28 March 2019
EMA/220146/2019
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Referral under Article 30 of Directive 2001/83/EC

Septanest and associated names

Articaine (hydrochloride)/ adrenaline (tartrate))

Procedure number: EMEA/H/A-30/1461

Note:

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

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1. Background information

Referral of the matter to the CHMP

On 4 June 2018 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 summary of product characteristics (SmPC), labelling, package leaflet (PL) and quality Module of the medicinal products: Septanest and associated names (see Annex I of CHMP opinion). The divergences occurred due to different national decisions adopted by Member States concerning the authorisation of the above-mentioned products.

2. Scientific discussion

2.1. Introduction

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 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 (44 lbs) of body weight]. The product is a solution for injection, for the infiltration and the perineural use in the oral cavity.

Articaine as most amide-type local anaesthetics 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, adrenaline, performs a dual action. Firstly it decreases the vascular perfusion at the site of injection and consequently it reduces the rate of absorption of the anaesthetic into the circulation. The delayed absorption of local anaesthetics allows more local anaesthetic to diffuse into the nerve thereby providing a longer duration of pain control and improves the depth of anaesthesia.

Septanest and associated names has been approved across European Union Member States (MS), Iceland and Norway in the form of 57 marketing authorisations (MAs). 39 purely national MAs, divided into 19 MAs for Septanest with strength articaine/adrenaline 40/0.005 mg/ml and 20 MAs with strength articaine/adrenaline 40/0.01 mg/ml. There is also one Mutual Recognition Procedure (MRP) involving 9 MS where both strengths are registered. The MAs were granted between 1988 and 2017 with an uneven level of information registered. Moreover the MAs have been subject to a number of lifecycle management activities (variations, renewals, validation), which have led to several divergent decisions by the National Competent Authorities (NCAs). As a consequence, 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 fully harmonised.

In view of these divergences concerning the authorisation of the above mentioned medicinal product, in 4th June 2018 Septodont, the MAH for Septanest and associated names, 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.

2.2. Critical Evaluation

In the context of this procedure, for the product information (PI) harmonisation the marketing authorisation holder (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 to be harmonised, as well as the supportive data.

2.2.1. Product information

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 divergences concern the type of anaesthesia, the procedures in which the use of the medicinal product is indicated, the preservatives, the choice of preparation to use and the risk of bleeding. The CHMP noted that the terminology used in the individual local SmPCs differs among MS

The main evidence supporting the efficacy in the above indication is derived from 8 clinical studies conducted in adults and children. The studies compare:
- one strength (0.01 mg/ml) of articaine / adrenaline fixed-dose combination (FDC) versus another strength (0.005 mg/ml)
- articaine / adrenaline FDC versus adrenaline alone
- articaine / adrenaline FDC versus combination of other local anaesthetics with adrenaline.

One study compared the anaesthetic efficacy of Septanest to a widely marketed formulation of articaine combined with adrenaline 0.005 mg/ml (Alphacaine® N).

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. Articaine 40 mg/ml with adrenaline provides a rapid onset as well as an adequate duration of anaesthesia. Anaesthesia is achieved within the first few minutes after the injection of the drug and persists over an adequate time for routine dental treatments. The rate of failure to achieve adequate surgical haemostasis was low. It is noted that articaine 40 mg/ml with 0.01 mg/ml adrenaline was more effective than articaine 40 mg/ml with 0.005 mg/ml adrenaline in reducing blood loss during periodontal surgery and allowing good visualisation of the surgical site. Therefore, for most routine dental procedures, the formulation with adrenaline 0.005 mg/ml (1:200 000) is preferred, while the formulation with 0.01 mg/ml (1:100 000) is preferred for more complex procedure such as requiring pronounced haemostasis. The MAH has also submitted a randomised, crossover study including 62 children aged between 5 and 13 years which compared articaine 40 mg/ml in combination with adrenaline 0.005 mg/ml versus lidocaine 20 mg/ml in combination with adrenaline 0.01 mg/ml in terms of time to onset of anaesthesia, efficacy, and duration of numbness of the soft tissues. The duration of anaesthesia was shown to be significantly longer for articaine than for lidocaine (3.43 ±0.7 h vs 3.0 ±0.8 h, p=0.003). No other difference regarding the efficacy of the anaesthesia was observed between the two drugs.

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 to clinical studies and literature, the MAH has also submitted guidelines by the American Academy of Pediatric 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.

The MAH proposed to haromise the wording of indication in line with this of the MRP procedure *"Local and loco-regional anaesthesia in dental procedures"*, which was endorsed by CHMP.

The CHMP have reviewed all available data and considered that they support the proposed indication.

In the German SmPC, information on preservatives is also included in the Section 4.1. It is mentioned that the product does not contain any polyhydroxybutyric (PHB) ester type preservative, therefore it can be administered to patients allergic to PHB ester. The rational to maintain this statement is unclear since Septanest and associated names contains only E223 sodium metabisulfite, which indeed is not of PHB ester type. Therefore, the MAH's proposal not to include information for patients allergic to PHB ester in the proposed SmPC was endorsed by the CHMP. The revised wording is in line with the SmPC guideline.

Regarding statement on the choice of preparation to be used the CHMP considered that it is more appropriate for such information to be included in the section 4.2 of the SmPC Posology and method of administration.

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.

Local and loco-regional anaesthesia in dental procedures. *{(Invented) name and associated names (see Annex I)} is indicated in adults, adolescents and children above 4 years of age (or from 20 kg (44 lbs) of body weight).*

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).

i. Adults and adolescents (12 to 18 years of age)

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.

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 was 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 (4 to 11 years of age)

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 safety of this medicinal product in children under 4 years old has not been established. The following standard wording *as per* the SmPC Guideline should be included: "*The safety of {(Invented) name and associated names} in children aged 4 years and below has not been established. No data are available."*

iii. Special populations

The statements regarding the risk of possible accumulation of the product leading to toxicity have been maintained for the below populations:

- Elderly patients: Pharmacokinetic changes are observed with aging for absorption, distribution, metabolism, and elimination and affect the particular pharmacokinetics of the drug. One study

[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.

comparing two different dosages of articaine 40 mg/ml without adrenaline (60 mg/1.5 ml and 120 mg/3 ml) in elderly subjects (59-68 years) and young volunteers (20-37 years) revealed that the clearance and the volume of distribution of articaine was significantly lower in elderly than in young volunteers. After repeat use, elevated plasma levels may occur in elderly patients. Therefore, the lowest effective dose and careful monitoring for overdose signs in case of repeated use is recommended.

- Patients with renal disorders: In patients with severe renal insufficiency, both substances may potentially accumulate, since up to 75% of articainic acid is excreted unchanged through the kidneys and the rest is glucuronidated by the kidneys before excretion. This can lead to systemic toxicity. Similarly to the elderly patients, the lowest effective dose and careful monitoring for overdose signs in case of repeated use is recommended.

- Patients with hepatic disorders: Although all amide-type local anaesthetics are metabolised in the microsomes of the liver, articaine is mainly hydrolyzed by unspecific plasma esterases in the tissue and blood. The CHMP noted that hepatic metabolism appears minimally relevant based on pharmacokinetic data, however there are no clinical data supporting this. Since patients with hepatic impairment are at risk of possible accumulation leading to toxicity, the CHMP considered that information for a possible accumulation in this population should be included in this section.

- Patients with plasma cholinesterase deficiency: Contrary to all amide-type local anaesthetics, articaine is mainly metabolised by plasmatic cholinesterases. Therefore articaine should be used with caution in these patients as a cholinesterase deficiency may lead to a deficiency in metabolism of articaine to inactive metabolites and an augmentation of active articaine. Therefore, the lowest dose leading to effective anaesthesia is recommended.

The MAH proposed to omit several recommendations on reduced doses included in some local SmPCs as there were no supporting data to justify their maintenance. For example the recommendation for reducing to half the doses in elderly patients and patients more than 70 years old is not considered justified. Regarding the dose reduction in patients with pre-existing conditions such as chest angina, there are not enough data to support this statement therefore the CHMP agreed to omit this statement. Warnings for these patient populations with pre-existing conditions should be included in section 4.4.

Method of administration

There was different terminology, used in local SmPCs, regarding the method of use, aspiration technique, rate of injection and precautions before use.

The method of use was harmonised according to the standard term "*Infiltration and perineural use in oral cavity*" as defined by EDQM (European Directorate for the Quality of Medicines & HealthCare).

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. This information is therefore maintained in this section.

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.

The final agreed wording for this section of the SmPC is reflected in Annex III of the CHMP opinion.

Section 4.3 – Contraindications

Articaine/adrenaline is contraindicated in patients with a history of hypersensitivity to articaine, to adrenaline or to any of the excipients of the finished product.

There are several reports of cross-reactivity with amide local anaesthetics while using different routes of administration. It appears that cross-reactivity may occur very rarely but, as precautionary measure, articaine/adrenaline is contraindicated in patients with a history of hypersensitivity to any other amide anaesthetic.

The overall estimated incidence of perioperative seizures related to local anaesthetic toxicity is 120 per 10,000. Although in dental practices, local anaesthetics administered in therapeutic dosages do not interact with standard antiepileptic drugs, the situation for patients with uncontrolled epilepsy may be different. Indeed, seizures may result from accidental intravascular injection of local anaesthetic and CNS depression of specific pathways. As this adverse drug reaction can be life-threatening, patients with uncontrolled epilepsy should not be treated with articaine / adrenaline.

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

The contraindication of concomitant use of articaine / adrenaline with monoamine oxidase inhibitors (MAOIs). Historically, the administration of local anaesthetics containing vasopressors has been absolutely contraindicated for patients receiving MAOIs because of the increased risk of hypertensive crisis. However, it has been demonstrated that such an interaction occurs only among phenylephrine and MAOIs, but not epinephrine, levonordefrin, norepinephrine. Similarly, the review by Gomez-Moreno et al. 2009[2], and Yagiela 1999[3] stated that there is no shown interaction between adrenaline and MAO-inhibitors. Based on the above rational, the MAH has suggested to remove the contraindication. The CHMP endorsed the proposal.

The contraindication for anaesthesia in the distal part of the extremities was not considered relevant since articaine / adrenaline is not indicated in fingers and toes anaesthesia.

In patients receiving treatment with antiplatelets / anticoagulants, with past medical history of coagulation disorders and with haemorrhagic diathesis the needle may cause risk of severe bleeding during the injection or during an invasive procedure such as teeth extraction. However, as the risk of bleeding is considered more related to the procedure rather than the product's properties or effects and this information is included in section 4.4 Special warnings of the SmPC, the deletion of this contraindication was endorsed by the CHMP.

The contraindication to patients with hepatic insufficiency has been removed since it is not substantiated by data. Articaine's metabolism is primarily due to plasma esterases, not hepatic enzymes. Therefore, no risk of accumulation of articaine in patients with hepatic impairment is expected.

Migraine was included as another contraindication is some local SmPCs, however this is not supported by data. The CHMP endorsed the deletion of this contraindication.

Some local SmPCs contained the contraindication of the medicinal product in children below 4 years of age as the safety of the medicinal product in this population has not been established. The CHMP took

[2] Gomez-Moreno, G.; Guardia, J.; Cutando, A.; Calvo-Guirado, J. L. (2009): Pharmacological interactions of vasoconstrictors. In Med. Oral Patol. Oral Cir. Bucal. 14(1), E20-E27.

[3] Yagiela, J. A. (1999): Adverse drug interactions in dental practice. Interactions associated with vasoconstrictors. Part V of a series. In J. Am. Dent. Assoc. 130(5), pp. 701–709.

into consideration that the lack of clinical data itself in a population does not consist an evidence to support contraindication for this population and therefore the removal of the contraindication is supported.

The following divergences from local SmPCs were not included by the MAH in the proposed harmonised SmPC as they are available in other sections of the proposed SmPC and there are not sufficient information to consider the following conditions as contradictions: Myasthenia gravis (4.4. Special warnings), Cardiovascular disorders (4.4. Special warnings), Conduction disorders and pacemaker (4.4. Special warnings), Intravascular injection (4.2 Posology, 4.4. Special warnings), Concomitant use with beta blockers (4.4. Special warnings, 4.5 Interactions.), Concomitant use with tricyclic antidepressants (4.4 Special warnings, 4.5 Interactions), Tachycardia/arrhythmia (4.4 Special warnings), Coronary bypass (4.4. Special warnings), Sulfite hypersensitivity, especially in patients with asthma (4.4 special warnings, 4.8 Undesirable effects), Renal insufficiency (4.2 Posology and method of administration - Special populations) Inflamed area (4.4. Special warnings), Contraindications due to presence of adrenaline (cardiovascular diseases, diabetic patients, thyrotoxicosis, narrow angle glaucoma, pheochromocytoma) (4.4. Special warnings), Concomitant use with guanethidine-type drugs (4.5 Interactions), Porphyria (4.4. Special warnings), Swollen area / inflammation / infection (4.2 Posology and method of administration). The CHMP endorsed this proposal.

The final agreed wording for this section of the SmPC is presented below and is reflected 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. This section 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 regarding safety relate 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. After accidental intravascular injection, the high plasma concentrations of articaine / adrenaline may result in CNS stimulatory effects followed by CNS depression, as well as in depression of cardiovascular functions. In case of intraneural injection, it is possible that the drug moves in a retrograde manner along the nerve. This can lead to nerve injury. To avoid nerve damage, the needle should always be withdrawn slightly if paraesthesia occurs during injection.

The rational for inclusion of the above warnings and precautions for use is well justified in view of the seriousness of the risk and endorsed by the CHMP.

With regards to the warnings for patients with hepatic disease, the CHMP noted that articaine is primarily metabolised by plasma esterases. However, the CHMP considered that hepatic disease is a condition of which dentists should be cautious of, since it may lead to a decreased metabolism of articaine, and recommended that this section of the SmPC should contain information on cautious use of the product in patients with severe hepatic disease.

Concerning the MAH's proposal to remove the warning on possible positive results on doping tests, the CHMP noted that The World Anti-Doping Agency (WADA) 2018 List of Prohibited Substances and

Methods does include epinephrine (adrenaline). However it is stated that adrenaline is not prohibited in local administration, (e.g. nasal, ophthalmologic) or when it is co-administration with local anaesthetic agents. Therefore, the deletion of this warning was considered acceptable by the CHMP.

With regards to information on allergic reaction, it is noted that allergy is non-dose-dependent and can occur at very low doses. It is noted that there are several alternatives for this product; therefore in case of risk of allergic reaction the dentist/physician is encouraged to choose a different medicine. This information has been included into Section 4.4 (Warnings) of SmPC with reference to section 4.3 of the SmPC.

The final agreed wording for this section of the SmPC is reflected in Annex III of the CHMP opinion.

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

There are no major deviations in the proposed SmPC from the information included in the SmPC agreed during the MRP procedure.

After having reviewed the submitted data and the MAH's response the CHMP agreed to maintain the following interactions: 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, Phenothiazines.

Toxicity of local anaesthetics is additive when they are administered in combination. Combined use of local anaesthetics at total doses that significantly exceed the doses recommended in treatment guidelines can cause local anaesthetic adverse effects such as convulsions, respiratory depression and cardiac arrest.

For patients receiving benzodiazepines or opioids, reduced doses of articaine / adrenaline are recommended due to additive effects, since there is an increased risk of adverse reactions when central nervous system depressants are combined.

Halogenated anaesthetics sensitize the heart to the arrhythmogenic effects of catecholamines and can alter the dose of epinephrine that induces ventricular arrhythmias. Although isoflurane and sevoflurane do not change the sensitivity of the myocardium to exogenously administered epinephrine, others such as halothane, enflurane, thiopental and propofol that are all indicated in general anaesthesia, do increase the arrhythmogenic effect of the adrenergic drugs. Although topical and local adrenaline appear to be relatively safe for use during general anaesthesia using halogenated anaesthetics, when adrenaline enters the systemic circulation, the combination becomes dangerous and should be avoided. CHMP requested the maintenance of the statement in the SmPC.

With regards to the postganglionic adrenergic blocking agents, their prolonged use in treating hypertension may lead to up-regulation of postsynaptic α and β adrenergic receptors and an inhibition in catecholamines reuptake. An increase in receptors number and/or sensitivity may result in a potential hyper-response to adrenergic vasoconstrictors with hypertension and other cardiovascular adverse effects. Therefore careful aspiration prior to administration and a reduced dose of adrenaline is recommended.

Concomitant use of a non-selective β-blocker with local anaesthetic containing adrenaline can lead to serious drug-induced hypertension and lead to cardiac arrest. However, considering that only a small amount of local anaesthetic is used in most dental procedures, a severe systemic reaction is, although possible, unlikely. A reduced dose of the medicinal product is however recommended.

Tricyclic antidepressants act on the central and peripheral nervous systems by blocking the reuptake of certain neurotransmitters, most notably norepinephrine and serotonin thus increasing their concentration. Significant increases in blood pressure and disturbances of the normal cardiac rhythm may occur, therefore a dose reduction of the product is recommended when there is concomitant use of tricyclic antidepressants.

In healthy volunteers a single dose of entacapone, a Catechol-O-methyl transferase (COMT) inhibitor coadministered with adrenaline increased the heart rates up to 80%. Ventricular tachycardia has also been reported. A single dose of entacapone followed by an intravenous infusion of adrenaline may result in increased chronotropic and arrhythmogenic effects of adrenaline. Therefore a reduced amount of adrenaline in dental anaesthesia should be given to patients on COMT inhibitors.

In patients treated with antiarrhythmics, due to the increased fragility resulting from the underlying heart condition, adrenaline may precipitate or aggravate angina pectoris or produce ventricular arrhythmia. Therefore, dosage adjustments and careful aspiration prior to administration is recommended.

Ergot-type oxytocic drugs (e.g., methysergide, ergotamine, ergonovine) produce arterial vasoconstriction by stimulating alpha-adrenergic and serotonin receptors and inhibiting EDRF release. Adrenaline produces vasoconstriction by stimulation of α1 receptors in mucous membrane, β1 receptors in the heart (increasing heart rate, strength of contraction and myocardial oxygen consumption) and the β2 receptors. If Ergot-type oxytocic drugs are coadministered with drugs with vasoconstrictive properties, there is a risk of interactions producing manifestations of excessive vasoconstriction and additive or synergistic increase in blood pressure and/or ischaemic response may occur. As a precautionary measure, the use of the product is recommended under strict medical supervision.

The pharmacological interaction between vasoconstrictor and sympathomimetic vasopressors (mainly cocaine but also amphetamines, phenylephrine, pseudoephedrine, oxymetazoline) has been clearly shown in both human and animal experiments. Cocaine stimulates noradrenaline release and inhibits its reuptake in adrenergic nerve terminals, producing a state of catecholamine hypersensitivity. In addition, cocaine inhibits the reuptake of dopamine and serotonin leading to hypertension, myocardial infarction, and even sudden death in patients actively abusing cocaine. The risk of adrenergic toxicity in dental procedures is particularly high in case of accidental intravascular injection in patients with high cocaine blood levels. If any sympathomimetic vasopressor has been used within 24 hours, the planned dental treatment should be postponed.

Antipsychotic agents such as phenothiazines and butyrophenones exhibit alpha-1 adrenergic blocking activity and may inhibit or reverse the vasopressor effect of adrenaline, resulting in hypotension. Accidental intravascular injection could potentially worsen the hypotension frequently associated with the phenothiazines. In patients treated with phenothiazines, adrenaline should be used with caution.

Monoamine oxidase (MAO) is an enzyme responsible for the metabolism of catecholamines. Epinephrine, a direct-acting, catecholamine sympathomimetic, may interact with a coadministered MAO inhibitors (MAOIs) leading to increased risk of hypertensive crisis. The presence of a MAOI can result in reduced metabolism and enhanced and/or prolonged receptor stimulation. Therefore, dosage adjustments and strict medical monitoring is recommended.

Warnings regarding H2-antihistamines and selective serotonin reuptake inhibitors (SSRIs) have been removed as there are not sufficient data to support their maintenance. Given that articaine metabolism is primarily due to plasma esterases, inhibitors of P450 isoenzymes such as cimetidine are unlikely to decrease its metabolism or increase the risk of adverse effects.

Warnings regarding the risk of bleeding if the product is used concomitantly with anticoagulants and risk of allergic reactions attributable to sodium metabisulfite and information regarding the amount of sodium have not been included in this section of the SmPC because these information are already included in section 4.4 of the SmPC - Special warnings and precautions for use.

The final agreed wording for this section of the SmPC is reflected in Annex III of the CHMP opinion.

Section 4.6 – Fertility, pregnancy and lactation

The information on pregnancy and breastfeeding differed among MSs. The CHMP agreed on a common wording, rejecting detailed information regarding the pre-clinical studies that did not provide valuable information for healthcare professionals.

Fertility

A complete series of *in vitro* and *in vivo* tests to evaluate the genotoxic potential of articaine / adrenaline and articaine alone did not reveal any genotoxic effect of these products.
Reproduction studies in rats and rabbits at doses up to more than 10 times the recommended maximum articaine dose in humans (6.8 mg/kg) showed that this drug, with or without adrenaline 0.01 mg/ml, has no effect on fertility. No embryotoxic, teratogenic or peri- or post-natal toxic effects is shown, even at doses toxic to the parental animals.

Pregnancy

The developmental toxicity of the combination articaine with adrenaline was assessed in rats and rabbits. The dose range tested covered several articaine doses and showed no or minimal maternal toxicity. No effects on embryo-foetal development were observed in either species, even at dose levels causing slight maternal toxicity. It was concluded that articaine/adrenaline did not produce any teratogenic effects on the foetus up to doses equivalent to approximately 11 times (in rats) and 6 times (in rabbits) the maximum therapeutic dose in humans.

The developmental of peri- and postnatal toxicity of articaine with adrenaline was assessed in rats. The duration of pregnancy was within the normal limits of the controls for all treated groups, the parturition did not show any disturbance, the number of alive pups was not influenced at any of the tested dose levels and stillbirths were within normal limits and were not substance-related. Overall, no peri- and post-natal toxicity was observed with all experimented doses.

In conclusion, these reproduction studies performed in rats and rabbits at doses up to more than 10 times the recommended maximum articaine dose in humans showed that articaine with adrenaline 0.01 mg/mL, has no embryotoxic, teratogenic or peri- or post-natal toxic effects, even at doses toxic to the parental animals.

With regards to the clinical data a study including 823 pregnant women at 13 to 21 weeks' gestation found that scaling and root planning, for periodontitis using local anaesthetics as needed, did not increase adverse foetal outcomes, however, it did lower preterm birth rates. It was noted that an update in the Journal of the Canadian Dental Association mentioned that it is safe to use local anaesthetics during pregnancy. A randomized clinical study showed that routine, essential dental care, nonsurgical periodontal care, and the use of topical or local anaesthesia for dental procedures were not associated with any adverse serious medical events or adverse pregnancy outcomes.

Adrenaline and articaine cross the placenta barrier, although articaine does it to a lesser extent than other local anaesthetics. Serum concentrations of articaine measured in new born infants were approximately 30% of maternal levels. The local anaesthetics and vasoconstrictors may be safely used in dentistry and administered to the pregnant or nursing women but after a careful analysis of the benefit-risk balance has been made. Moreover, aspiration must always be carried out to minimize the likelihood of intravascular injection.

Breastfeeding

Preclinical data has showed no peri-and post-natal toxicity was observed with all experimented doses up to the F2 generation. Data on breastfeeding come from a pre-clinical study in 80 pregnant/lactating female compared the upcoming of any adverse effect of articaine combined with adrenaline 0.01 mg/ml administered subcutaneously in several doses versus a physiological solution as a control and observed the development of the resulting offspring from conception through weaning. The study did not show any toxicity or disturbance in the development, duration and the outcome of pregnancy.

It was also noted that according to the Swiss dental journal, local anaesthetics such as articaine with adrenalin in a dilution of 1: 200 000 can be used for dental treatment at any time of pregnancy or lactation period.

However the CHMP acknowledged that no clinical studies including breastfeeding women have been performed with articaine / adrenaline. Further, clinically relevant quantities of articaine have been found in breast milk. Based on the hypothesis of worst case scenario of highly toxic drugs, the time lapse for breastfeeding can be estimated to be approximately 4.7 hours. Considering the lack of clinical data and the above hypothesis, nursing mothers are advised not to breastfeed 5 hours following anaesthesia with the product.

The final agreed wording for this section of the SmPC is reflected in Annex III of the CHMP opinion.

Section 4.7 – Effects on ability to drive and use machines

This medicinal product may impair reactivity abilities when driving and using machines because many of the pharmacological actions of articaine have an impact on the CNS. Adverse reactions such as dizziness (including vertigo, vision disorder and fatigue) may occur following the administration of this product. These types of CNS adverse reactions usually manifest very early, especially knowing that articaine has a rapid onset of action of 1.4 to 3.6 minutes. Therefore, the CHMP considered that this product may have a minor influence on the ability to drive and use machines and recommended, as a precautionary measure that patients should avoid driving or using machines until normal sensation is restored following the dental procedure.

The final agreed wording for this section of the SmPC is reflected in Annex III of the CHMP opinion.

Section 4.8 – Undesirable effects

The summary of the safety profile provides information about the most serious and/or most frequently occurring adverse reactions. The most common and severe complications are due to high plasma levels which may result from overdose, rapid absorption from the injection site or from inadvertent intravascular injection of the local anaesthetic solution. Adverse reactions of local anaesthetics either target the CNS or are mediated by the autonomic nervous system via receptors on effector organs in the cardiovascular, respiratory, gastrointestinal and other systems.

The safety profile is based on the Septodont global safety database, which describes reactions related to high plasma level, sensory disturbances, hypersensitivity and injection site reaction. It includes a tabulated presentation of the adverse reactions (Preferred Terms) according to the MedDRA system organ classification, which is discussed in detail and supported by spontaneous reporting, clinical studies and literature retrieved from the Septodont global safety database.

Some divergences from local SmPCs have been harmonised with acceptable justification. Information regarding overdose is detailed in section 4.4 of the SmPC and signs of overdose are described in section 4.9 of the SmPC. Intravascular injection, injection in tissues highly vascularized are described in section 4.2. So, this information is considered already included in the harmonised SmPC.

The information proposed by the MAH is in line with the SmPC guideline and current QRD template and also with the SmPC from the MRP procedure. The proposed wording is considered as acceptable by the CHMP.

The final agreed wording for this section of the SmPC is reflected in Annex III of the CHMP opinion.

Section 4.9 – Overdose

While considered generally safe, local anaesthetic agents can be toxic if administered inappropriately, or at excessive doses, and overdose reactions may occur.

The two main types of overdose which may occur during local anaesthesia with articaine are absolute overdose and relative overdose, which lead to elevated blood levels of the drug in its target organs where the drug exerts its clinical action and consequently have similar toxicity manifestations. Absolute overdose with local anaesthetics is the result of injection of excessive doses, while relative overdose refers to the injection of a non-toxic dose in cases such as inadvertent injection into a vein, accidental puncture of a small artery in the region of the injection, such that the local anaesthetic reaches the brain in a retrograde direction, with an abnormally rapid absorption of a normal dose into the systemic circulation and delayed metabolism of the drug or its delayed elimination from the plasma.

The MAH has proposed to remove several statements that are either in other sections of the SmPC or where there is insufficient supporting evidence to maintain them, which was agreed by the CHMP.

Information about the time to onset and description of slow or delayed onset for absolute dosing overdose has been included at the request of the CHMP. In addition, due to the seriousness of overdose symptoms physicians/dentists are expected to implement protocols that foresee the necessity of a timely endotracheal intubation with assisted ventilation.

The final agreed wording for this section of the SmPC is reflected 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. No difference was observed in pharmacodynamic properties between the adult and the paediatric populations.

The section Mechanism of Action and Pharmacodynamic effects is very similar to the SmPC from the MRP. The CHMP requested that more robust information regarding the mechanism of action and pharmacodynamic to be included in this section and this request has been addressed satisfactory by the MAH.

The final agreed wording for this section of the SmPC is reflected in Annex III of the CHMP opinion.

Section 5.2 – Pharmacokinetic properties

The MAH provided information on absorption, distribution, biotransformation and elimination supported by literature. Some deletions were made, as the information was either mentioned in other SmPC sections or they did not add any useful information to the prescriber.

The final agreed wording for this section of the SmPC is reflected in Annex III of the CHMP opinion.

Section 5.3 – Preclinical safety data

The MAH discussed the data from the literature, regarding studies using articaine only single dose and repeat-dose toxicity, genotoxicity, reproductive toxicity and local tolerance.

Moreover, the MAH discussed safety/toxicity studies with the combination articaine/adrenaline including, single dose toxicity (mouse, s.c. administration), repeated dose toxicity studies (rat and dog, s.c. administration, 4 weeks duration, with TK data), genotoxicity (*in vivo* micronucleus assay) and reproductive toxicity studies (fertility, embryo-foetal and pre- post-natal development).

Preclinical data reveal no special hazard for humans at therapeutic doses, based on conventional studies of safety pharmacology, chronic toxicity, reproductive toxicity and genotoxicity. At high therapeutic doses, articaine has cardio depressant properties and can exert vasodilatory effects. Adrenaline exhibits sympathomimetic effects.

In embryotoxicity studies with articaine, no increase in the foetal mortality rate or malformations were observed at daily i.v. doses of up to 20 mg/kg (rat) and 12.5 mg/kg (rabbit). However, some effects on fertility and teratogenicity were observed in animals treated with adrenaline only at exposures much higher than the maximum human exposure.

In embryofoetotoxicity studies with articaine and adrenaline, no increase in malformations was observed at daily s.c. doses of articaine up to 80 mg/kg (rat) and 40 mg/kg (rabbit).

In a fertility and early embryonic development study in rats no adverse effects on male or female fertility were noted at doses causing parental toxicity.

For this section of the SmPC, the MAH proposed to include information regarding the results of repeated dose toxicity (subchronic studies) and reproductive toxicity studies (fertility, embryo-foetal and pre- and postnatal development) conducted with the combination and results of genotoxicity studies conducted with the combination and the mono components. The CHMP endorsed this proposal.

The final agreed wording for this section of the SmPC is reflected in Annex III of the CHMP opinion.

Other Sections of the SmPC

Sections 2 (qualitative and quantitative composition), 6.1 (list of excipients), 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 clarity, consistency and completeness.

Package Leaflet (PL)

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 at least 90% of test participants were able to locate the requested information and at least 90% of test participants were able to understand the information. This study has been made in accordance with regulatory requirements. The test protocol and the study sample were considered appropriate.

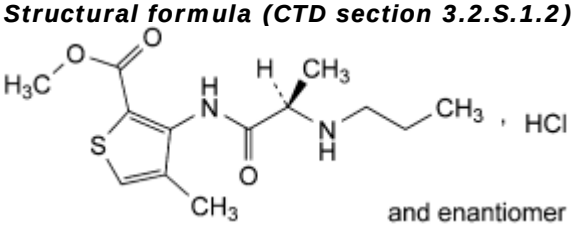
2.2.2. Module 3 - Quality

Drug substance (CTD module 3.2.S)

Articaine hydrochloride

The MAH proposed to harmonize this section by updating the European Pharmacopoeia certificate of suitability (CEP) for the active substance articaine hydrochloride, from an already approved manufacturer.

Structural formula (CTD section 3.2.S.1.2)



Molecular formula: $C_{13}H_{21}ClN_2O_3S$

Relative molecular mass: 320.8

Stereochemistry: Racemate

Impurities (CTD section 3.2.S.3.2)

<Confidential information deleted>

Specification (CTD section 3.2.S.4.1)

Specifications for articaine hydrochloride drug substance are described in Ph. Eur. current version 01/2017:1688.

Analytical procedures (CTD section 3.2.S.4.2)

Active substance is analysed according to methods stated in Ph. Eur. monograph for Articaine hydrochloride. Both drug substance manufacturers hold certificates of suitability for this drug substance.

Microbial contamination is performed according to monographs Ph. Eur. 2.6.12.

Bacterial endotoxins test is performed by turbidimetric kinetic method, following Ph. Eur. 2.6.14.

Heavy metals test is performed as an internal test following Ph. Eur. 2.4.8 pending the outcome of the risk assessment performed and the implementation of a risk-based control strategy of elemental impurities as per ICH Q3D guideline.

Validation of analytical procedures (CTD section 3.2.S.4.3)

No validation is considered necessary for Ph. Eur. methods and the methods described in the CEP.

Validation reports are presented for the microbial contamination by filtration method and bacterial endotoxins by kinetic turbidimetry method.

Batch analysis (CTD section: S.4.4)

The certificates of analysis of three batches released by both drug substance manufacturers have been provided.

All tested parameters are well within the specification limits.

Justification of Specifications (CTD section 3.2.S.4.5)

Articaine hydrochloride is the subject of a monograph 01/2017:1688 in the Ph. Eur. The specifications proposed by the drug product manufacturer conform to the compendial requirements, as well as ICH.

Reference standards or materials (CTD module 3.2.S.5)

Reference standards of the drug substance manufacturer have been assessed by the EDQM during assessment of the CEP. It is accepted that no information is presented in the quality dossier as reference to the CEP has made by the applicant.

Container closure system (CTD section 3.2.S.6)

Information included in this section on the container closure system for drug substance by both manufacturers was presented and deemed acceptable by the CHMP.

Stability (CTD section 3.2.S.7)

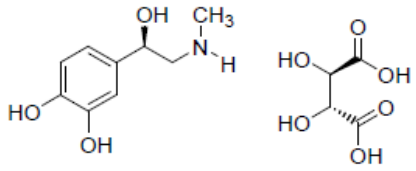
The re-test period 5 years is stated in the valid certificates of suitability issued by the EDQM for articaine hydrochloride.

Drug substance (CTD module 3.2.S)

Adrenaline tartrate

The MAH proposed to harmonize 3.2.S sections by updating European Pharmacopoeia certificate of suitability (CEP) for the active substance Adrenaline tartrate, from an already approved manufacturer.

Structural formula (CTD section 3.2.S.1.2)



Molecular formula: $C_{13}H_{19}NO_9$

Relative molecular mass: 333.3

Stereochemistry: The form selected is (-)-Adrenaline (L-Adrenaline).

Characterisation (CTD section 3.2.S.3)

<Confidential information deleted>

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

Specification (CTD section 3.2.S.4.1)

The specifications of adrenaline tartrate drug substance are described in Ph. Eur. current version 01/2008:0254.

Analytical procedures (CTD section 3.2.S.4.2)

Active substance is analysed according Ph. Eur. monograph for Adrenaline tartrate. Both drug substance manufacturers hold certificates of suitability for this drug substance as such there is no need for description of analytical procedure.

Microbial contamination is performed according to monograph Ph. Eur. 2.6.12.

Bacterial endotoxins test is performed by turbidimetric kinetic method, following Ph. Eur. 2.6.14.

Validation of analytical procedures (CTD section 3.2.S.4.3)

No validation is considered necessary for Ph. Eur. methods and the methods described in the CEP.

A validation reports are presented for the microbial contamination and bacterial endotoxins tests.

Batch analysis (CTD section: S.4.4)

The certificates of analysis of three batches released by both drug substance manufacturers have been provided.

All tested parameters are well within the specification limits.

Justification of Specifications (CTD section 3.2.S.4.5)

Adrenaline tartrate is the subject of a monograph 01/2008:0254 in the Ph. Eur. The specifications proposed by the drug product manufacturer conform to the compendial requirements, as well as ICH. The proposed specifications are also in accordance with those approved for the drug substance manufacturers, as per current CEP.

Reference standards or materials (CTD module 3.2.S.5)

Reference standards of the drug substance manufacturer have been assessed by the EDQM during assessment of the CEP. It is accepted that no information is presented in the quality dossier.

Container closure system (CTD section 3.2.S.6)

Information included in this section on the container closure system for drug substance by both manufacturers is presented and acceptable.

Stability (CTD section 3.2.S.7)

The corresponding retest periods are stated in the valid certificates of suitability issued by the EDQM for adrenaline tartrate. No storage conditions are mentioned in the certificates of suitability. The stability data have been assessed by the EDQM.

Drug product (CTD section 3.2.P)

Description and composition of the drug product (CTD section 3.2.P.1)

Articaine HCl 40 mg/ml + Adrenaline 0.005 or 0.01 mg/ml is a clear and colourless solution for injection.

Container

The characteristics of the primary packaging components for both strength of the drug product are presented in the table below:

Primary packaging components		**Nature of materials**	**Reference to standards**
Cartridge		Type I glass	Ph. Eur. 3.2.1
Plunger		Synthetic rubber closure type I	Ph. Eur. 3.2.9
Cover	**Cap***	Aluminium	Not applicable
	Seal	Synthetic rubber closure type I	Ph. Eur. 3.2.9

**not in contact with the solution*

MAH proposed to delete the 1 ml presentation, currently registered in Austria, Belgium, Germany and Netherlands. The marketing cessation of 1 ml presentation was related to commercial reasons.

The MAH clarified that in Belgium, Netherlands and Poland, 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 cartridges. Therefore the MAH has included the nominal volume of 1.7 ml for the cartridge of both drug products. This is endorsed by the CHMP.

Pharmaceutical development (CTD section 3.2.P.2)

Drug substance (CTD section: P.2.1.1)

Articaine hydrochloride (CTD section: P.2.1.1.1)

Articaine hydrochloride is a local anaesthetic among amide-type local anaesthetics. The drug substance is free soluble in water and known to be very stable. The 40 mg/ml concentration is the most commonly used concentration in dental anaesthesia.

Adrenaline tartrate (CTD section: P.2.1.1.2)

Adrenaline tartrate is the most efficient and most currently used vasoconstrictor in dentistry. Adrenaline tartrate, expressed in Adrenaline base, is used at a 0.0050 mg/ml or 0.01 mg/ml concentration.

Excipients (CTD section: P.2.1.2)

The following excipients with a known effect according to European Commission guideline *"Excipients in the label and package leaflet of medicinal products for human use"* are used in the manufacture of the drug product: Sodium metabisulfite (E223), Sodium chloride, Disodium edetate and Sodium hydroxide.

The drug product contains less than 1 mmol of sodium (23 mg) *per* cartridge, *i.e.* it is considered as essentially "sodium free".

Drug product (CTD section: P.2.2)

Formulation development (CTD section: P.2.2.1)

The drug product formula has been marketed since more than 20 years in the European Union.

Overages (CTD section: P.2.2.2)

Adrenaline tartrate is sensitive to oxidation and thermolabile. An acceptable overage has been included for the drug substance Adrenaline tartrate to compensate losses during the whole manufacturing process.

Physicochemical and biological properties (CTD section: P.2.2.3)

The drug product is a local anaesthetic solution for injection. It is prepared and tested according to the requirements of monograph "*Parenteral preparations (0520)*" of the Ph. Eur. Its pH is adjusted with Sodium hydroxide in solution and its tonicity is adjusted with Sodium chloride.

Tests are carried out according to general monographs of the Ph. Eur. and general monographs of the USP, where relevant.

The drug product is sterile. Cartridges containing the solution for injection are autoclaved at a minimum temperature of 121°C for 15 minutes according to the relevant monographs of the Ph. Eur. and USP.

Manufacturing process development (CTD section: P.2.3)

The manufacturing process used consists in four principal steps, preparation of primary packaging elements, preparation of solution, filtration and distribution. The critical steps are mention in part 3.2.P.3.4.

Container closure system (CTD section: P.2.4)

The primary container comprises 1.8 ml, Ph. Eur. Type I glass cartridge, sealed at base and top by a synthetic rubber.

The stability results demonstrated compatibility of packaging materials for sterile products that can withstand sterilization. Absorption study confirmed no adsorption of the drug substances onto rubber closures and glass cartridge. The results of photostability study and freezing testing indicate that the product requires special precautions for storage which are presented in the PI.

Microbiological attributes (CTD section: P.2.5)

Requirements of the Ph. Eur. for sterile preparations are applicable. A test for integrity of the closure system has been performed.

Compatibility (CTD section: P.2.6)

Not applicable. The solution is aqueous.

Description of the manufacturing process and process controls (CTD section 3.2.P.3.3)
The manufacturing process is adequately described in the dossier.

The tests, the acceptance criteria and the testing analytical procedures performed during the manufacturing process are provided.

Control of Critical Steps and Intermediates (CTD section 3.2.P.3.4)

The following critical steps are identified: control of the bulk solution, holding time of the bulk solution in the storage tank and terminal sterilization (recording of pressure, temperature and duration of the whole autoclaving cycle).

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

The validation batches were in compliance with the finished product specifications. The manufacturing process consisting on mixing (preparation of solution), filling and terminal sterilisation is considered as validated.

Conventional terminal sterilisation cycle of the drug product (121°C for 15 minutes) complies with the recommendations of the Ph. Eur.

Results of analysis and validation reports have been adequately provided.

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

The excipients Sodium hydroxide, Sodium chloride, Sodium metabisulfite, Disodium edetate, Water for injections and Nitrogen are stated to comply with the relevant current edition Ph. Eur. monographs.

Specifications and analysis certificates have been submitted for all of the excipients.

Analytical procedures (CTD section: P.4.2)

Ph. Eur. methods are used for control of the excipients.

Validation of analytical procedures (CTD section: P.4.3)

No validation of the analytical control methods has been performed since all the analytical control methods are according to Ph. Eur.

Justifications of specifications (CTD section: P.4.4)

Not applicable. All the excipients are defined in the Ph. Eur.

Excipients of human and animal origin (CTD section: P.4.5)

Not applicable.

Novel excipients (CTD section: P.4.6)

Not applicable.

Control of Drug Product (CTD section 3.2.P.5)

Specifications (CTD section 3.2.P.5.1)

The specification for the both strength of the drug product have been harmonized and established according to the Ph. Eur. and EU regulatory requirements.

Analytical procedures (CTD section 3.2.P.5.2)

The analytical methods have been adequately described.

Validation of Analytical procedures (CTD section 3.2.P.5.3)

The applicant provided acceptable validation reports.

Batch analytical data (CTD section 3.2.P.5.4)

Batches analyses data was presented for both strengths and are acceptable. The results show that each batch complies with the specifications of the drug product.

Characterisation of impurities (CTD section 3.2.P.5.5)

Characterisation of impurities is documented.

Justification of specifications (CTD section 3.2.P.5.6)

Justification is provided for each parameter and respective limit included in the release and end of shelf-life specifications for both strengths of the drug product.

Reference standards or materials (CTD section 3.2.P.6)

Reference standards used in the control at release and end of shelf-life of the drug product are provided. It is stated that secondary or working standards for Articaine hydrochloride and Adrenaline tartrate are established with reference to primary reference standards and chosen among batches of drug substance. These standards are totally controlled *versus* their current monograph in the Ph. Eur.

Besides, working standards for drug substance are calibrated against primary reference standards once a year.

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

The MAH stated that in Belgium, Italy and Spain only the natural quality of the rubber closure type has been registered. As the natural rubber closure type is no longer used, the MAH proposed to keep only the synthetic rubber closure type and remove the natural rubber closure type from the dossier, in accordance with Ph. Eur. monograph 0520 “Parenteral preparations”, “parenteral preparations are supplied in glass containers (3.2.1) or in containers such as plastic containers (3.2.2, 3.2.2.1 and 3.2.9) or prefilled syringes. (…)”.

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. 3.2.9 “Rubber closures for aqueous parenteral preparations for powder and for freeze-dried powders”).

The synthetic rubber closure quality is already approved in almost all Member States where the drug product is registered.

Adequate information on the packaging material was presented and is acceptable

Stability (CTD section 3.2.P.8)

Stability summary and conclusion (CTD section P.8.1)

The MAH proposed to update the storage conditions. In addition, the MAH made editorial changes regarding the labelling statements in order to comply with QRD template.

Results of stability studies on the two formulations in commercial batches at 25°C ± 2°C / 60 % RH ± 5 % RH (long-term), at 40°C ± 2°C / 75 % RH ± 5 % (accelerated) and at 30°C ± 2°C / 75 % RH ± 5 % RH (intermediate conditions) were provided. The stability protocol was also provided. All the tests are performed in accordance with the validated procedures described in section 3.2.P.5.2.

Stability studies were performed as per EMA guideline CPMP/QWP/122/02, rev.1 “Guideline on Stability testing: stability testing of existing active substance and related finished products” for ICH climatic zone II.

In support of stability studies, results obtained on batches packaged in the authorised container of the drug product are presented. Stability studies were conducted at 25°C ± 2°C / 60 % RH ± 5 % RH (long-term conditions) up to 24 months on both strength of the finished product. Stability studies were also conducted at 30°C ± 2°C / 75 % RH ± 5 % RH (intermediate conditions) up to 24 months and at 40°C ± 2°C / 75 % RH ± 5 % (accelerated conditions) up to 6 months on both strength of the finished product.

The storage recommendation “Store below 25°C” is supported by relevant data. Based on the stability results, the MAH proposed the additional labelling: “In order to protect from light, keep the cartridges in the tightly closed outer carton. Do not freeze”. This is endorsed by the CHMP.

3. Recommendation

Based on the review of all available data, the CHMP recommended the revision and harmonisation of the product information for Septanest and associated names. The final agreed wording of the product information is reflected in Annex III of the CHMP opinion.

4. Grounds for 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 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 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 MAH in support of the proposed harmonisation of the product information;
- In addition, the committee reviewed the totality of the documentation submitted by the MAH 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.