, pH, optical rotation, impurity, loss on drying, sulphated ash, related substances, residual solvents, and assay. Skip tests for biological tests (bioburden, pathogens and bacterial endotoxins) were also submitted. Furthermore, tests for identification and quantification of residual solvents were included as stated on the corresponding CEP. Batch analytical data demonstrating compliance with this specification have been provided for at for at least two batches of each production site.

Stability of drug substance

The active substance is stable for 5 years, no special storage conditions are required when stored as described in the CEP. 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 choice of excipients is justified and their functions explained. The physicochemical properties of the proposed drug product have been discussed in view of literature. As the chosen excipients are common, it is acceptable that no compatibility studies with the drug substance are performed. No functionality related characteristics are relevant for these excipients. The choice of filtration and aseptic filling as sterilisation method for the drug product has been justified and were considered acceptable.

Manufacturing process

The manufacturing process has been validated according to relevant European guidelines. Process validation data on the product have been presented for a range of batch sizes in accordance with European guidelines. The manufacturing process consists of dissolving the active substance in water for injection, addition of sodium chloride, pH adjustment, aseptic filtration, aseptic filling of cartridges, sealing and packaging. The compounding and filling operations are considered adequately validated on three commercial size batches (both minimum and maximum batch size). The filter validation is acceptable as a means of sterilisation of the finished product instead of by heat, as steam sterilisation could not be used with the type of final container.

Control of excipients

The excipients comply with Ph. Eur. requirements. These specifications are acceptable.

Microbiological attributes

The drug substance is intended to be administered as parenteral drug product. It is aseptically packed. The relevant microbiological tests have been included in the quality control of the product and all the phases in the manufacturing process are conducted according to the Good Manufacturing Practices, limiting the risk of contamination and complying with the recommendation of the European Pharmacopoeia in relation to the microbiological quality for this type of pharmaceutical form (Parenteral Preparations 0520). Limits for these tests were established by the MAH and are considered acceptable. Furthermore, to demonstrate the suitability of the container closure system for parenteral preparations, the MAH has submitted descriptions, technical drawings, specifications and CoA's for the primary and secondary packaging components. The submitted information is considered acceptable.

Quality control of drug product

The finished product specifications are adequate to control the relevant parameters for the dosage form. The specification tests are according to the Ph. Eur. and United States Pharmacopoeia (USP), including tests for appearance, colour, pH, osmolality, extractable volume, subvisible particulates, visible particles, sterility and bacterial endotoxins. In-house methods are used for identification (two methods), assay and related substances. Release and shelf-life specifications are identical, except for the limit for total impurities. Limits in the specification have been justified and are considered appropriate for adequate quality control of the product. Satisfactory validation data for the in-house analytical methods have been provided. Batch analytical data from three batches from the proposed production sites have been provided, demonstrating compliance with the specifications.

A risk assessment about elemental impurities as per ICH Q3D has been submitted, no risks were identified. A risk evaluation concerning the presence of nitrosamine impurities in the finished product has been provided and is acceptable.

Container closure system

The used primary and secondary packing material for this product fulfil the requirements of the Ph.Eur. for closures for containers for aqueous parenteral preparations and for cytotoxic

activity. It is verified that an aqueous extract of the elastomeric material has no cytotoxic activity, no acute systemic toxicity neither intracutaneous reactivity. This material meets the typical USP physicochemical extraction characteristic of elastomeric closures for injections. Hence, it was considered not necessary to perform any further interaction study between product and container, since neither adsorption nor absorption effects of the components of the solution to the container have been observed.

Stability of drug product

Stability data on the product have been provided from 18 batches (produced with drug substance from both suppliers) in accordance with the ICH stability guideline. Samples were stored at 25°C/60% RH and 30°C/65% RH (both 60 months) and 40°C/75% RH (6 months). The tests included for the whole stability period were appearance, colour, pH, osmolality, assay and related substances. Additional tests included at the beginning and end of the period were subvisible particles, sterility and bacterial endotoxins. No trend is observed for the studied parameters. Photostability studies were also performed and showed that the product is stable when exposed to light. Based on the submitted stability data, a shelf life of 5 years was granted. No specific storage conditions need to be included in the SmPC or on the label.

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 Mepicart has a proven chemical-pharmaceutical quality. Sufficient controls have been laid down for the active substance and finished product.

The following post-approval commitments were made by the MAH:

- to submit the study on log K_{ow} (partition coefficient n-octanol/water, which is commonly used as a measure of hydrophobicity) in a separate variation procedure;
- to update the PI (product information) with paediatric information (in line with the contraindication in children below 4 years of age, ca. 20 kg body weight) via a separate variation procedure.

III. NON-CLINICAL ASPECTS

III.1 Ecotoxicity/environmental risk assessment (ERA)

The MAH submitted an ERA. However, this was considered incomplete. Therefore, a commitment was made by the MAH to perform a study on the log K_{ow} and to submit the study report. See post-approval commitments in section II.4.

III.2 Discussion on the non-clinical aspects

Pharmacology

Mepivacaine hydrochloride is a well-known substance with a known pharmacodynamic profile. Therefore, no new studies on pharmacology were conducted by the MAH and information based on the overview of the public literature has been submitted instead. This is acceptable. Mepivacaine is a local anaesthetic of the amide type, which acts by blocking the sodium channels of the neuronal membranes, temporarily blocking the nerve impulse conduction and producing temporary loss of sensation in a limited area (Kumar et al., 2015; Song et al., 2011). Mepivacaine can act on the central nervous system and the cardiovascular system; however, the plasma levels achieved due to its use in local anaesthesia are normally not high enough to cause adverse effects (Simone et al., 1997).

Pharmacokinetics

As mepivacaine hydrochloride is a well-known substance with an extensive history of use, no new pharmacokinetics studies are required. The MAH has instead provided an overview of the public literature data, the submitted information is considered acceptable.

Absorption and distribution of mepivacaine (like all amide local anaesthetics) varies depending on many factors, such as site and method of administration, blood flow characteristics, plasma protein binding, plasma pH, and the physical properties of the local anaesthetic (i.e., pKa (acid dissociation constant), hydrophobicity, etc.). Mepivacaine is widely distributed into organs and tissues, with higher concentrations encountered in highly perfused organs, such as liver, lungs, heart and brain (Santos et al., 1987). The substance can transfer into the placenta by passive diffusion. Mepivacaine is extensively metabolised in the liver primarily by CYP1A2 enzymes. General pathways include aromatic ring and side-chain hydroxylation, N-dealkylation, and hydrolysis of the amide bond. In rats, the predominant metabolite found in the urine is 3'-hydroxymepivacaine (≈60%), while in humans almost equal excretion of both 3'-hydroxy- and 4'-hydroxymepivacaine is observed. Almost all of the hydroxylated metabolites are recovered in the urine as glucuronide or sulphate conjugates (Masten & Carson, 2000; Meffin & Thomas, 1973; Reynolds, 1971; Thomas & Meffin, 1972). Bile excretion is significantly higher in rats than in humans, with over 50% excreted into bile in rats. However, most of the dose excreted in the bile is reabsorbed into the intestine and excreted via the urinary tract Masten & Carson, 2000.

Toxicology

As mepivacaine hydrochloride is a well-known substance with an extensive history of use, no new toxicologic studies are required. The MAH has instead provided an overview of the public literature data, the submitted information is considered acceptable.

For the single dose and repeated dose, there is a substantial amount of data on acute toxicity of mepivacaine by different administration routes in different species. Information submitted by the MAH on single dose toxicity of mepivacaine is acceptable. No repeated dose toxicity studies with mepivacaine have been recovered from public literature. This is acceptable, considering the envisaged clinical use of mepivacaine, its well-known pharmacological and pharmacokinetic profile and extensive history of use.

For genotoxicity, the MAH refers to the publicly available *in vivo* micronucleus assay (Nai et al., 2015) in which two groups of eight male rats were injected intraperitoneally with mepivacaine 2% solution at a dose level of 4.4 mg/kg either once or for 5 consecutive days. Single dose animals were euthanised 24 hours post-application; repeated dose animals were euthanised after five days of administration. 2000 polychromatic erythrocytes (1000 per slide) prepared from the bone marrow were scored per animal. There was no statistically significant increase in the number of micronuclei compared to the negative control (saline) with either single or repeated dosing. Although the study has a number of limitations, it is considered acceptable to draw the conclusion that mepivacaine does not cause an increased incidence of micronucleated polychromated erythrocytes *in vivo*. No data have however been provided on the bacterial gene mutation test (Ames test) which led to a major objection being raised during the 1st, 2nd and 3rd rounds of assessment. The MAH has subsequently resolved this by providing additional considerations on the structure-activity relationship and an *in silico* evaluation of the genotoxic potential of mepivacaine using the accepted quantitative structure–activity relationship models (QSAR models) in accordance with ICH M7 guideline.

Mepivacaine belongs to the amide class of local anaesthetics which are characterised by three structural features: lipophilic aromatic ring, intermediate ester or amide linkage and terminal amine giving clinical properties to the molecule (Becker & Reed, 2012). Mepivacaine is a close structural analogue of bupivacaine and ropivacaine, differing only by the nature of the alkyl substituent at the tertiary amine function (methyl in mepivacaine, versus respectively propyl and butyl groups in ropivacaine and bupivacaine), and can also be considered structurally similar to lidocaine which contains diethylamine moiety instead of the substituted piperidine ring. As mepivacaine does not contain additional structural groups and as the DNA reactivity of the molecule is determined by its chemical functionalities, it can be agreed that information on genotoxicity of mepivacaine can be derived from information on its structural analogues, with additional reassurance provided by the use of two *in silico* QSAR methods. For bupivacaine, a summary report of the National Toxicology Program (NTP) study is available, which was conducted in *S. typhimurium* TA100, TA1535, TA97 and TA98 strains up to the dose level of 10 mg/plate both with and without metabolic activation (10% and 30% rat and hamster S9). The results were clearly negative. As the NTP studies are generally accepted as well-conducted and reliable, this result can be also extrapolated to mepivacaine. Furthermore, the MAH has submitted the results of the two QSAR models, one statistical-based and one

expert-rule based, as recommended by ICH M7 guideline. The predictions for mepivacaine were negative in both cases. Taken together, the submitted data are considered to be sufficient to cover the endpoint of the bacterial gene mutation test (Ames test) for mepivacaine. With this, the major objection regarding genotoxicity was resolved.

No information on carcinogenicity of mepivacaine was provided by the MAH. As mepivacaine is used incidentally and not continuously for the period over 6 months, no carcinogenicity data are required in accordance with ICH S1A Guideline.

For reproductive toxicity, the MAH has referred to the EMA report (EMA, 1999) for the establishment of the maximum residue limit (MRLs) for mepivacaine and to the two references cited in the registry of toxic effects of chemical substances (RTECS). However, no adequate safety assessment could be derived based on this information, as neither of these sources provided sufficient details for assessment. This led to a major objection raised in the 1st and 2nd round of assessment. The MAH has subsequently provided the original publications of Smith et al. (1986) and Banhaway et al. (1977) cited in the RTECS database for mepivacaine. In the first paper, eight pregnant females rats were injected with 6 mg/kg mepivacaine on GD11 into the master muscle of the jaw. Rats were allowed to litter naturally, and the pups were weighed, sexed and culled to three/sex within 24 hours of birth. The pups were then subjected to a number of faecal occult blood (FOB) tests and foot shock sensitivity 5 days after completion of the shuttle box testing. No necropsies were performed. The authors concluded that mepivacaine altered development of negative geotaxis and adult food shock sensitivity following shuttle box testing, and possible activity.

Banhawy et al. (1977) reported administering 0.1 or 0.25 mL of 4% mepivacaine hydrochloride solution intraperitoneally to CFHB male rats with subsequent sacrifice and histopathological testis examination after 6 or 12 hours, 1, 2 or 10 days. The authors reported “severe” or “partial” damage in 30-50% of seminiferous tubules (the site of spermatogenesis in the mammalian testis) in 18 of 20 treated rats. Damage was evident as early as 6 hours after the injection in both treatment groups. Damaged tubules were characterised by the presence of pyknotic nuclei and evidence of cell shedding from the epithelium. This cell loss continued and some tubules contained cell debris in the lumen up to 24 hours after the injection. The epithelium of damaged tubules always had a vacuolated appearance (containing cluoles or cavities within a cell). In all four animals killed 10 days post-administration, many normal tubules were present in the testis and all stages of spermatogenetic cycle were present. In some tubules, resurgence of spermatogenesis was at an early stage, but about 10% of tubules were more seriously affected and no spermatogenic activity was evident. Intraperitoneal administration of mepivacaine to male rats was thus concluded to have adverse effects on the testicular function and spermatogenesis.

No further information on reproductive and developmental toxicity of mepivacaine is available in the public domain. The current version of the SmPC for a comparable product (Scandonest) includes a warning that mepivacaine should be preferably avoided during pregnancy and that nursing mothers are advised not to breastfeed within 10 hours following anaesthesia with mepivacaine. These warnings are considered to mitigate the risk to a

pregnant woman, an unborn foetus and a suckling child. The same warnings are proposed by the MAH for Mepicart. In view of the submitted information, the proposed warnings in the SmPC and the anticipated limited exposure to mepivacaine during the envisaged use, the major objection about the lack of information on reproductive and developmental toxicity was resolved.

No information on the local tolerance, antigenicity, immunotoxicity, dependence or metabolites was provided by the MAH. However, considering the long history of mepivacaine use as a local anaesthetic, this is acceptable.
As the manufacturer has the certificate of suitability issued for the active substance used in the manufacture of the drug product, no studies on impurities are required.

IV. CLINICAL ASPECTS

IV.1 Introduction

Mepivacaine hydrochloride is a well-known active substance with established efficacy and tolerability. The dossier is based on well-established use of the active substance. The MAH submitted a clinical overview for the justification of the proposed indications and posology, which is acceptable.

IV.2 Pharmacokinetics

Mepicart is a locally applied and it is a mainly locally acting product. Mepivacaine is systemically available after local administration and maximum concentrations are reached after 30-60 minutes at maximally 1.70 µg/mL after administration of 108 mg (Goebel et al., 1978).

For Mepicart, the quantitative composition regarding the active substance and the qualitative composition regarding the excipients is the same as for other mepivacaine-containing products, registered in EU countries and for the same indication, such as Carbocaine and Scandonest. Although only one publication concerned a product with the same concentration of mepivacaine and the same excipients as Mepicart and contained information regarding pharmacokinetics, it can be considered sufficient for a bridge from a pharmacokinetic point of view, considering that the excipients (NaCl, NaOH for pH adjustment, HCl for pH adjustment, water) are not expected to influence absorption. The excipients are the same as for other mepivacaine-containing products for this indication. The physico-chemical characteristics are considered similar as those for other solutions containing 3% mepivacaine.

Mepivacaine is 75-78% protein bound. It is widely distributed. Mepivacaine crosses the placenta and it is excreted mainly via the urine with less than 10% unchanged parent compound. The plasma half-life is 2-3 hours for adults and 9 hours for new-borns (Medscape, 2020; Sweetman, 2009). Mepivacaine is largely metabolised through hydroxylation by CYP1A2

and to a smaller extent by CYP3A. The hydroxyl metabolites are excreted as glucuronide conjugates (Brockmann, 2014). Since mepivacaine becomes systemically available and since it is metabolised in the liver and excreted largely via the urine (EMA, 2000), Mepicart should be used with caution in patients with renal and hepatic impairment. No relevant consequences are expected of gender, race, weight and age, because Mepicart is a locally acting product.

Pharmacokinetic interactions may occur with strong inhibitors of CYP1A2 such as fluvoxamine, fluoxetine, caffeine, grapefruit juice, fluoroquinolone antibiotics, verapamil, mexiletine and zileuton and with moderate CYP1A2 inhibitors paroxetine and sertraline. Metabolism by CYP1A2 is not expected to be fully functional before the age of 3 years (Brockmann, 2014). Levonordefrin had no significant effect on plasma levels when co-administered with mepivacaine (Chin et al., 2003).

IV.3 Pharmacodynamics

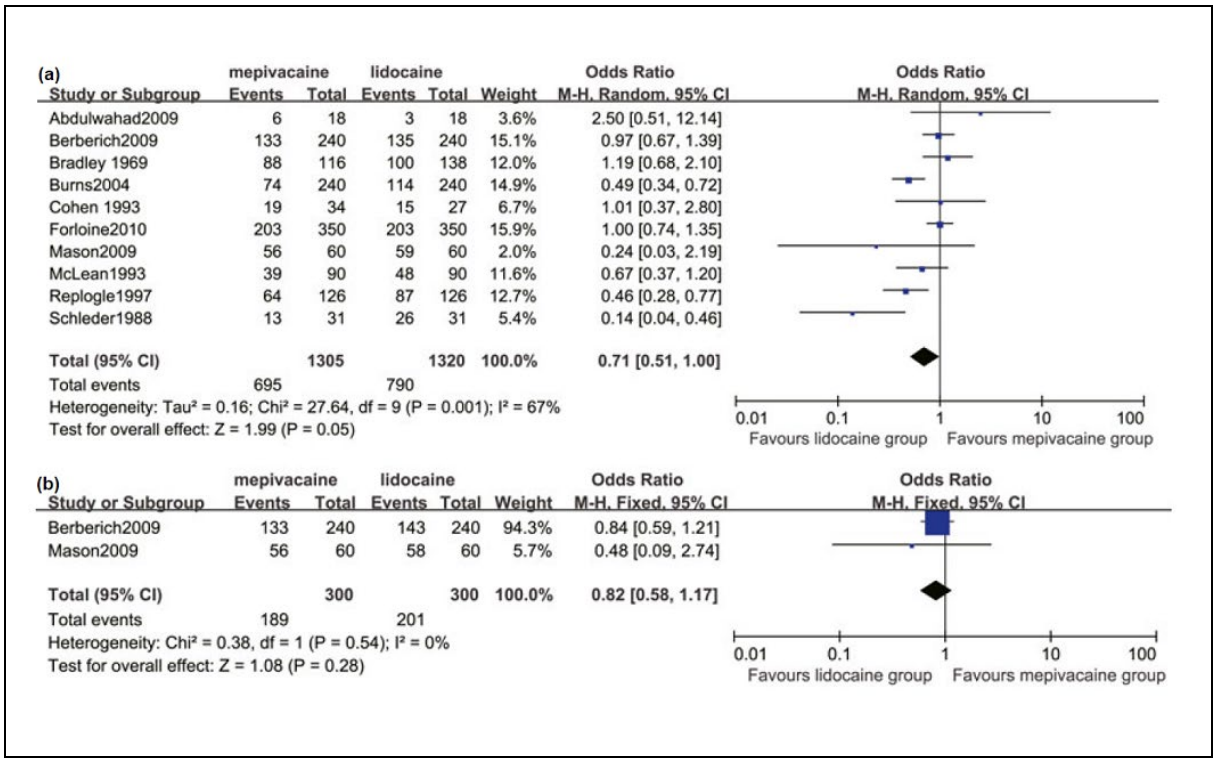
Mepivacaine is a well-known local anaesthetic of the amide-type. Mepivacaine reversibly inhibits the conduction of nerve impulses by decreasing or blocking sodium (Na+) flow during propagation of the nerve action potential. Mepivacaine 3% also displays vasoconstrictive properties, and therefore, it can be used without vasoconstrictors in contrast to other local anaesthetics such as lidocaine. It has been shown in meta-analyses of randomised trials, that plain mepivacaine 3% caused less increment of heart rate than lidocaine + epinephrine (Su et al., 2014). Overall, the pharmacodynamic characteristics are sufficiently addressed in the submitted clinical overview and in the SmPC.

IV.4 Clinical efficacy

The MAH provided two meta-analyses from the literature of the clinical studies performed with mepivacaine 3%.

Su et al. (2014) conducted a meta-analysis of randomised controlled trials which objective was to assess the efficacy and safety of mepivacaine compared with lidocaine used in local anaesthesia in dentistry. Twelve studies on mepivacaine 3% were included. There was a tendency for a difference between 3% mepivacaine plain and 2% lidocaine + 1:100,000 epinephrine), although this was not shown for the comparative randomised trials with 2% lidocaine + 1:50,000 epinephrine).

Figure 1. (Source: Su et al., 2014): Meta-analyses of success rate of local anaesthesia in comparing 3% mepivacaine with 2% lidocaine with 1:100,000 adrenaline (a), 3% mepivacaine with 2% lidocaine with 1:50,000 adrenaline (b).



In the most recent Cochrane overview on injectable local anaesthetic agents for dental anaesthesia (St George et al., 2018), the reviewers pooled the results of six cross-over studies measuring the success of local anaesthesia of maxillary and mandibular teeth with healthy pulps, tested with an electric pulp tester. Pooling suggested no evidence of a difference of the rates of successful anaesthesia between lidocaine 2% + 1:100,000 epinephrine versus mepivacaine 3% (RR 0.92, 95% CI 0.83 to 1.02), or versus lidocaine + 1:50,000 epinephrine (RR 0.97, 95% CI 0.88 to 1.07).

Bridging to the clinical efficacy data from the literature is considered justified for Mepicart 30 mg/ml solution for injection. The composition and/or physico-chemical characteristics (e.g., pH and osmolality) of this product are the same as compared to the other products that were described in the literature and conform the Ph.Eur. and USP. EC-sourced mepivacaine products were also used in several clinical studies (Isaksson et al., 1966; Rodriguez et al., 2001; Mojica et al, 2017; Cuvillon et al., 2018).

Overall, the efficacy of mepivacaine 3% has been established in multiple randomised studies in a broad range of dental anaesthetic procedures (inferior alveolar nerve blocks, maxillary infiltration or blocks), and can be considered on par with standard of care treatment with lidocaine 2% + epinephrine. The onset of anaesthesia was rapid and similar between both drugs.

IV.5 Clinical safety

Next to an overview of the literature, reference is made to an article 30 procedure for Scandonest, the EMA provided a harmonised SmPC, including all information important for safety (EMA, 2018).

Adverse reactions following administration of mepivacaine are similar to those observed with other local amide anaesthetics. As can be read from section 4.8 of the SmPC, headache is a common adverse event (AE). All the other AEs are reported to be rare, or of unknown frequency.

Adverse event of interest

Neurotoxic events are rare with mepivacaine use in dentistry (Aps & Badr, 2020). Based on indirect comparisons, the risk of neurotoxic events like paraesthesia and prolonged hypoesthesia, is lower for mepivacaine than for articaine. For intrathecal use, neurotoxic events were more common for lidocaine than for mepivacaine (Schug & Raajkumar, 2008). Systemic central nervous system (CNS) effects may occur after accidental intravenous injection and overdose. These central effects could include light headedness, dizziness, restlessness, drowsiness, disorientation, shivering, muscle twitching, tremors of the face and extremities, generalised seizures, and respiratory depression.

Like other local anaesthetics, mepivacaine may cause cardiac events, such as bradycardia, hypotension and decreased cardiac output. This only occurred at accidental intravenous injection and overdose in dentistry. In meta-analyses, Su et al., (2014) showed that the heart rate was higher for lidocaine 2% epinephrine versus mepivacaine 3%. The authors concluded that plain mepivacaine is a good option for cardiovascular compromised patients and the elderly, as it can be applied without a vasoconstrictor, and therefore has lower risk of hypertension and palpitations.

Allergic reactions are also rare for mepivacaine. These may be of the immediate IgE related type or the delayed type. In general, local anaesthetics of the amide-type like mepivacaine have a lower potential for allergic reactions than amino-type local anaesthetics.

Special populations

According to the Paediatric Workshare (2010) mepivacaine can be safely used in children from the age of 4 years with 20 kg of body weight. For younger children, there is not sufficient information regarding efficacy and safety. This has been incorporated in the SmPC.

Overall, the safety profile of mepivacaine is well established, and has been adequately described in the SmPC. Bridging to the clinical safety data from the literature is considered justified for Mepicart 30 mg/ml solution for injection. The composition and/or physico-chemical characteristics (e.g., pH and osmolality) of this product are the same as compared to the other products that were described in the literature and conform the Ph.Eur. In several of the described clinical studies, EC (European Commission) sourced mepivacaine was used.

At the dosage levels used in dentistry, the risk of systemic effects is low. Allergic reactions are reported, but they are in general rare.

IV.6 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 Mepicart.

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

Important identified risks	None
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.7 Discussion on the clinical aspects

Mepivacaine has been used and is registered for the requested indications in the RMS and the CMS countries for at least ten years. Based upon clinical data and the longstanding clinical experience, the use of mepivacaine in the proposed indications can be considered well-established with demonstrated efficacy. The proposed dose for both indications is in line with current recommendations. On the basis thereof, the efficacy of Mepicart can be considered acceptable.

The safety profile of mepivacaine in the proposed indications can be considered well-established and acceptable. The proposed posology for its indications is in line with current recommendations. The adverse events of mepivacaine are well characterised and adequately covered by the SmPC's of currently available mepivacaine products.

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 four participants, followed by two rounds with ten participants each. The questions covered the following areas sufficiently: traceability, comprehensibility and applicability and design/layout. 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

Mepicart 30 mg/ml solution for injection has a proven chemical-pharmaceutical quality. The documentation in relation to this product is of sufficiently high quality in view of the European regulatory requirements.

From a clinical point of view, the proposed indication as local and loco-regional anaesthesia in dental surgery, as well as the proposed posology are in line with current mepivacaine hydrochloride use and recommendations in the RMS and CMS countries, in which mepivacaine hydrochloride has been registered for more than ten years. Based upon clinical data and the longstanding clinical experience, the use of mepivacaine hydrochloride in the proposed indications can be considered well-established with demonstrated efficacy and acceptable safety.

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 well-stablished used has been demonstrated for Mepicart, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 5 July 2022.

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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/5377/001/ IB/001	Changes (Safety/Efficacy) to Human and Veterinary Medicinal Products: - Other variation.	Yes	24-10-2022	Approved	N.A.
NL/H/5377/001/ IB/003	Change in the (invented) name of the medicinal product.	Yes	26-05-2023	Approved	N.A.