Annex II

Scientific conclusions

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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. Scandonest contains 30 mg/mL of mepivacaine hydrochloride.

Mepivacaine was first approved in 1960 by the US Food and Drug Administration. In the EU, Scandonest is authorised in 22 Member States (MS) through national procedures, and in 5 MSs (Sweden, Finland, Portugal, Spain, Malta) through mutual recognition procedure (MRP).

On 25 August 2017 Septodont on behalf of all marketing authorisation holders (MAHs) presented to the European Medicines Agency a referral under Article 30 of Directive 2001/83/EC, in order to harmonise the national summary of product characteristics (SmPC), labelling, package leaflet and quality Module 3 of the medicinal products Scandonest and associated names (see Annex I of CHMP opinion).

Overall summary of the scientific evaluation by the CHMP

Only the most major changes have been discussed in details below. However, all sections of the PI have been harmonised.

Section 4.1 - Therapeutic indications

The MAH has provided a summary of the literature and studies to support the indication “anaesthesia in dental procedures”. The CHMP deemed the submitted evidence adequate to support the indication in adults and in children from 4 years of age (ca. 20 kg body weight).

The CHMP is of the opinion that in case of vasoconstrictor contraindication there are alternative options, such as other local anaesthetics (procaine, bupivacaine and lidocaine), general anaesthesia and nitrous oxide. The CHMP noted that there is literature evidence that mepivacaine provides vasoconstrictive features compared with anaesthetics from other pharmaceutical groups, however this cannot consist an indication itself. Therefore, the CHMP recommended that the statement regarding mepivacaine’s use when vasoconstrictor is contraindicated should be moved from section 4.1 to 5.1 (pharmacodynamic properties) of the SmPC.

The CHMP considers that the data submitted in support of the chiropody procedures 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 revised therapeutic indications in section 4.1 of the SmPC are:

{(Invented) name and associated names, 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 methods of administration

Posology

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.

For the recommended doses the patient's body weight has to be taken into account. The maximum recommended dose is 4.4 mg/kg of body weight with an absolute maximum recommended dose of 300 mg. 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. This information should be reflected in the SmPC section 4.2 with a cross reference to section 4.5 (Interactions with other medicinal products).

The recommended posology in children of an average 0.75 mg (0.025 ml) of mepivacaine solution per kg of body weight is in line with the work-sharing procedure led by EMA in 2010 in accordance with Article 45 of the Paediatric Regulation 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.

Mepivacaine is largely metabolised in the liver by microsomal enzymes and the principal route of excretion is via the kidney. Consequently, metabolism and elimination of mepivacaine can be significantly altered by the presence of hepatic or renal diseases. Pharmacokinetic changes are also observed with aging. As a precautionary measure and due to lack of data in this potentially more vulnerable population, the lowest dose leading to efficient anaesthesia should be applied.

The recommendations on lower doses for patients with reduced health and pre-existing conditions such as vascular obliterations, arteriosclerosis or diabetes-related nerve damage are not supported by sufficient data and are not endorsed by the CHMP. 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) has been however endorsed by the CHMP.

The relevant posology section for the mepivacaine use in chiropody procedure will be removed as the CHMP supported the deletion of this indication.

Method of administration

The wording for the method of use was harmonised to the standard terms "infiltration and perineural use" taking in consideration the requirements from the EDQM (European Directorate for the Quality of Medicines & HealthCare). Information for medical staff on how to avoid a blood vessel penetration during injection as well as instructions to avoid injections to inflamed or infected tissues are maintained in the SmPC. The rate of 1 ml/min is considered ideal as it does not produce tissue damage during or after anaesthesia and any serious reaction in the event of accidental intravascular injection.

Section 4.3 – Contraindications

Mepivacaine is contraindicated in patients with a history of hypersensitivity to the product, to any other amide anaesthetics or to any of the excipients. As a result of the review of mepivacaine during a work-sharing procedure in accordance to Article 45 of Regulation No 1901/2006, in 2010, the use of mepivacaine is contraindicated in children below 4 years of age (and less than 20kg of body weight).

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. Therefore, mepivacaine is contraindicated in patients with atrioventricular disorders not compensated by a pacemaker.

In the presence of high blood levels, local anaesthetics cross the blood-brain barrier. As the drug concentration rises in the brain, the excitatory pathways are inhibited and CNS depression occurs. 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. Thus, local anaesthetics should not be used in epileptic patients whose seizures are poorly controlled.

Therefore, the CHMP concluded in the inclusion of the contraindications summarised below:

- *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.*

Other Sections

In section 4.4, the warnings have been re-organised in five categories: patients with cardiovascular disorders, hepatic disease, kidney disease, epileptic and elderly patients. Other warnings not related with the above categories were harmonised, such as for patients with coagulation disorder and co-administration of antiplatelet/anticoagulant medicines. Moreover information on managing dose-related toxicity and other acute emergencies has been included.

Interactions with other medicinal products (section 4.5) have been summarised in additive interactions with other local anaesthetics, H2 antihistaminics, sedatives, antiarrhythmic drugs, CYP1A2 inhibitors and propranolol.

The CHMP agreed on a common wording, on fertility, pregnancy and lactation (section 4.6) with data supported from pre-clinical studies. No clinical data on fertility and nursing mothers are available on humans.

A harmonised version of section 4.8 of adverse events has been agreed by the CHMP after assessing data from global pharmacovigilance database and literature and in line with data assessed in previous periodic update assessment reports (PSURs).

In section 4.9 regarding overdose, two different types are described; absolute and relative overdose. A harmonised description of the symptoms and the management of overdose has been agreed in accordance with the EMA SmPC guideline (2009).

Sections 2 (qualitative and quantitative composition), 3 (pharmaceutical form), 4.7 (Effects on ability to drive and use machines), 5.1 (pharmacodynamic properties), 5.2 (pharmacokinetic properties), 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.

Labelling and Package Leaflet

Changes introduced in the SmPC were consistently reflected in the labelling, with some sections left to be completed nationally. The package leaflet (PL) was amended in accordance with the changes made to the SmPC. In addition minor editorial changes were introduced to improve readability.

Module 3 - Quality

The finished product is presented as a solution for injection containing 30 mg/ml of mepivacaine hydrochloride as active substance. Other ingredients include sodium chloride, sodium hydroxide and water for injection. The updated sections of Module 3 sections include: Active substance, Control of active substance, Specification, Finished product, Description and composition of the finished

substance, Manufacture, Description of manufacturing process and process controls, Process validation and/or evaluation, Control of Excipients, Control of Finished substance, Specifications, Analytical procedures, Container Closure System and Stability. The harmonisation of the quality aspects of this product is considered to be acceptable and adequately justified.

Grounds for the CHMP opinion

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 product information.