Annex II

Scientific conclusions

Scientific conclusions

Articaine inhibits the conduction of nerve impulses by decreasing or blocking sodium (Na+) and potassium (K+) flows during propagation of the nerve action potential. The vasoconstrictor decreases the vascular perfusion at the site of injection and consequently it reduces the rate of absorption of the anaesthetic into the circulation.

Septanest and associated names is a fixed-dose combination product containing articaine hydrochloride 40 mg/ml and adrenaline tartrate. It is available in 2 strengths: articaine/adrenaline 40/0.005 mg/ml and articaine/adrenaline 40/0.01 mg/ml.

Septanest and associated names is authorised in the European Union (EU) in the form of 57 marketing authorisations (MAs); 39 purely national MAs and a Mutual Recognition Procedure (MRP) involving 9 Member States (MS). The MAs were granted between 1988 and 2017 with an uneven level of information registered.

On 4 June 2018 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 Septanest 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

Septanest and associated names is indicated for the local and loco-regional anaesthesia in dental procedures in adults, adolescents and children above 4 years of age [or from 20 kg (44lbs) of body weight].

The main evidence supporting the efficacy in the above indication is derived from 8 clinical studies conducted in adults and children. The results of these studies indicate that articaine 40 mg/mL with 0.01 mg/mL or with 0.005 mg/mL adrenaline is effective as a local dental anaesthetic in adults and children above 4 years old. Moreover the MAH has submitted bibliographic data from publications regarding the efficacy, safety and pharmacology of articaine 40 mg/mL alone or with adrenaline in dental local anaesthesia. In addition, the MAH made reference to guidelines by the American Academy of Paediatric Dentistry on the use of local anaesthesia for paediatric dental patients (2015) in which articaine 40 mg/mL solution with adrenaline 0.01 mg/mL is listed among the injectable local anaesthetics that can be considered for children.

Section 4.2 – Posology and method of administration

Posology

The MAH proposed harmonised dosing recommendations based on the doses studied in clinical trials and supported by pharmacodynamic and pharmacokinetic data. This proposal is also 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).

For routine dental procedures in adults the lowest dose leading to effective anaesthesia should be used. The content of up one cartridge of articaine is usually sufficient. For more extensive procedures

one or more cartridges may be required. The dose should be calculated according to the patient's bodyweight and the total dose for all injected sites should not exceed the maximum recommended dose of 7.0 mg per kg of bodyweight with an absolute maximum recommended dose of 500 mg.

The recommended dose is supported by clinical and literature data. A crossover, double blind Phase III study, comparing articaine/adrenaline 1:100 000 and 1:200 000, with a total of 11.9 mL (1.7 mL in each of 7 cartridges) of each formulation administered intra-orally to each subject, showed that the difference in adrenaline concentration did not lead to any significant difference in plasma levels of articaine and that no toxicity was observed on patients. An excessive plasma concentration of articaine may result in cardiovascular toxicity, while high levels of adrenaline in the blood may lead to cardiovascular stimulation. Data obtained after intraoral administration of articaine 40 mg/mL with adrenaline 0.01 mg/mL at the maximum recommended dose for articaine showed that the maximum therapeutic dose of 500 mg does not produce signs of intoxication (cardiovascular issues) in healthy patients.

The maximum recommended dose of 7 mg/kg of articaine (with an absolute maximum dose of 385 mg articaine for a healthy child of 55 kg bodyweight) in dental procedures for paediatric population is in line by the latest recommendations from the American and European Academy of Pediatric Dentistry. Similarly, in a review by Leith and colleagues[1], the authors analysed numerous publications employing articaine in children, concluding that 7 mg/kg of articaine is an acceptable maximum dose in a paediatric population.

The MAH proposed not to specify the usual dose in children due to the lack of dose selection study in paediatric patients. Only the maximum dose was largely reported in literature and guidelines and acknowledged in the current practice. The CHMP considered that information about usual doses is important to prevent misinterpretation of dosing recommendations and usage of only maximum doses. The CHMP noted that the usual average dose of articaine was not established in clinical trials. However, the existing data suggests that doses ranging from 2.4 to 3.5 mg/kg are effective for most paediatric patients. Therefore, the CHMP is of the opinion that in the absence of data from clinical trial for the usual doses in paediatric population, the approximate range of usual effective doses should be specified in this subsection as well as recommendation to use the lowest effective dose. The quantity to be injected should be determined by the weight of the child and the magnitude of the operation.

The recommendations on lower doses for patients with renal disorders, hepatic disorders, plasma cholinesterase deficiency and elderly patients are maintained. The statement regarding the risk of possible accumulation of the product leading to toxicity in these populations has been however endorsed by the CHMP.

There was different terminology, used in local SmPCs, regarding the method of administration, aspiration technique, rate of injection and precautions before use. The CHMP did not endorse the omission of the wording regarding avoidance of administration into inflamed or infected tissues as injection of local anaesthetics into such tissues may result in decreased effectiveness of the anaesthetics. The rate of 1 ml/min is considered optimal as it does not produce tissue damage during or after anaesthesia, as well as any serious reaction in the event of accidental intravascular injection.

Other Sections of the SmPC

The data supporting contraindications included in section 4.3 of the SmPC was discussed by the MAHs and the rationale provided for keeping them in the SmPC was agreed by the CHMP for patients with a

[1] Leith, R.; Lynch, K.; O'Connell, A. C. (2012): Articaine use in children. A review. In Eur Arch Paediatr Dent 13 (6), p. 293-296.

history of hypersensitivity to articaine, to adrenaline or to any of the excipients of the finished product and patients with epilepsy not adequately controlled by treatment.

The section 4.4 of the SmPC (Warnings) has been summarized to include the below categories: patients with cardiovascular disorders, epileptic patients, patients with plasma cholinesterase deficiency, patients with renal disease, patients with severe hepatic disease, patients with myasthenia gravis treated by acetylcholinesterase inhibitors, patients with porphyria, patients with concomitant treatment with halogenated inhalation anaesthetics, patients receiving treatment with antiplatelets / anticoagulants and elderly patients. The most important safety concerns are risks related to the central nervous and cardiovascular systems. In the subsection precautions for use, precautions are included for risk associated with accidental intravascular injection and risk associated with intraneural injection.

Interactions with other medicinal products (section 4.5 of the SmPC) have been summarised in additive interactions with other local anaesthetics, sedatives, halogenated volatile anaesthetics, postganglionic adrenergic blocking agents, non-selective beta-adrenergic blockers, tricyclic antidepressants, catechol-O-methyl transferase inhibitors, drugs causing arrhythmias, ergot-type oxytocic drugs, sympathomimetic vasopressors and phenothiazines.

The CHMP agreed on a common wording, on fertility, pregnancy and lactation (section 4.6 of the SmPC) with data supported from pre-clinical studies, rejecting detailed information regarding the pre-clinical studies that did not provide valuable information for healthcare professionals. No clinical data on fertility and nursing mothers are available on humans.

A harmonised version of section 4.8 of the SmPC regarding adverse events has been agreed by the CHMP after assessing data from the MAH's global pharmacovigilance database and literature data.

In section 4.9 of the SmPC 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. Information about the time to onset and description of slow or delayed onset for dosing overdose has been included at the request of the CHMP.

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) of the SmPC 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 some editorial changes were introduced to improve readability.

Module 3 - Quality

The finished product is presented as a solution for injection containing articaine hydrochloride 40 mg/ml and adrenaline tartrate in 2 strengths: articaine/adrenaline 40/0.005 mg/ml and articaine/adrenaline 40/0.01 mg/ml.

Other ingredients include sodium metabisulfite, sodium chloride, disodium edetate and sodium hydroxide and water for injection. The updated sections of Module 3 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

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 Marketing Authorisation Holder.

In conclusion, based on the assessment of the Marketing Authorisation Holder's proposals and responses and following the discussions of the Committee, the CHMP adopted harmonised wording of product information and quality documentation for Septanest and associated names.

Whereas

- The Committee considered the referral under Article 30 of Directive 2001/83/EC for the harmonisation of the product information as requested by the Marketing Authorisation Holder;
- The Committee considered the divergences in the product information identified in the notification for Septanest and associated names, for the indications, posology, contraindications, special warnings and precaution for use, as well as the remaining sections of the product information;
- The Committee reviewed the totality of the data submitted by the Marketing Authorisation Holder in support of the proposed harmonisation of the product information;
- In addition, the Committee reviewed the totality of the documentation submitted by the Marketing Authorisation Holder in support of the proposed harmonised Quality documentation (Module 3);
- The Committee considered the harmonised product information and Quality documentation (Module 3) for Septanest and associated names to be acceptable;

The CHMP recommended the variation to the terms of the marketing authorisations for which the product information is set out in Annex III for Septanest and associated names (see Annex I).

The CHMP as a consequence, concluded that the benefit-risk balance of Septanest and associated names remains favourable, subject to the agreed changes to the product information.