EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Referral under Article 30 of Directive 2001/83/EC

Scandonest and associated names

INN/active substance: mepivacaine

Procedure number: EMEA/H/A-30/1455

Note:

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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List of abbreviations

ADRs	Adverse Drug Reactions
CDS	Core Data Sheet
CEP	Certificate of Suitability to the monograph of the European Pharmacopoeia
CHMP	Committee for Medicinal Products for Human Use
CNS	Central Nervous System
EC	European Commission
EDQM	European Directorate for the Quality of Medicines & HealthCare
EMA	European Medicines Agency
EU	European Union
GMP	Good Manufacturing Practice
HPLC	High Performance Liquid Chromatography
IPC	In Process Control
MA	Marketing Authorisations
MAA	Marketing Authorisation Application
MAH	Marketing Authorisation Holder
MG	Myasthenia Gravis
MRP	Mutual Recognition Procedure
MS	Members States
NSAIDs	Non-steroidal Anti-inflammatory Drugs
Ph. Eur.	European Pharmacopoeia
PI	Product Information
PL	Package Leaflet
PSUR	Periodic Safety Update Report
QRD	Quality Review of Documents
RMS	Reference Member State
SmPC	Summary of Product Characteristics
SOC	System Organ Class
TLC	Thin Layer Chromatography
UK	United Kingdom

1. Background information

On 25 August 2017 Septodont on behalf of all marketing authorisation holders (MAHs) presented to the European Medicines Agency a request for referral under Article 30 of Directive 2001/83/EC, in order to harmonise the national summary of product characteristics (SmPC), labelling, package leaflet (PL) and quality Module of the medicinal products:Scandonest and associated names (see Annex I of CHMP opinion).

The CHMP appointed Romaldas Mačiulaitis (Lithuania) as rapporteur and Fátima Ventura (Portugal) as co-rapporteur.

Scandonest is nationally authorised in the following European Union (EU) Members States (MS): Austria, Belgium, Bulgaria, Croatia, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Ireland, Italy, Latvia, Lithuania, Luxembourg, Malta, Netherlands, Norway, Poland, Portugal, Romania, Slovakia, Slovenia, Spain, Sweden and United Kingdom (UK).

2. Scientific discussion

2.1. Introduction

Scandonest contains 30 mg/ml of mepivacaine hydrochloride, which is chemically known as (1-methyl-2-piperidyl) formo-2',6'-xylidide. Mepivacaine is an intermediate-acting local anaesthetic, which inhibits the conduction of nerve impulses by decreasing sodium (Na^+) flow during propagation of the nerve action potential. As the action of mepivacaine progressively develops in the nerve, the threshold for electrical excitability gradually increases. The rate of rise of the action potential declines and impulse conduction slows down. The probability of propagation of the action potential thus decreases and the nerve conduction eventually fails, providing anaesthesia for limited period of time.

Mepivacaine was first approved in 1960 by the US Food and Drug Administration. In the EU, Scandonest is authorised in 22 MSs through national procedures, and in 5 MSs (Sweden, Finland, Portugal, Spain, Malta) through mutual recognition procedure (MRP). The national authorisations (MAs) were granted between 1966 and 2017 in the EU Member States. The information in the product information (PI) among the various MS and in the quality part (Module 3) of the marketing authorisation dossier is not harmonised.

In view of these divergences concerning the authorisation of the above mentioned medicinal product, Septodont, the MAH for Scandonest, notified the European Medicines Agency (EMA) of a request for referral under Article 30 of Directive 2001/83/EC in order to harmonise these divergences across the EU.

Scandonest is indicated for local and loco-regional anaesthesia in dental procedures in adults and children above 4 years of age (from 20 kg of body weight) and is used as solution for injection.

2.2. Critical Evaluation

In the context of this procedure, for the PI harmonisation the MAH submitted the clinical data assessed during the marketing authorisation applications (MAAs), published literature and cumulative safety experience with the product as reported in the MAH's drug safety database and reflected in the appropriate sections of the MAH's Core Data Sheet (CDS).

With regards to the quality Module 3, the MAH submitted the relevant parts of the Module.

2.2.1. Product information

Section 4.1 – Therapeutic Indications

The following wording was proposed by the MAH for section 4.1 Therapeutic indications of the SmPC:

Mepivacaine 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).

Local anaesthesia in chiropody procedures

This product is particularly indicated when the use of vasoconstrictor is contraindicated.

Scandonest is currently indicated for local and loco-regional anaesthesia in dental procedures in adults and children above 4 years of age (from 20 kg of body weight). The terminology used in the individual local SmPCs differs as described below.

In Sweden, Finland, Portugal, Spain and Malta, Bulgaria, Estonia, Greece, Ireland, Lithuania, Netherlands, Norway, Poland, Romania, Slovakia, mepivacaine is indicated for local anaesthesia for dental procedures. In some SmPCs local anaesthesia is defined as “infiltration and nerve-block anaesthesia”. The exact wording of indication slightly varies among the above MS, with some SmPCs referring to “minor” or “short duration” dental procedures.

In Austria, Croatia, Hungary, and Slovenia the above indication is complemented with the statement for use in children above 4 years of age (c.a. 20 kg of body weight). In Denmark, mepivacaine is indicated for “conduction and infiltration analgesia”.

The MAH has provided a summary of the literature and studies to support the indication “anaesthesia in dental procedures”. CHMP considers that the submitted evidence is adequate to support the indication in adults and in children.

The indication for usage of mepivacaine for children above 4 years old (c.a. 20 kg of body weight) for dental procedures was discussed in a worksharing procedure in 2010 under Article 45 of the Paediatric Regulation (EC) No 1901/2006 (AT/W/0002/pdWS/001). The contraindication in children below 4 years resulted from the same worksharing procedure. No sufficient supportive data with mepivacaine in children below 4 years of age including dose recommendation for children less than 20 kg was provided.

In seven MSs, namely Belgium, Luxembourg, France, Germany, Hungary, Italy, Latvia and Slovenia the indication includes also the statement: “the medicinal product is (particularly) indicated when the use of vasoconstrictor is contraindicated”.

The MAH claimed that if vasoconstrictor is contraindicated, the only options for anaesthesia are mepivacaine, general anaesthesia or nitrous oxide. The CHMP is of the opinion where vasoconstrictor is contraindicated, there are alternative options other than those mentioned before, such as other local anaesthetics (procaine, bupivacaine and lidocaine). The CHMP noted that there is literature evidence that mepivacaine provides vasoconstrictive features compared with anaesthetics from other pharmaceutical groups, however this cannot support an indication in itself. The CHMP recommended that the statement regarding mepivacaine use when vasoconstrictor is contraindicated should be moved from section 4.1 to 5.1 (pharmacodynamic properties) of the SmPC. The MAH endorsed the proposal.

Only in one MS (UK), mepivacaine is indicated for local anaesthesia in dental and chiropody procedures.

Chiropody is the branch of medicine concerned with the diagnosis and treatment of diseases of the feet. In the EU, the regulation of medical professionals' qualifications and areas of expertise among MSs differs. For example, in the UK the chiropodists, may legally obtain and administer local anaesthetics and perform minor surgical procedures on the foot, while in some other MSs the chiropodists are not authorised to breach intact skin. Thus, in many MSs the chiropody procedures are performed by surgeons or dermatologists.

The supporting data for this indication are based on one study, where mepivacaine was used in 28 patients in chiropody practice, however no detailed analysis was provided. The CHMP noted that the procedures performed in this study (hallux valgus repair or manipulations of toe) are rather orthopaedic than chiropody procedures and therefore the extrapolation of results to the claimed indication is not supported. The MAH also made reference to another publication which is an "Atlas of regional anaesthesia" where information on anatomical guidance for performing ankle block is provided. Mepivacaine 1% w/v is mentioned as one of the possible anaesthetic options. This procedure would be effective for anaesthesia during chiropody procedures, however this kind of local block is usually performed for more extensive orthopaedic procedures.

The CHMP considers that the data submitted in support of this indication are not adequate to establish the efficacy of using mepivacaine for all chiropody applications and recommended the deletion of this indication. This recommendation is also supported by the inconsistency of recognition and professional rights of chiropodist profession across EU. The MAH agreed with the deletion of the above indication.

The final agreed wording for this section of the SmPC is presented below and can also be found in Annex III of the CHMP opinion.

{(Invented) name and associated names (see Annex I) strength pharmaceutical form} 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).

Section 4.2 – Posology and method of administration

The MAH proposed harmonised dosing recommendations based on the doses studied in clinical trials and supported by pharmacodynamic and pharmacokinetic data and in line with international, European and national guidelines. The doses recommended in various national SmPCs vary per indication and population group (adults, children and special population).

Dental procedures

i. Adults

For dental procedures in adults the lowest dose leading to effective anaesthesia should be used. For more extensive procedures one or more cartridges may be required, without exceeding the maximum recommended dose of 4.4 mg/kg of bodyweight with an absolute maximum recommended dose of 300 mg. Various maximum recommended doses of mepivacaine 30 mg/ml are reported in numerous reference dental anesthesia textbooks. For the maximum quantity the patient's bodyweight has to be taken into account. Hence, in case of a 70 kg healthy adult, the maximum recommended dose will be 300 mg mepivacaine. Thereby, for all patients more than 70 kg of body weight, the maximum number of cartridges that can be administered is limited to 5.5 cartridges for the 1.7 ml, and 4.5 for the 2.2 ml cartridge, for a total of 10 ml of the product. This is referred in numerous anaesthesia textbooks, is in line with recommended dosing in various literature sources, databases, and is considered acceptable.

If sedatives are used to reduce patient anxiety, lower doses of the anaesthetic should be used, since there is increased risk of adverse effects when central nervous system (CNS) depressants are

combined. The CHMP is of the opinion that this information should be reflected in the SmPC section 4.2 with a cross reference to section 4.5.

ii. Children

The proposed posology in children of an average 0.75 mg/kg (0.025 ml) of mepivacaine solution per kg of body weight is in line with the outcome of the worksharing procedure under Article 45 of the Paediatric Regulation (EC) No 1901/2006 (AT/W/0002/pdWS/001). The quantity to be injected should be determined by the age and weight of the child and the magnitude of the operation. A discrepancy in the proposed text of the paediatric population and posology table has been identified. The paediatric population is defined as “children from 4 years of age (ca. 20 kg body weight)”, while the table with the maximum recommended posology lists only doses for children with 25kg of body weight and more. The MAH has been asked to justify this discrepancy, which has been corrected to include maximum allowed doses for children from 20kg of bodyweight and more.

iii. Special populations

The MAH proposed to maintain the statement regarding the risk of possible accumulation of the product leading to toxicity in special populations (elderly and patients with renal and hepatic impairment), which was endorsed by the CHMP. Pharmacokinetic changes are observed with aging for absorption, distribution, metabolism, and elimination and affect the particular pharmacokinetics of the drug. As all amide-type local anaesthetics, mepivacaine is largely metabolised in the liver by microsomal enzymes and the principal route of excretion is via the kidney. Metabolites are excreted in the urine with less than 10% of unchanged mepivacaine. Consequently, metabolism and elimination of mepivacaine can be significantly altered by the presence of hepatic or renal diseases. The CHMP noted that according to the EMA SmPC Guideline (2009)[1], section 4.2 should contain information regarding repeated usage and recommended to include this information, since mepivacaine has potential for accumulation, especially, if the liver function is impaired. This was accepted by the MAH. Several local SmPCs contained a recommendation to reduce the recommended dose by half in elderly patients, but there is no supportive data for this statement. As a precautionary measure and due to lack of data in this potentially more vulnerable population, in this section it is mentioned that the lowest dose leading to efficient anaesthesia should be applied to elderly population.

The MAH made proposals regarding several other divergences among local SmPCs including divergences on the cartridge volume, the frequency of administration, the reduction of recommended dosage by half, the risk of accumulation in elderly patients (as discussed above) and lower doses in patients with reduced general health and pre-existing conditions such as vascular obliterations, arteriosclerosis or diabetes-related nerve damage. All these points are discussed in the following paragraphs.

With regards to the volume of cartridge, mepivacaine is marketed in two different volumes of cartridges: 1.7 ml and 2.2 ml. In the MRP and in most of the national MAs, the nominal filling volume is erroneously indicated as 1.8 ml instead of 1.7 ml. The volume of 1.8 ml actually corresponds to the total capacity of the cartridge and was initially improperly considered as the nominal filling volume of the cartridge. The proposed removal of warnings regarding frequency of injections is acceptable considering the product’s half- life (1.5 – 2h) and that the product is considered almost entirely eliminated within 14 hours. This should also be considered in relation to the use of mepivacaine in dental setting.

The recommendation on lower doses to be used in patients with reduced health, is considered too general by the CHMP and does not provide any specific information, while for the reduced dose

[1] https://ec.europa.eu/health/sites/health/files/files/eudralex/vol-2/c/smpc_guideline_rev2_en.pdf

recommendation to patients with pre-existing conditions such as vascular obliterations, arteriosclerosis or diabetes-related nerve damage there are not enough data to support this specific dosing guidelines for patients with above mentioned conditions. Warnings for these patient populations will be included in section 4.4.

Chiropody procedures

In view of lack of supportive evidence for mepivacaine use in chiropody procedure, the CHMP supports the deletion of this indication. The MAH agreed. The relevant posology section will be removed.

Method of administration

There was different terminology, used in local SmPCs, regarding its method of use such as local injection (block or infiltration), local infiltration or blockade, local or conduction, local or regional sub-mucous intraoral injection, intraoral submucosal regional or topical administration and others. The text was harmonised to the standard terms “infiltration and perineural use” as defined by EDQM (European Directorate for the Quality of Medicines & HealthCare).

The CHMP did not endorse the proposed wording of the MAH regarding the method of injection technique and the risk of accidental intravascular injection and discussed an alternative wording in order to provide information to medical staff on how to ensure that the needle does not penetrate a blood vessel during injection. The rate of 1 ml/min is considered optimal as it does not produce tissue damage during or after anaesthesia and any serious reaction in the event of accidental intravascular injection.

Injection to inflamed or infected tissues should be avoided and anaesthesia should not be applied to damaged skin. The CHMP requested this information to be included in this section. The MAH agreed with this addition.

The final agreed wording for this section of the SmPC can be found in Annex III of the CHMP opinion.

Section 4.3 – Contraindications

Some contraindications have been proposed by the MAH for this section.

Allergic reactions to amide local anaesthetics are rare and the most important safety concerns relate to the CNS and cardiovascular system. Mepivacaine is contraindicated in patients with a history of hypersensitivity to mepivacaine, to any other amide anaesthetics (as cross-sensitivity may occur) or to any of Scandonest excipients.

As a result of the review of mepivacaine during a worksharing procedure under Article 45 of Regulation (EC) No 1901/2006 in 2010, the use of mepivacaine was contraindicated in children below 4 years of age (and less than 20 kg of body weight). This recommendation is maintained by the CHMP.

Local anaesthetics as cardiovascular depressants exert a negative inotropic and chronotropic effect on the myocardium and produce peripheral vasodilation. This may lead to hypotension and circulatory collapse. The vasodilation effect is responsible for the increase of blood flow in the tissues which promotes bleeding at the injection sites especially in dental use, reduces the duration of action and increases blood concentrations with greater likelihood of overdose reactions. Local anaesthetics should not be used in patients with uncontrolled complete heart block (including atrioventricular node block) which is not compensated by a pacemaker. Heart block may also occur as a result of high doses of local anaesthetic, of slow metabolic degradation and of unintentional intravascular injection. Therefore, due to its potential cardiovascular depressant effect, mepivacaine is contraindicated in patient with atrioventricular disorders not compensated by a pacemaker.

In the presence of high blood levels, local anaesthetics cross the blood-brain barrier. This produces depression in inhibitory pathways, allowing excitatory pathways unopposed and results in dizziness, auditory and visual disturbances, mental confusion, muscle tremors, and ultimately generalised tonic-clonic seizures. This is manifested by lethargy, coma and respiratory depression or respiratory arrest. Epileptic patients have hyper excitable cortical neurons at a site within the brain where the convulsive episode originates "epileptic focus". Although in dental practices, local anaesthetics administrated in therapeutic dosages do not interact with standard antiepileptic drugs, the situation for patients with uncontrolled epilepsy may be different. Therefore, local anaesthetics should not be used in epileptic patients whose seizures are poorly controlled.

The final agreed wording for this section of the SmPC is presented below and can also be found in Annex III of the CHMP opinion.

- *Hypersensitivity to the active substance (or any local anaesthetics agent of the amide type) or to any of the excipients listed in section 6.1,*
- *Children below 4 years of age (ca. 20 kg body weight),*
- *Severe disorders of atrioventicular conduction not compensated by pace maker,*
- *Poorly controlled epileptic patient.*

The MAH reviewed several divergences from the local SmPCs which were removed from the final SmPC. These divergences are presented briefly below:

Porphyria/Acute intermittent porphyria / Hepatic porphyria

This contraindication was listed in several local SmPCs. There is a controversy around the use of mepivacaine in patients with porphyria. For example, the French Porphyria Centre recommends mepivacaine to be contraindicated in patients with the condition and The Oxford Handbook of Anaesthesia (2017) classifies mepivacaine as "Definitely unsafe" and lists other local anaesthetics, such as bupivacaine, procaine, procainamide as possible alternatives. In contrast, the Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies mepivacaine as probably not porphyrinogenic when used in local anaesthetic procedures. Similarly, the European Porphyria Network, lists mepivacaine as safe for patients with porphyria. Based on grounds of insufficient evidence supporting this contraindication and the above mentioned controversies, the MAH proposed to remove porphyria contraindication from the SmPC. The CHMP considered that although not confirmed by data, this concern of mepivacaine use in patients with porphyria cannot be ruled out and should be mentioned in the SmPC. The CHMP concluded to remove the contraindication and add a warning for patients with porphyria in section 4.4 of the SmPC.

History of malignant hyperthermia

In the past, amide local anaesthetics were thought to cause malignant hyperthermic reactions in susceptible patients. More recent data showed that malignant hyperthermia can occur when patients with genetic susceptibility to this condition are exposed to inhalational general anaesthetics or succinylcholine, but not to local anaesthetics. Literature supports that local anaesthetics have been used safely in humans who were susceptible to malignant hyperthermia and according to The Oxford Handbook of Anaesthesia (2017) all local anaesthetics are considered safe for these patients. Therefore, removal of this contraindication is considered acceptable by the CHMP.

Co-administration with guanetidine and related compounds (see section 4.5)

Guanetidine is an antihypertensive agent that acts by inhibiting selectively transmission in post-ganglionic adrenergic nerves. The product which is relieved does not contain a catecholamine and

mepivacaine does not use the adrenergic receptors, therefore this interaction is not applicable. The CHMP endorses the MAH's proposal for deletion.

Severe bradycardia

Severe bradycardia is included in severe conduction disorders and those are already listed as contraindication, therefore this sentence was redundant and consequently removed.

Severe cardiac excitation

Mepivacaine acts in the myocardium in a similar manner to their action on nerves. It inhibits the conduction of nerve impulses by decreasing or blocking sodium flow during propagation of the nerve action potential. As the aesthetic action progressively develops in the nerve, the threshold for electrical excitability gradually increases, the rate of rise of the action potential declines and impulse conduction slows. The probability of propagation of the action potential thus decreases, and nerve conduction eventually fails. On the myocardium, it results in a decrease of electrical excitability, conduction rate and force of contraction. The wording for severe cardiac excitation is not clear and is not supported by data. Patients with cardiovascular disorders are mentioned in the section 4.4 of the SmPC. Therefore the CHMP endorses the MAH's proposal not to include this contraindication.

Severe hypotonia / Severe arterial hypotension

The statement regarding severe hypotonia is not supported by relevant data. Moreover, there was no case of severe hypotononic patients receiving mepivacaine as dental anaesthetic retrieved in literature search or in the MAH's Global pharmacovigilance database. The CHMP endorses the MAH's proposal not to include this contraindication. Instead a warning in section 4.4 has been added.

Decreased cholinesterase levels

Cholinesterases are a group of enzyme lysing choline based esters. There is a group of local anaesthetics that are metabolised by cholinesterase – esters. Among the amide local anaesthetics, only articaine is metabolised by plasma cholinesterase. Since mepivacaine is entirely metabolised in the liver by the cytochrome P450, there is no effect on low plasma cholinesterase level in patients receiving mepivacaine. In conclusion, no supportive data are available to support a contraindication in patients with decreased cholinesterase levels. Therefore, the CHMP endorses the MAH's proposal to remove this contraindication.

Myasthenia gravis

Myasthenia Gravis (MG) is a chronic neuromuscular disorder associated with an antibody-mediated autoimmune attack directed toward the acetylcholine receptors at the neuromuscular junctions. Ester-type local anaesthetics, such as procaine, that are hydrolysed by plasma cholinesterases and have decreased effectiveness in MG patients on anticholinesterase therapy should be avoided in myasthenic patients. However amide-type local anaesthetics, such as mepivacaine and lidocaine, are metabolised in the liver by the cytochrome P450 and not by plasma cholinesterase. There are no supportive data for this contraindication, thus the CHMP endorses the non-inclusion in the SmPC.

Intravascular injection; It is essential to ensure the needle does not perforate a blood vessel during the injection; Toxic reactions are possibly associated to accidental intravascular administration or overdose

According to the SmPC guideline (2009), contraindications are situations where the medicinal product must not be given for safety reasons. The above information should therefore not be considered as a contraindication. The risk associated with intravascular injection and overdose shall be addressed in sections 4.2, 4.8 and 4.9. Since information regarding safer injection technique is kept in the SmPC, this deletion of the contraindications is acceptable by the CHMP.

Do not use if you are pregnant or think you might be pregnant

Clinical studies were not performed in pregnant women and exposure with mepivacaine 3% (w/v) during pregnancy were reported in the literature, with no supporting evidence supporting the harmful effect of mepivacaine on the foetus during dental use. Moreover, animal studies did not indicate direct or indirect harmful effects with respect to reproductive toxicity. In literature search, there is a controversy regarding the use of local anaesthetics in pregnant woman. A search performed in the MAH's Global safety database found 2 non-serious case reports and 1 serious case with exposure during pregnancy. The pregnant patients received mepivacaine 3% (w/v) for dental treatment. No effects on foetus were reported in the 2 cases. The third case described hypospadias in a newborn whose mother received mepivacaine during pregnancy, however there is no causal relationship between hypospadias and mepivacaine. According to the guideline on SmPC, lack of data are not sufficient to lead to a contraindication, therefore the CHMP agrees with the MAH's proposal not to include this contraindication. Relevant information is included in Section 4.6 of the SmPC.

Severe liver disease

As all amide-type local anaesthetics, mepivacaine is largely metabolised in the liver by microsomal enzymes undergoing extensive hepatic biotransformation with less than 5% of urinary excretion of the unchanged drug. However, there is no sufficient evidence to support a contraindication to patients with liver disease. Therefore, the MAH proposed to remove this contraindication from section 4.3 and include a warning in section 4.4. Use in patients with hepatic disease should be done with caution by using the lowest dose leading to anaesthesia. The CHMP also considered that information on possible accumulation of medicine should be provided in section 4.2 as well, which has been accepted by the MAH.

The final agreed wording for this section of the SmPC can be found in Annex III of the CHMP opinion.

Section 4.4 – Special warnings and precautions for use

Apart from the contraindications requalified in warnings, as discussed in the previous section, several other warnings have been harmonised.

Several warnings were in place in some or all MSs with slightly different wordings. The MAH proposed to rearrange the warning in five categories: patients with cardiovascular disorders, epileptic patients, patients with a hepatic disease, patients with a kidney disease, elderly patients.

Regarding the warnings on patients with cardiovascular disorders, the CHMP considered appropriate to include the proposed harmonised warnings (peripheral vascular disease, arrhythmias particularly of ventricular origin, heart failure, hypotension and caution in patients with impaired cardiac function). Provisions, rejected from local SmPCs, which contained information regarding cardiovascular precautions and special warnings were considered acceptable as information on mepivacaine use in patients with cardiovascular disorders are included already in section 4.3 (as contraindication) and in section 4.2 (as risk associated with an accidental intravascular injection) of the SmPC. Omission of provision on long QT syndrome was also considered acceptable, as no such safety concerns have been identified. In contrast, the CHMP requested the maintenance in the SmPC of a warning on patients with high blood pressure, since this is an important part of population visiting dentists.

Moreover, other warnings not related with the above categories were harmonised. A harmonised wording of the warning regarding injection into an inflamed or infected area already present in some MSs was also proposed to be implemented across all MSs, which was accepted. This warning should be cross-referenced with section 4.2 of the SmPC where more information regarding use of mepivacaine in infected skin/mucous areas is provided. With regards to the risk of biting trauma, the CHMP agreed

that patients should be warned about the risk of anaesthesiophagia (various biting traumas) and therefore should be advised not to eat until the effects of local anaesthetics have worn off and normal sensation has been restored to the lips, tongue and membranes.

The CHMP considered that provisions on the potential occurrence of toxic reactions, the maintenance of verbal contact, the monitoring of vital functions and the availability of resuscitative equipment at hand should be maintained. Moreover, information on precautions for patients receiving antiplatelet and anticoagulants medication or with coagulation disorders should be maintained due to the risk of bleeding, even though the risk of bleeding is not associated with mepivacaine itself, but with the procedure. In addition, considering the wide choice of alternative medications a general warning on the use of alternative medication in the risk of any allergic reaction to mepivacaine, should be included in this section with cross-reference to section 4.3. Both the injection technique and the risk associated with injection to blood vessel or intraneural injection is well described in Section 4.2 of the SmPC. Thus, the CHMP agrees, that this information can be omitted from this section. CHMP also considers that despite the controversial literature regarding porphyria, a warning should be maintained in section 4.4.

The final agreed wording for this section of the SmPC can be found in Annex III of the CHMP opinion.

Section 4.5 – Interaction with other medicinal products and other forms of interaction

Several interactions were in place in one or more MSs. After having reviewed the submitted data and the MAH's response the CHMP agreed to maintain the following interactions: additive interactions with other local anaesthetics, H2 antihistaminics (cimetidine), sedatives, antiarrhythmic drugs.

It is noted that the cytochrome CYP1A2 has an important involvement in mepivacaine metabolism in the liver; the usage of inhibitors of CYP1A2 may decrease its metabolism and increase the risk of adverse effects. Thus, the CHMP considered important to mention the interaction between strong inhibitors of CYP1A2 (ciprofloxacin, enoxacin, fluvoxamine, cimetidine) and mepivacaine metabolism. Another interaction that has been added during the harmonisation exercise is the propanol-mepivacaine interaction as supported by a recent double blind, randomized, 2-way crossover study[2].

Due to the lack of supportive data, the following interactions have been deleted of the SmPC: psychopharmaceutical drugs, tricyclic antidepressants, alcohol consumption, monoamine oxidase (MAOIs) inhibitors, antimyasthenics, hyaluronidase, other anaesthetics (apart from those mentioned earlier) such as chloroform, halothane, cyclopropane, trichloroethylene and St John's wort (herbal medicine). The interaction with anticonvulsant drugs is reworded as interaction with sedatives, as anticonvulsant drugs is not a specific term. The CHMP also considered acceptable the omission of the interaction with disinfectant solutions as this is rather a risk of contamination of the cartridge rather an actual interaction.

Some local SmPCs included the interaction of heparin, non-steroidal anti-inflammatory drugs (NSAIDs) and plasma substitutes with mepivacaine. Heparin and NSAIDs are respectively anticoagulant and antiplatelet drugs, while large volumes of some plasma substitutes can increase the risk of bleeding through depletion of coagulation factors. CHMP noted that bleeding may be more severe in patients treated with antithrombotic or anticoagulants compared to patients not using these medications, but this is related to the dental procedure itself and the mechanism of action of antithrombotic / anticoagulant treatment and not to mepivacaine. This information is already included in section 4.4 of the SmPC, and therefore has been deleted from section 4.5 Interaction with other medicinal products.

The final agreed wording for this section of the SmPC can be found in Annex III of the CHMP opinion.

[2] Popescu SM et al. Effect of propranolol on mepivacaine serum concentrations in dental practice. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 2008;105:e19-23

Section 4.6 – Fertility, pregnancy and lactation

The information on pregnancy and breastfeeding was different among MSs. The CHMP agreed on a common wording, rejecting some local SmPCs which provided too detailed information regarding the pre-clinical studies that did not provide valuable information for healthcare professionals.

Data on fertility comes from two pre-clinical studies in rats and to date, no clinical data including pregnant women or history of pregnant women receiving mepivacaine are available. There have been some retrospective studies of pregnant women receiving local anaesthesia for emergency surgery early in pregnancy (first trimester). However, these studies have not shown that local anaesthetics cause birth defects. No nursing mothers were included in the clinical studies with mepivacaine at 30 mg/ml. Considering the lack of data for mepivacaine and in the hypothesis of the worst-case scenario of highly toxic drugs, the delay for breastfeeding is 4 to 5 maternal drug half-lives, nursing mothers should not breastfeed within 10 hours following anaesthesia with this product. A relevant statement is reflected in section 4.6.

The final agreed wording for this section of the SmPC can be found in Annex III of the CHMP opinion.

Section 4.7 – Effects on ability to drive and use machines

Many of the pharmacological actions of mepivacaine have an impact on the CNS. Adverse reactions such as dizziness (including vertigo, vision disorder and fatigue) may occur following the administration of mepivacaine and usually they manifest very early, taking into consideration that mepivacaine has a rapid onset of approximately 3 - 5 minutes. Mepivacaine has a short duration of action (approximately 30 minutes for pulpal anaesthesia). Therefore, as a precautionary measure, the CHMP considered that patients should be advised to avoid driving or using machines until normal sensation is restored and the adverse reactions that may affect their abilities to drive and use machines should be mentioned in this section, with a cross-reference in section 4.8 (undesirable effects).

The final agreed wording for this section of the SmPC can be found in Annex III of the CHMP opinion.

Section 4.8 – Undesirable effects

The post-marketing safety experience is based on the information collected from unsolicited sources entered in the global safety database and also on a review of the safety data issued from literature. Cumulatively, 380 case reports (736 adverse drug reactions - ADRs) were reported in the Septodont global pharmacovigilance database for this medicinal product: 106 reports (28%) were serious and 274 reports (72%) were non-serious including 147 reports of lack of therapeutic effect.

There were some divergences in the ADRs in the local SmPCs. The MAH provided harmonised version of section 4.8 by analysing data form global pharmacovigilance database. The proposed frequency and naming of ADRs is acceptable and in line with data provided in previous periodic safety update reports (PSURs).

The CHMP considered that several adverse events, like agitation, anxiety/nervousness tremor and speech disorder might be warning signs before CNS depression and suggested the following footnote to this ADR to be added: "*Several adverse events, like agitation, anxiety / nervousness tremor, speech disorder may be warning signs before CNS depression. In attendance of these signs, patients should be requested to hyperventilate and surveillance should be instituted (see section 4.9)*." The MAH agreed with this addition.

The CHMP also proposed some amendments in the frequency and the system organ class (SOC) of several ADRs: the frequency of the ADR 'myocardial depression' to be changed to 'not known', as no cases were reported and no clinical trials have been conducted. 'Vertigo' should be moved to the SOC

'Ear and labyrinth disorders' as this is the primary SOC for this ADR. Moreover the ADR 'Hyperthermia' should be included under the SOC 'General disorders and administration site conditions' with frequency 'not known'. The MAH has proposed to delete the ADR 'Methaemoglobinemia' which is present in some local SmPCs, due to the lack of supportive evidence. No report of Methaemoglobinemia with mepivacaine was identified in literature and in the Septodont Global pharmacovigilance database. This was considered acceptable by the CHMP.

The final agreed wording for this section of the SmPC can be found in Annex III of the CHMP opinion.

Section 4.9 – Overdose

According to information provided in the literature, there are two main types of overdose which may occur during local anaesthesia with mepivacaine: absolute overdose and relative overdose. Both types of overdose result in excessive plasma levels and consequently have similar toxicity manifestations. Absolute overdose is the result of injection of excessive doses. Relative overdose refers to the injection of a non-toxic dose under particular circumstances, in which excessive amount of drug is found in blood: inadvertent injection into a blood vessel, abnormally rapid absorption of a normal dose into the systemic circulation and delayed metabolism of the drug or delayed elimination from the plasma. The proposed description of overdose symptoms is accepted by the CHMP.

The CHMP considered that it is important to emphasize that acidosis during convulsions exacerbates the toxic effects of local anaesthetics and agreed to maintain this provision.

The MAH proposed to remove the provision on the risk of myocardial failure associated with mepivacaine overdose, due to inconclusive literature search. However, the CHMP is of the opinion that this statement should be maintained since local anaesthetics are known to be pro-arrhythmic and their usage for patients with cardiovascular disorders is limited. The CHMP is also of the opinion that a statement regarding the inefficiency of dialysis in treating mepivacaine overdose should be maintained in this section.

The MAH took also the opportunity to harmonise information on the overdose management as per the EMA SmPC guideline (2009) by removing any recommendation and dosage indications of other medicinal products. This was accepted by the CHMP. In contrast, deletion of statements regarding methods to increase the elimination of the product and the emphasis in the importance of treating acidosis were not endorsed by the CHMP. These statements have been maintained.

The final agreed wording for this section of the SmPC can be found in Annex III of the CHMP opinion.

Section 5.1 – Pharmacodynamic properties

The proposed information is in line with current knowledge of pharmacodynamic properties of local anaesthetics, in dental procedures. Since the chiropody indication is not supported by sufficient data, this section will be deleted for this indication. The CHMP proposed that the onset of action and the duration of analgesia should be provided as a time interval, rather than concrete number, while the mechanism of action should be explained in a more detailed way, providing the parameters that influence the onset and duration of the local anesthetic, such as pH of tissue, pKa, lipid solubility, local anesthetic concentration, diffusion in the nerve of local anesthetic, etc.

In section 4.1 of the SmPC the MAH has highlighted the possibility to use mepivacaine in cases when vasoconstrictor is contraindicated. The CHMP is op the opinion that in case of vasoconstrictor contraindication, not only mepivacaine can be used but also other local anesthetics such as procaine, bupivacaine and lidocaine. There is evidence that mepivacaine provides vasoconstrictive features compared with anaesthetics from other pharmaceutical groups, however this cannot consist an indication itself. The CHMP required that the statement "Studies reviled, that mepivacaine has

vasoconstrictive properties. This property could be beneficial when the use of vasoconstrictor is contraindicated." should be moved from section 4.1 (indications) to 5.1 of the SmPC. The MAH agreed.

Information on bioavailability should be maintained in this section.

The final agreed wording for this section of the SmPC can be found in Annex III of the CHMP opinion.

Section 5.2 – Pharmacokinetic properties

The MAH provided information on absorption, distribution, metabolism and elimination supported by literature. No studies were performed by the MAH. The provided information is concise and overall accepted, however the CHMP identified some provisions that are missing from this section, such as information regarding maximum plasma level and absorption, information on specific the hepatic enzymes involved in metabolism, information on plasma half-life and on risk for accumulation. The MAH agreed to maintain the information in this section.

The final agreed wording for this section of the SmPC can be found in Annex III of the CHMP opinion.

Section 5.3 – Preclinical safety data

The MAH discussed data from the literature regarding single dose and repeat-dose studies, genotoxicity, reproductive and development toxicity studies. The general toxicity studies demonstrated a good safety margin. The reproductive and development toxicity study did not demonstrate teratogenic effects with mepivacaine.

Few statements present in certain local SmPCs were deleted as they are either mentioned in other sections (e.g. half-life) or they are not supported by sufficient evidence.

The final agreed wording for this section of the SmPC can be found in Annex III of the CHMP opinion.

Other Sections

Sections 2 (qualitative and quantitative composition), 3 (pharmaceutical form), 6.1 (list of excipients), 6.2 (incompatibilities), 6.3 (shelf life), 6.4 (special precautions for storage) 6.5 (nature and contents of container) and 6.6 (Special precautions for disposal and other handling) have been updated in line with their respective harmonised Quality documentation provided in Module 3 and in line with the latest QRD template. The proposed harmonised text was accepted by CHMP with minor changes for consistency and completeness or clarity.

Labelling

Changes introduced in the SmPC were consistently reflected in the labelling.

Package Leaflet

The PL was amended in accordance with the changes made to the SmPC. In addition minor editorial changes were introduced to improve readability.

The MAH conducted a readability user testing that showed that 90% of participants were able to find and understand the information within the PL. The test protocol and the study sample were considered appropriate. However the CHMP identified some points of clarification to be discussed by the MAH, in order to better elaborate the design of the test, the presentation and analysis of the evaluation system and the results.

The MAH is required to provide the following clarifications:

- A detailed discussion on the critical safety issues in order to identify the key safety messages.

- A presentation and analysis of the results separated by each phase.

- A clear and detailed description of the evaluation system, which explains the three basic steps (find the information, understand the information and use the information) that were checked in the context of the assessment.

- The analysis that elaborates how a question was considered correctly or incorrectly answered.

- A description of the changes (if any) to the PL between the different rounds (pilot, 1st and 2nd), following the results obtained. If there were any changes, a new PL with track changes reflecting the PL differences between the different rounds should be provided.

In case the applicant cannot provide the requested information, a new readability test should be submitted. The new readability test should be in line with the "Guideline on the Readability of the labelling and package leaflet on medicinal products for human use".

The MAH is requested to address these points in a post-referral phase. The answers to be submitted to the reference member state (RMS) or relevant NCAs.

2.2.2. Module 3 - Quality

Introduction

The finished product is presented as a solution for injection containing 30 mg/ml of mepivacaine hydrochloride as active substance.

Other ingredients are: sodium chloride, sodium hydroxide (for pH-adjustment) and water for injection.

The product is available in single use type I glass cartridge, sealed at its base by a mobile type I synthetic rubber and at the top by a type I synthetic rubber seal kept in place by an aluminium cap as described in section 6.5 of the SmPC. The cartridges with fill volume of 1.7 ml or 2.2 ml are available, delivering 51 mg and 66 mg of mepivacaine hydrochloride, respectively.

Within this procedure, the MAH has provided the harmonised updated Module 3 sections which are discussed below.

Active substance (CTD module 3.2.S)

Sections 3.2.S have been harmonised by updating the Certificate of Suitability to the monograph of the European Pharmacopoeia (CEP) for the active substance mepivacaine hydrochloride, from already approved manufacturers. Valid certificates of suitability have been provided.

Control of active substance (CTD section 3.2.S.4)

Specification (CTD section 3.2.S.4.1)

Active substance specifications were provided for both active substance manufacturers and are in line with respective Ph. Eur. monograph supplemented with the additional information from each Certificate of Suitability issued by EDQM. Upon request during the procedure, the MAH updated the active substance specifications with the addition of compendial tests for bioburden European Pharmacopoeia (Ph.Eur.) 2.6.12 and endotoxins (Ph.Eur. 2.6.14). The suitability of these microbiological methods for mepivacaine hydrochloride was demonstrated. Batch analysis was also provided and the data show compliance with the acceptance criteria for microbial contamination and bacterial endotoxins. For the other tests, the analytical methods are pharmacopoeial. Batch analytical results have been provided for three recent batches of the active substance from both manufacturers. All results remained within the specifications limits. The updated specifications are acceptable.

Finished product (CTD section 3.2.P)

Description and composition of the finished substance (CTD section 3.2.P.1)

Scandonest is a clear and colourless solution for injection. The qualitative and quantitative composition has not been affected by the harmonisation procedure.

During the procedure the number of presentations has been harmonised to include both the 1.7 ml and the 2.2 ml; before the harmonization procedure, the 2.2 ml was only marketed in the UK and IE. Additionally, in many MSs, the nominal filling volume was erroneously indicated as 1.8 ml, which is the total capacity of the cartridge; hence, during the procedure, the nominal volume was amended to 1.7 ml.

Manufacture (CTD section 3.2.P.3)

Description of manufacturing process and process controls (CTD section 3.2.P.3.3)

The manufacturing process used for the manufacture of the finished product consists of four principal steps: preparation of primary packaging elements, preparation of solution, filtration and distribution. As part of the harmonization procedure, the description of the manufacturing method has been updated by stating the use of 0.22 µm nitrogen filters. Acceptable control of the integrity of the sterilising filter for nitrogen, used during the preparation of the solution, including the relevant acceptance criteria has also been listed. The proposed widening of the In-Process Control (IPC) limits for the pH of the bulk solution for all MS, has been adequately justified based on the experience gained over time on the manufacturing process and on various analytical results obtained in batches produced between 2013 and 2016. The presence of the IPC assay for NaCl has also been harmonised among member states and it has been introduced in LT, LV, UK, where it was not present.

Process validation and/or evaluation (CTD section 3.2.P.3.5)

The conventional terminal sterilisation cycle of the finished product (121°C for 15 minutes) complies with the recommendations of the European Pharmacopoeia. Results of analysis and validation reports have been provided with the submission of the procedure; they include verification of the homogeneity of the batches and control of pH, assay of sodium chloride, control of distribution and filling in cartridge, and microbiological purity. During the procedure, section 3.2.P.3.3 "*Description of manufacturing process and process controls*" was updated to include the filter integrity test (bubble test) and the relevant parameters. To support the approved 5 days maximum holding time from filtration to sterilisation, validation data from three batches of the same size of Scandonest, manufactured in 2016, of another product containing mepivacaine hydrochloride 20 mg/mL and adrenaline 0.01 mg/mL were provided. This formulation is considered a worse case scenario as it is more sensitive to degradation than the formulation subject to this referral procedure. The holding time of these three batches was in all cases above 4 days with one of the batches held for almost 5 days. The data obtained complied with the specifications with no trend being observed for any degradation. As such the proposed holding time of 5 days from filtration to sterilisation of the bulk of finished product is considered adequately justified.

Control of Excipients (CTD section 3.2.P.4)

During the procedure, section 3.2.P.4 has been harmonised by updating with nitrogen's control for all MSs and by updating the control of sodium hydroxide (pellets) in line with the monograph "Sodium hydroxide (0677)" of the Ph. Eur. current edition, instead of the in-house procedure. The excipients are controlled following the analytical methods and specifications in line with the Pharmacopoeia. Recent satisfactory Certificates of Analyses have also been provided.

Control of Finished substance (CTD section 3.2.P.5)

Specifications (CTD section 3.2.P.5.1)

The specifications for finished medicinal product have been harmonised in line with Ph. Eur. and European regulatory requirements. The following tests have been added to the specifications: Assay of Sodium Chloride (limits based on guidance, literature and MAH acquired experience of the manufacturing process), Bacterial Endotoxins, Identification of Mepivacaine Hydrochloride by High Performance Liquid Chromatography (HPLC) in addition to the Thin Layer Chromatography (TLC) test (before the harmonisation the HPLC test was part of the proposed shelf-life specifications in some Member States), and Sub-visible particles (according to the requirements of Ph.Eur. monograph 0520 "Parenteral preparations", and complying with the test described in the Ph. Eur. monograph 2.9.19 "Particulate contamination: sub-visible particles"). The Mean Volume test has been replaced by the pharmacopoeial Extractable Volume (in line with current Pharmacopoeia requirements) for administration of nominal dose.

The following tests have been removed from the specifications:

- NaCl identification test (since NaCl is neither antioxidant nor preservative, the identification test is not necessary*).*
- Osmolality test (it is accepted that osmolality is indirectly controlled through the determination of sodium chloride content since the only components of the formulation contributing to osmolality of the formulation are sodium chloride and sodium hydroxide and that sodium hydroxide is used in small amount in the adjustment of the pH of the solution, hence the test for osmolality can be omitted from the specifications).
- Physical tests (as mechanical resistance tests are maintained in the specifications of the packaging element on the empty cartridges).

Analytical procedures (CTD section 3.2.P.5.2)

During the harmonisation procedure, the MAH updated the chromatographic conditions of the HPLC method for the Assay of finished product. The equivalence of the two HPLC methods has been demonstrated with six batch data of finished product tested according to the updated and current HPLC methods (*i.e.* former conditions vs. new upgraded conditions). The TLC is the analytical procedure used by the MAH for the identification of mepivacaine hydrochloride since its first registration. This TLC method was slightly updated a few years ago and some minor changes were made on the chromatographic conditions, which have been harmonised during the procedure.

Container Closure System (CTD section 3.2.P.7)

Two different rubbers closure for the vials, namely natural and synthetic rubbers, both complying with pharmacopoeial requirements, have been available among Member States prior to this harmonisation procedure. During the procedure, the proposal to retain only the synthetic rubber closure has been agreed. The plunger and the seal (as part of the cap) currently used by the MAH are made with synthetic rubber, which is supplied with the technical documentation and the appropriate certificate of conformity to Ph. Eur. No changes have been implemented to the plunger.

Stability (CTD section 3.2.P.8)

The Module 3 has been updated with satisfactory stability data, obtained from seven commercial batches of the finished product stored for up to 36 months under long term (25°C ± 2°C / 60 % RH ± 5 % RH) and intermediate (30°C ± 2°C / 75 % RH ± 5 % RH) conditions and for up to 6 months under accelerated conditions (40°C ± 2°C / 75 % RH ± 5) according to the ICH guidelines. The batches of

the finished product were packed in the approved primary packaging in both containers (1.7 ml cartridge and in the 2.2 ml cartridge). All the tests have been performed in accordance with the validated procedures described in section 3.2.P.5.2.

Based on available stability data, the proposed shelf-life of 36 months and storage conditions “do not freeze” as stated in the SmPC (section 6.3) are acceptable.

Section 3.2.P.8.2 has been harmonised by including post approval stability protocol and stability commitment in order to comply with the Good Manufacturing Practices (GMP). In addition, the MAH made editorial changes regarding the labelling statements in order to comply with the QRD template.

Conclusions on the chemical, pharmaceutical and biological aspects

The harmonisation of the quality aspects of this product is considered to be acceptable and adequately justified.

3. Recommendation

Based on the review of all available data the CHMP recommended the revision and harmonisation of the product information for Scandonest and associated names.

The indication agreed is:

{(Invented) name and associated names (see Annex I) strength pharmaceutical form} 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).

The final agreed wording of the product information can be found in Annex III of the CHMP opinion.

4. Conclusions

The basis for this referral procedure was a harmonisation of the SmPC, labelling and package leaflet as well as a harmonisation of the Module 3 at the request of the MAH.

In conclusion, based on the assessment of the MAHs’ proposals and responses and following the discussions of the Committee, the CHMP adopted harmonised sets of product information and quality documentation of Scandonest and associated names.

Whereas

- The Committee considered the referral under Article 30 of Directive 2001/83/EC;
- The Committee considered the identified divergences for Scandonest and associated names, for the indications, posology, contraindications, special warnings and precaution for use, as well as the remaining sections of the SmPC, labelling and package leaflet;
- The Committee reviewed the data submitted by the MAH in support of the proposed harmonisation of the product information, including based on the documentation submitted and the scientific discussion within the Committee;
- In addition, the Committee reviewed the documentation submitted by the MAH in support of the proposed harmonised Quality documentation (Module 3);

The CHMP recommended the variation to the terms of the marketing authorisations for which the summary of product characteristics, labelling and package leaflets are set out in Annex III for Scandonest and associated names (see Annex I).

The CHMP concluded that the benefit-risk balance of Scandonest and associated names remains favourable, subject to the agreed changes to the terms of the marketing authorisation.