LÄKEMEDELSVERKET
MEDICAL PRODUCTS AGENCY

Public Assessment Report
Scientific discussion

Septocaine and Septocaine forte
(articaine hydrochloride, adrenaline tartrate)

SE/H/325/01-02/E01

This module reflects the scientific discussion for the approval of Septocaine and Septocaine forte. The procedure was finalised on 2016-02-16. For information on changes after this date please refer to the module 'Update'.

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I. INTRODUCTION

The application for Septocaine and Septocaine forte, solution for injection, 40 mg/ml/10 micrograms/ml, 40 mg/ml/5 micrograms/ml, is a Known active substance application made according to Article 8(3) of Directive 2001/83/EC. The applicant, Specialites SEPTODONT, applies for a marketing authorisation in CY, DE, FR, HR, SI, and SK through this repeat use procedure with Sweden acting as reference member state (RMS). The product was first approved through a National Procedure and then through MRP with FI and PT as concerned member states (CMS).
Septocaine is an amide-type of local anaesthetic containing articaine (carticaine) 40 mg/ml combined with either adrenaline 5 µg/ml (***Septocaine***), or adrenaline 10 µg/ml (***Septocaine forte***). Both solutions are intended for local and regional anaesthesia in dental practice.

For approved indications, see the Summary of Product Characteristics.

For recommendations to the marketing authorisation not falling under Article 21a/22 of Directive 2001/83 and conditions to the marketing authorisation pursuant to Article 21a or 22 of Directive 2001/83/EC to the marketing authorisation, please see section VI.

II. QUALITY ASPECTS

II.1 Drug Substance

The structure of the drug substance has been adequately proven and its physico-chemical properties are sufficiently described.

The manufacture of the drug substance has been adequately described and satisfactory specifications have been provided for starting materials, reagents and solvents.

The drug substance specification includes relevant tests and the limits for impurities and degradation products have been justified. The analytical methods applied are suitably described and validated.

Stability studies confirm the retest period.

II.2 Medicinal Product

The medicinal product is formulated using excipients listed in section 6.1 in the Summary of Product Characteristics.

The manufacturing process has been sufficiently described and critical steps identified.

The tests and limits in the specification are considered appropriate to control the quality of the finished product in relation to its intended purpose.

Stability studies have been performed and data presented support the shelf life and special precautions for storage claimed in the Summary of Product Characteristics, sections 6.3 and 6.4.

III. NON-CLINICAL ASPECTS

Pharmacodynamic, pharmacokinetic and toxicological properties of articaine hydrochloride and adrenaline (adrenaline tartrate) are well known. As both active substances are well-known and widely used in dentistry as combination products, no further non-clinical studies are required. The overview is mainly a bibliographic submission containing published data and new genotoxicity, reproductive toxicity and repeated-dose toxicity studies and one biotransformation study. Standard battery of genotoxicity tests were all were negative for articaine hydrochloride. In addition, no novel toxic effects in rat and dog, beyond those already known for articaine, were observed. In summary, the provided non-clinical overview is considered appropriate.

IV. CLINICAL ASPECTS

IV.1 Introduction

IV.2 Pharmacokinetics

Septocaine is a local anaesthetic of amide-type (articaine) and the pharmacokinetic assessment (systemic exposure) is therefore mainly of interest from a safety perspective. Adrenaline PK was not assessed in this application as the levels are likely to be close to or below the detection limit.

IV.2.1 Absorption

Following maxillary infiltration of 68 mg and 204 mg articaine hydrochloride (40 mg/mL) with adrenaline 0.005 mg/mL, peak plasma concentrations (C_{max}) of articaine were observed at 0.4 and 0.8 h reaching 384 ± 165 and 899 ± 363 ng/ml (mean ± SD), respectively. In addition, in published clinical studies describing the pharmacokinetic profile for articaine hydrochloride 80 mg (40 mg/mL with adrenaline 0.010 or 0.005 mg/mL), the T_{max} observed value was approximately 0.2 h, with C_{max} ranging from 400 to 2100 ng/mL.

IV.2.2 Distribution

The binding of articaine to human serum albumin was moderate, in the range 69-81%, and α/β-globulins (63-73%). Binding to γ-globulin (8.6-24%) was much lower. The estimated volume of distribution after injection in the vestibular fold was small (approximately 4 L/kg).

IV.2.3 Elimination

Data indicate that the metabolism is the major elimination pathway for articaine. Plasma concentrations of articaine and articainic acid were shown to decrease rapidly following submucosal injection. Very little articaine was detected in plasma from 12 to 24 hours following injection. Clearance as estimated in the clinical trial was 1879 (±431) mL/min and 2323 (±561) mL/min (mean ± SD) after 68 and 204 mg dose, respectively. Following dental

injection, the initial plasma half-life of articaine was shown to be ca. 20 min. The terminal plasma half-life was 1.6-1.8 h.

- **Excretion**

No mass balance study has been performed. However, >50% of the dose was eliminated in the urine mostly as articainic acid (95%), within 8 hours of administration. Within 24 hours, approximately 57% (after 68 mg dose) and 53% (after 204 mg dose) of the dose was eliminated in the urine. The fraction excreted as parent compound in urine was estimated to 2%.

- **Metabolism**

Articaine is subject to hydrolysis of its carboxyl group by unspecific esterases in the tissue and in blood forming articainic acid. This hydrolysis is very fast and about 90% of articaine is inactivated by this way. Articaine is additionally metabolised, as a minor pathway, in liver microsomes via cytochrome P450 metabolism, also forming articainic acid. Articainic acid is further metabolised to form articainic acid glucuronide. The peak plasma concentrations (C_{max}) of articainic acid were observed at 0.9 and 1.3 h following maxillary infiltration of 68 mg and of 204 mg of articaine hydrochloride (40 mg/mL + adrenaline 0.005 mg/mL), reaching, 1429 ± 514 and 3793 ± 796 ng/ml (mean ± SD), respectively.

IV.2.4 Dose proportionality

The exposure of articaine and articainic acid increased approximately in proportion to increase in dose in the range investigated (68 to 204 mg).

IV.2.5 Special populations

- **Impaired renal function**

There is no data available in subjects with impaired renal function. The lack of pharmacokinetic data in renally impaired subjects is acceptable, considering the relatively low systemic expose and single occasion treatment with articaine.

- **Impaired hepatic function**

There is no data available in subjects with impaired liver function. Articaine is mainly metabolised via plasma esterases, and therefore not dependent on the liver for the Phase I metabolism. Thus, the lack of data in subjects with impaired liver function is acceptable.

- **Gender**

Both male and female subjects were included in the presented study and publications, but there was no direct comparison between genders. No difference in exposure due to gender is expected.

- **Race**

Hispanic, Caucasian and Blacks were included in the presented study and publications, but there was no direct comparison between races. No difference in exposure due to race is expected.

- **Elderly**

Due to the lack of clinical data, caution should be advised and administration of the lowest dose leading to efficient anesthesia in elderly patients >70 years.

- **Paediatrics**

In children (range 3-12 years, n=27) administered 2 mg/kg articaine 4% with adrenaline (1:2000000) during intubation anaesthesia. The estimated clearance values are lower compared with adults in other studies. The C_{max} indicate higher exposure in children (1380 ng/mL) than in adults. However, the doses/kg administered was higher in children compared to adults.

IV.2.6 Interactions

No data on pharmacokinetic interactions has been presented, which is deemed acceptable considering the low extent of systemic exposure, short half-life and single occasion treatment.

IV.3 Pharmacodynamics

Septocaine is a sodium channel blocker of the amide-type containing adrenaline in two different concentrations to support a long-lasting local anaesthesia. The addition of a vasoconstrictor reduces the clearance of articaine from the local depot to the systemic circulation. This combination is beneficial for efficacy and, to some extent, for preventing systemic effects of the local anaesthetic. On the other hand, the combination with adrenaline restricts the use of the product to patients with normal tolerance to and elimination of catecholamines.
The pharmacology of similar local anaesthetics with adrenaline has previously been thoroughly investigated and found safe to the medically healthy patient.

IV.4 Clinical efficacy

The National approval of this Repeat-use procedure was based on two controlled clinical efficacy trials in adults including 100 patients on Septocaine (articaine 40 mg/ml) and 100 on the comparator Alphacaine (articaine 40 mg/ml, containing the preservative methyl parahydroxybenzoate) are presented. Both agents produced appropriate anaesthesia for dental surgery in these studies. An additional efficacy study including 158 adult patients (articaine 40 mg/ml) and 59 patients (lidocaine) demonstrated that both substances containing adrenaline 10 µg/ml had equal anaesthetic potency when similar injected volumes were used.
Dose finding studies as regards the adrenaline content have not been presented. However, the results from the combined results of the two clinical trials appear to indicate that the higher dose (10 µg/ml) is superior to the lower (5 µg/ml) dose of adrenaline for maintaining a necessary duration of the anaesthesia for complicated dental operations.
There were no reports of any serious adverse events in these studies (safety population n = 450).

Three controlled clinical trials including 70 paediatric patients (4 years of age and older) have demonstrated that articaine 40 mg/ml + adrenaline 10 µg/ml has similar anaesthetic efficacy as a lidocaine 20 mg/ml + adrenaline 10 µg/ml.
Supporting trials in 156 children showed no differences between adrenaline-containing articaine, prilocaine or mepivacaine.
Supporting trials in 142 children showed, as for adults, that articaine 40 mg/ml + adrenaline 5 µg/ml has an efficacy profile suitable only for minor dental operations.
There were no reports of any serious adverse events in these studies (safety population n = 330).

No significant differences with regard to cardiovascular and neurological safety in adults were found in three other studies conducted by the MAH comparing articaine 40 mg/ml +

adrenaline 10 µg/ml and lidocaine 20 mg/ml + adrenaline 10 µg/ml. The number of patients receiving articaine was 882.
Similarly, no cardiovascular or neurological safety differences in adults were found between articaine 40 mg/ml + adrenaline 10 µg/ml, lidocaine 20 mg/ml + adrenaline 10 µg/ml or prilocaine 30 mg/ml + adrenaline 10 µg/ml in a published independent study (n = 1700).

IV.5 Clinical safety

The safety population in the National approval of this Repeat-use procedure consisted of 50 patients who received Septocaine and 50 patients who received Septocaine forte at single occasions before dental surgery. The average dose of Septocaine was 4.38 ml and of Septocaine forte 3.73 ml. In single cases, necessary re-injections were made but the total dose never exceeded 9 ml (5 cartridges x 1.8 ml). These populations are regarded too small to reveal any expected or unknown safety risk.

The complementary documentation presents a safety population of 242 patients. In the articaine group (158 patients) mean volumes of 2.4 ml (0.4-6.8 ml) and 4.3 ml (0.9-13.2 ml) were injected before simple and complex operations, respectively. The active control substance (lidocaine) was given in similar volumes in a total of 82 patients. Articaine (4%) and lidocaine (2%), both with 10 µg/ml adrenaline showed few side effects. The reactions were mainly local (numbness, tingling sensation) and reversible and occurred in less than 10% of the patients with no difference between agents.

IV.6 Risk Management Plans

The MAH has submitted a risk management plan, in accordance with the requirements of Directive 2001/83/EC as amended, describing the pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to Septocaine and Septocaine forte.

Summary of the safety concerns

Summary of safety concerns	
Important identified risks	**- Persistent paraesthesia**
Important potential risks	None
Important missing information	None

Pharmacovigilance Plan: Safety concerns and overview of planned pharmacovigilance actions

Safety concern	**Proposed routine and additional PhV activities**	**Objectives**
Persistent paraesthesia	Routine pharmacovigilance • Specific approach to reports of paraesthesia and suspected paraesthesia: Ensure that reported symptoms are in accordance with the diagnosis and MedDRA coding. • Evaluate similar terms: hyperesthesia, hypoesthesia, dysesthesia, dysgeusia, ageusia and burning sensation. • Ensure the locations of the injection as well as location of paraesthesia are provided – with as	Increase the completeness of case information and case follow-up. Implementation of the same measures for all Company local anaesthetics will ensure comparability of data

	much detail on the suspected site of injury (nerve involved). • Routine follow up for non-serious as well as serious cases on evolution and outcome at 1 month, 6 months and up to 1 year. • Collection of information on suspicion of injury (electric shock and positive blood aspiration upon injection). • Applicable Company procedures will be update to reflect specific focus on paraesthesia. <u>Additional pharmacovigilance activities</u> • Due to the relative rarity of the condition, additional studies or other PV activities are not expected to be beneficial.	between various products.

V. USER CONSULTATION

The package leaflet has been evaluated via a user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC. The language used for the purpose of user testing the PIL was English.
The results show that the package leaflet meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Septanest and Septanest forte are shown to have similar efficacy profile as well-established local anaesthetics as lidocaine and prilocaine in dental practice. Recent efficacy data support the RMS's earlier positive opinion as expressed in the Repeat use procedure in 2003.
The safety profile is also similar to those of lidocaine and prilocaine.

There have been safety signals indicating an increased risk of neurotoxicity (manifested as paraesthesia) from articaine compared to e.g. lidocaine.
However, an actual causal relationship has been heavily questioned both by academic authors and by the pharma industry. This safety issue is adequately handled by the RMP.

List of recommendations not falling under Article 21a/22 of Directive 2001/83 in case of a positive benefit risk assessment

Quality	To submit a variation to update the specifications of the drug products Articaine HCl 40mg/ml with Adrenaline 0,01 mg/ml and Articaine HCl 40mg/ml with Adrenaline 0,005 mg/ml for the description, to comply with the provisions of the general monograph of European Pharmacopoeia "Parenteral preparations (0520)". Submit within this variation amended sections 2.3.P.1.2

	and 3.2.P.1.2 “Composition of the drug product” to correct the typographical error concerning quantity. No later than **May 13th 2016.**
Product information	Submit a variation to amend the product information according to the agreements made on comments raised in the repeat use procedure SE/H/325/01-02/E01. No later than **May 13th 2016.**

List of conditions pursuant to Article 21a or 22 of Directive 2001/83/EC
N/A

VII. APPROVAL

The Mutual recognition procedure for Septocaine and Septocaine forte, solution for injection, 40 mg/ml/10 micrograms/ml, 40 mg/ml/5 micrograms/ml, was positively finalised on 2016-02-16.

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Public Assessment Report – Update

Scope	Procedure number	Product Information affected	Date of start of the procedure	Date of end of procedure	Approval/ non approval	Assessment report attached
						Y/N (version)

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