

IPAR



**Public Assessment Report for a
Medicinal Product for Human Use**

Scientific Discussion

Septanest
ARTICAINE HYDROCHLORIDE
Adrenaline tartrate
PA0196/017/002

The Public Assessment Report reflects the scientific conclusion reached by the Health Products Regulatory Authority (HPRA) at the end of the evaluation process and provides a summary of the grounds for approval of a marketing authorisation for a specific medicinal product for human use. It is made available by the HPRA for information to the public, after deletion of commercially sensitive information. The legal basis for its creation and availability is contained in Article 21 of Directive 2001/83/EC, as amended. It is a concise document which highlights the main parts of the documentation submitted by the applicant and the scientific evaluation carried out by the HPRA leading to the approval of the medicinal product for marketing in Ireland.

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I. INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the HPRA has granted a marketing authorisation for Septanest 40 mg/ml + 5 micrograms/ml, solution for injection and Septanest 40 mg/ml + 10 micrograms/ml, solution for injection from Septodont on 28th October 2022 for the following indication:

Local and loco-regional anaesthesia in dental procedures. Septanest is indicated in adults, adolescents and children above 4 years of age (or from 20 kg (44 lbs) of body weight).

Both products are generics of Septocaine and associated names 40 mg/ml + 5 micrograms/ml, solution for injection and Septocaine forte and associated names 40 mg/ml + 10 micrograms/ml, solution for injection by Septodont, approved in Europe since 2003.

The legal basis for this application was Article 10(1) of Directive 2001/83/EC as amended.

Both products are subject to medical prescription, which may not be renewed.

The product information for the reference product is in line with that agreed during an Article 30 procedure by EMA which completed in 2019. The product information for the generics products are in line with that of their reference products.

The Summary of Product Characteristics for (SmPC) for this medicinal product is available on the HPRA's website at www.hpra.ie

Name of the products	Septanest
Name(s) of the active substance(s) (INN)	Articaine hydrochloride, Adrenaline tartrate
Pharmacotherapeutic classification (ATC code)	N01BB58
Pharmaceutical form and strength(s)	Septanest 40 mg/ml + 5 micrograms/ml, solution for injection Septanest 40 mg/ml + 10 micrograms/ml, solution for injection
Marketing Authorisation Number(s) in Ireland (PA)	PA0196/017/001-002
Marketing Authorisation Holder	Septodont
HPRA reference	CRN009VWY

II. QUALITY ASPECTS

II.1. Introduction

This application is for Septanest 40 mg/ml + 5 micrograms/ml solution for injection and Septanest 40 mg/ml + 10 micrograms/ml solution for injection

II.2 Drug substance

The active substances are articaine hydrochloride and adrenaline tartrate both established active substances described in the European Pharmacopoeia, and manufactured in accordance with the principles of Good Manufacturing Practice (GMP)

The active substance specifications are considered adequate to control the quality and meet current pharmacopoeial requirements. Batch analytical data demonstrating compliance with the specifications has been provided.

II.3 Medicinal product

P.1 Composition

Septanest 40 mg/ml + 5 micrograms/ml, solution for injection

1 ml of solution for injection contains 40 mg of articaine hydrochloride and 5 micrograms of adrenaline (epinephrine) (as adrenaline tartrate).

Septanest 40 mg/ml + 10 micrograms/ml, solution for injection

1 ml of solution for injection contains 40 mg of articaine hydrochloride and 10 micrograms of adrenaline (epinephrine) (as adrenaline tartrate).

The excipients in the medicinal product are listed in section 6.1 of the SmPC.

A visual description of the product is included in section 3 of the SmPC.

P.2 Pharmaceutical Development

The product is an established pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines.

P.3 Manufacture of the Product

The product is manufactured in accordance with the principles of good manufacturing practice (GMP) at suitably qualified manufacturing sites.

The manufacturing process has been validated according to relevant European/ICH guidelines and the process is considered to be sufficiently validated.

P.4 Control of Other Substances (Excipients/*Ancillary Substances*)

All ingredients comply with Ph. Eur.

P.5 Control of Finished Product

The Finished Product Specification is based on the pharmacopoeial monograph for the dosage form, and the tests and control limits are considered appropriate for this type of product.

The analytical methods used are described in sufficient detail and are supported by validation data.

Batch analytical data for a number of batches from the proposed production site(s) have been provided, and demonstrate the ability of the manufacturer to produce batches of finished product of consistent quality.

P.6 Packaging material

The approved packaging for this product is described in section 6.5 of the SmPC.

Evidence has been provided that the packaging complies with Ph. Eur./EU legislation for pharmaceutical use.

P.7 Stability of the Finished Product

Stability data on the finished product in the proposed packaging have been provided in accordance with EU guidelines and support the shelf-life and storage conditions listed in sections 6.3 and 6.4 of the SmPC.

II.4 Discussion on Chemical, Pharmaceutical and Biological Aspects

The important quality characteristics of the product are well-defined and controlled. Satisfactory chemical and pharmaceutical documentation has been provided, assuring consistent quality of Septanest 40 mg/ml + 5 micrograms/ml solution for injection and Septanest 40 mg/ml + 10 micrograms/ml solution for injection.

III. NON-CLINICAL ASPECTS

III.1 Introduction

These active substances are a generic formulation of Septocaine 40mg/ml + 5 micrograms/ml, solution for injection and Septocaine forte 40 mg/ml + 10 micrograms/ml, solution for injection on the European market. No new preclinical data have

been submitted. As such, no pre-clinical assessment has been made on the application. This is acceptable for this type of application.

III.2 Pharmacology

Pharmacodynamic properties of articaine hydrochloride and adrenaline are well known. As articaine hydrochloride and adrenaline are widely used, well-known active substances, the applicant has not provided additional non-clinical studies and further studies are not required. A non-clinical overview based on literature review is, thus, appropriate.

III.3 Pharmacokinetics

Pharmacokinetic properties of articaine hydrochloride and adrenaline are well known. As articaine hydrochloride and adrenaline are widely used, well-known active substances, the applicant has not provided additional studies and further studies are not required. A non-clinical overview based on literature review is, thus, appropriate.

III.4 Toxicology

Toxicological properties of articaine hydrochloride and adrenaline are well known. As articaine hydrochloride and adrenaline are widely used, well-known active substances, the applicant has not provided additional studies and further studies are not required. A non-clinical overview based on literature review is, thus, appropriate.

III.5 Ecotoxicity/environmental risk assessment

Since Septanest 40mg/ml + 5 micrograms/ml, solution for injection and Septanest 40mg/ml + 10 micrograms/ml, solution for injection are generic products, they will not lead to an increased exposure to the environment.

III.6 Discussion on the non-clinical aspects

A non-clinical overview based on literature review of the pre-clinical pharmacology, pharmacokinetics and toxicology is adequate. Nonclinical sections of the SmPC are in accordance with that accepted for the reference product. There are no objections to approval of Septanest 40 mg/ml + 5 micrograms/ml, solution for injection and Septanest 40 mg/ml + 10 micrograms/ml, solution for injection from a non-clinical point of view.

IV. CLINICAL ASPECTS

IV.1 Introduction

Articaine HCl and Adrenaline tartrate are both well known active substances with established efficacy and tolerability.

The content of the SmPC approved during this national procedure is in accordance with that accepted for the reference products Septocaine and associated names 40 mg/ml + 5 micrograms/ml, solution for injection and Septocaine forte and associated names 40 mg/ml + 10 micrograms/ml solution for injection by Septodont.

For this generic application, the applicant has not submitted a bioequivalence study on the basis that this is a parenteral product for local administration. Review of the excipients does not suggest any potential differences in terms of local absorption.

The content of the SmPC approved during this national procedure is in accordance with that accepted for the reference products Septocaine and associated names 40 mg/ml + 5 micrograms/ml, solution for injection and Septocaine forte and associated names 40 mg/ml + 10 micrograms/ml solution for injection marketed by Septodont.

IV.2 Pharmacokinetics

The pharmacokinetic profile of both actives concerned are well characterised.

Adrenaline is readily absorbed, irrespective of route of administration, however absorption from subcutaneous tissues occurs relatively slowly because of local vasoconstriction. Adrenaline is metabolised by catechol-O-methyltransferase (COMT) and

monoamine oxidase (MAO), together producing 6 metabolites, including sulfate, and glucuronide conjugates. Adrenaline is primarily excreted in the urine.

Articaine:

Absorption: In three published clinical studies describing the pharmacokinetic profile of the combination articaine hydrochloride 40 mg/ml with adrenaline 10 or 5 micrograms/ml, T_{max} values were between 10 and 12 minutes, with C_{max} values ranging from 400 to 2100 ng/ml.

In clinical trials performed in children, C_{max} was 1382 ng/ml and T_{max} 7.78 min following infiltration of a dose of 2 mg/kg body weight.

Distribution: High protein binding of articaine was observed with human serum albumin (68.5- 80.8%), and α₂/β-globulins (62.5-73.4%). Binding to γ-globulin (8.6-23.7%) was much lower. Adrenaline is a vasoconstrictor added to articaine to slow down absorption into the systemic circulation and thus prolong maintenance of active articaine tissue concentration. The volume of distribution in plasma was about 4 l/kg.

Biotransformation: Articaine is subject to hydrolysis of its carboxyl group by unspecific esterases in the tissue and in blood. Since this hydrolysis is very fast, about 90% of articaine is inactivated by this way. Articaine is additionally metabolised in the liver microsomes. Articainic acid is the major product of cytochrome P450-induced metabolism of articaine, further metabolised to form articainic acid glucuronide.

Elimination: Following dental injection, the elimination half-life of articaine was c.a. 20-40 min. In a clinical trial, 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. More than 50% of the dose was eliminated in the urine, 95% as articainic acid, within 8 hours of administration. Within 24 hours, approximately 57% (68 mg) and 53% (204 mg) of the dose was eliminated in the urine. Renal elimination of unchanged articaine accounted for only about 2% of total elimination.

IV.3 Pharmacodynamics

Articaine, a local amide anaesthetic, reversibly blocks nerve conduction through a well-known mechanism commonly observed with other local amide anaesthetics. This consists in decreasing or preventing the large transient increase in the permeability of excitable membranes to sodium (Na⁺) that is normally produced by slight depolarisation of the membrane. These actions lead the anaesthetic action. As the anaesthetic action progressively develops in the nerve, the threshold for electrical excitability gradually increases, the rate of rise of the action potential declines and impulse conduction slows. The pK_a of articaine has been estimated at 7.8.

Adrenaline, as vasoconstrictor, acts directly on both α- and β-adrenergic receptors; β-adrenergic effects predominate. Adrenaline prolongs the effect duration of the articaine, and reduces the risk of excessive uptake of articaine into the systemic circulation.

Septanest has an onset of 1.5-1.8 min for infiltration and 1.4-3.6 min for nerve block.

The anaesthetic duration of articaine 40 mg/mL with adrenaline 1: 100 000 is of 60 to 75 minutes for pulpal anaesthesia and 180 to 360 minutes for soft tissue anaesthesia.

The anaesthetic duration of articaine 40 mg/mL with adrenaline 1: 200 000 is of 45 to 60 minutes for pulpal anaesthesia and 120 to 300 minutes for soft tissue anaesthesia.

No difference was observed in pharmacodynamic properties between the adult and the paediatric population.

IV.4 Clinical Efficacy

No clinical efficacy data are required as this is a generic application.

IV.5 Clinical Safety

No clinical safety data are required as this is a generic application.

Risk Management Plan

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 Septanest. The RMP is in line with the reference medicinal product.

Routine pharmacovigilance activities and routine risk minimisation measures are considered sufficient.

Periodic Safety Update Report (PSUR)

With regard to PSUR submission, the MAH should take the following into account:

- PSURs shall be submitted in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal. Marketing authorisation holders shall continuously check the European medicines web-portal for the
- DLP and frequency of submission of the next PSUR.
- For medicinal products authorized under the legal basis of Article 10(1) or Article 10a of Directive 2001/83/EC, no routine PSURs need to be submitted, unless otherwise specified in the EURD list.
- In case the active substance will be removed in the future from the EURD list because the MAs have been withdrawn in all but one MS, the MAH shall contact that MS and propose DLP and frequency for further PSUR submissions together with a justification.

IV.6 Discussion on the clinical aspects

As this approval concerns a generic application, there are no new efficacy or safety studies required as the applicant can refer to the data of the reference medical products.

V. OVERALL CONCLUSIONS

Septanest 40 mg/ml + 5 micrograms/ml solution for Injection and Septanest 40 mg/ml + 10 micrograms/ml solution for injection are generic forms of Septocaine and associated names 40 mg/ml + 5 micrograms/ml solution for injection and 40 mg/ml + 10 micrograms/ml solution for injection by Septodont. Septanest is a well-known medicinal product with a proven chemical-pharmaceutical quality and an established favourable efficacy and safety profile.

The SmPCs are consistent with that of the reference product, and with that of a recent EMA harmonisation procedure.

The MAH has provided written confirmation that systems and services are in place to ensure compliance with their pharmacovigilance obligations.

The HPRA, on the basis of the data submitted considered that Septanest 40 mg/ml + 5 micrograms/ml solution for injection and Septanest 40 mg/ml + 10 micrograms/ml solution for injection can be considered therapeutically equivalent to the reference product, and have a satisfactory risk/benefit profile, and therefore has granted a marketing authorisation.

VII. UPDATES

This section reflects the significant changes following finalisation of the initial procedure.

SCOPE	PROCEDURE NUMBER	PRODUCT INFORMATION AFFECTED	DATE OF START OF PROCEDURE	DATE OF END OF PROCEDURE
New National	N/A	SmPC Sections 1 to 9	28th October 2022	27th October 2027