Public Assessment Report

Scientific discussion

Articaine hydrochloride/Epinephrine NewLine Pharma 40 mg/ml + 0.01 mg/ml, solution for injection

(articaine hydrochloride/adrenaline tartrate)

NL/H/4156/001/DC

Date: 10 April 2019

This module reflects the scientific discussion for the approval of Articaine hydrochloride/Epinephrine NewLine Pharma 40 mg/ml + 0.01 mg/ml, solution for injection. The procedure was finalised at 6 September 2018. For information on changes after this date please refer to the ‘steps taken after finalisation’ at the end of this PAR.
### List of abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>ASMF</td>
<td>Active Substance Master File</td>
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<tr>
<td>CEP</td>
<td>Certificate of Suitability to the monographs of the European Pharmacopoeia</td>
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<td>CHMP</td>
<td>Committee for Medicinal Products for Human Use</td>
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<td>CMD(h)</td>
<td>Coordination group for Mutual recognition and Decentralised procedure for human medicinal products</td>
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<td>CMS</td>
<td>Concerned Member State</td>
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<tr>
<td>EDMF</td>
<td>European Drug Master File</td>
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<td>EDQM</td>
<td>European Directorate for the Quality of Medicines</td>
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<td>EEA</td>
<td>European Economic Area</td>
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<td>ERA</td>
<td>Environmental Risk Assessment</td>
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<td>ICH</td>
<td>International Conference of Harmonisation</td>
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<td>MAH</td>
<td>Marketing Authorisation Holder</td>
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<td>Ph.Eur.</td>
<td>European Pharmacopoeia</td>
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<td>PL</td>
<td>Package Leaflet</td>
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<td>RH</td>
<td>Relative Humidity</td>
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<td>RMP</td>
<td>Risk Management Plan</td>
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<tr>
<td>SmPC</td>
<td>Summary of Product Characteristics</td>
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<td>TSE</td>
<td>Transmissible Spongiform Encephalopathy</td>
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I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for Articaine hydrochloride/Epinephrine NewLine Pharma 40 mg/ml + 0.01 mg/ml, solution for injection from NewLine Pharma S.L.

The product is indicated for local or local-regional anaesthesia in dentistry and dental surgical procedures in patients at least 4 years old.

A comprehensive description of the indications and posology is given in the SmPC.

This decentralised procedure concerns a generic application claiming essential similarity with the European reference product (ERP) Articadent 1/100,000, solution injectable à usage dentaire which has been registered in France by Dentsply Sirona since 22 March 1999.

The concerned member states (CMS) involved in this procedure were Germany and the United Kingdom.

The marketing authorisation has been granted pursuant to Article 10(1) of Directive 2001/83/EC.

II. QUALITY ASPECTS

II.1 Introduction

Articaine hydrochloride/Epinephrine NewLine Pharma is a sterile, clear and colourless solution for injection for dental use with a pH between 2.7 – 4.5 and osmolality of approximately 267 mOsm/kg. Each ml of solution contains 40.00 mg of articaine hydrochloride and a quantity of adrenaline tartrate corresponding to 0.01 mg adrenaline.

The solution for injection is packed in a cartridge (type I glass) sealed at the base by a grey bromobutyl stopper and at the other end by a bromobutyl disk covered by an aluminium cap.

The excipients are: sodium chloride, sodium metabisulphite, hydrochloric acid, sodium hydroxide and water for injection

II.2 Drug Substances

The active substances are adrenaline tartrate and articaine hydrochloride. Both are established active substances and described in the European Pharmacopoeia (Ph.Eur.).
The CEP procedure is used for both active substances. Under the official Certification Procedures of the EDQM of the Council of Europe, manufacturers or suppliers of substances for pharmaceutical use can apply for a certificate of suitability concerning the control of the chemical purity and microbiological quality of their substance according to the corresponding specific monograph, or the evaluation of reduction of Transmissible Spongiform Encephalopathy (TSE) risk, according to the general monograph, or both. This procedure is meant to ensure that the quality of substances is guaranteed and that these substances comply with the Ph.Eur.

**Adrenaline tartrate**
Adrenaline tartrate is a white or greyish-white crystalline powder and freely soluble in water and slightly soluble in ethanol (96%).

**Manufacturing process**
CEPs have been submitted; therefore no details on the manufacturing process have been included.

**Quality control of drug substance**
The active substance specification is considered adequate to control the quality and meets the requirements of the monograph in the Ph.Eur. with additional tests for microbiological purity. Batch analytical data demonstrating compliance with this specification have been provided for a total of five batches.

**Stability of drug substance**
For one manufacturer the active substance is stable for four years and for the other manufacturer 42 months when stored under the stated conditions. Assessment thereof was part of granting the CEPs and has been granted by the EDQM.

**Articaine hydrochloride**
Articaine hydrochloride is a white or almost white crystalline powder and freely soluble in water and in ethanol (96%). The active substance is a chiral substance and is used as a racemic mixture.

**Manufacturing process**
CEPs have been submitted; therefore no details on the manufacturing process have been included.

**Quality control of drug substance**
The active substance specification is considered adequate to control the quality and meets the requirements of the monograph in the Ph.Eur. with additional tests for microbial purity and bacterial endotoxins. Batch analytical data demonstrating compliance with this specification have been provided for three batches.
Stability of drug substance
The active substance is stable for five years when stored under the stated conditions. Assessment thereof was part of granting the CEP and has been granted by the EDQM.

II.3 Medicinal Product

Pharmaceutical development
The product is an established pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines. The choice of excipients is justified and their functions explained. The aim of the formulation development was to obtain a solution for injection, articaine hydrochloride and adrenaline tartrate, suitable for injection at oromucosal level to provide local anaesthesia (infiltration and nerve-block anaesthesia) in dentistry and comparable to the referenced product Articadent (France). All excipients used are well known and are the same as in the reference product. The choices of the packaging and manufacturing process are justified. It is noted that articaine hydrochloride is provided as a racemate. It has been stated that the substance remains present in the drug as a racemate.

Manufacturing process
The manufacturing process consists of sterilising filtration followed by aseptic filling. Aseptic manufacturing is chosen due to the sensitive of adrenaline to high temperatures and the fact that the container system cannot be sterilised. The process has been validated according to relevant European guidelines. Process validation data on the product have been presented for five batches in accordance with the relevant European guidelines. Validation studies further include microbial challenge testing, media fills, solution compatibility and filter leachables.

Control of excipients
All excipients used comply with the requirements of the Ph.Eur. It is stated that parenteral grade sodium chloride is used. The specifications are acceptable.

Microbiological attributes
A test for the determination of sterility (according to Ph. Eur. current edition) and bacterial endotoxins (according to Ph. Eur. current edition) is routinely conducted. A microbiological load test in sterile products is routinely conducted on all drug substances and excipients of drug products.

Quality control of drug product
The finished product specifications are adequate to control the relevant parameters for the dosage form. The specification includes tests for appearance, colour, pH, identification, assay, related substances, extractable volume, sub-visible particle, sterility and bacterial endotoxins. Limits in the specification have been justified and are considered appropriate for adequate quality control of the product. Qualification data has been provided that demonstrates the D-adrenaline content of similar products on the market. This data has been assessed by a toxicology assessor. The D-adrenaline limit is acceptable. Satisfactory
validation data for the analytical methods have been provided. Batch analytical data from five batches from the proposed production site have been provided, demonstrating compliance with the specification.

**Stability of drug product**
Stability data on the product have been provided for five batches stored at 25°C/60% RH (up to 24 months, 15 months and 3 months), 30°C/65% RH (up to 12 months and 3 months for one batch) and 40°C/75% RH (up to 6 months, and 3 months for one batch). A photostability study showed that the product is not sensitive to light. On basis of the data submitted, a shelf life was granted of 18 months. The labelled storage conditions are ‘Store at a temperature below 30°C. Do not freeze’.

**Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies**
There are no substances of ruminant animal origin present in the product nor have any been used in the manufacturing of this product, so a theoretical risk of transmitting TSE can be excluded.

### II.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the member states consider that Articaine hydrochloride/Epinephrine NewLine Pharma has a proven chemical-pharmaceutical quality. Sufficient controls have been laid down for the active substance and finished product. No post-approval commitments were made.

### III. NON-CLINICAL ASPECTS

#### III.1 Ecotoxicity/environmental risk assessment (ERA)

Since Articaine hydrochloride/Epinephrine NewLine Pharma is intended for generic substitution, this will not lead to an increased exposure to the environment. An environmental risk assessment is therefore not deemed necessary.

#### III.2 Discussion on the non-clinical aspects

This product is a generic formulation of Articadent which is available on the European market. Reference is made to the preclinical data obtained with the innovator product. A non-clinical overview on the pharmacology, pharmacokinetics and toxicology has been provided, which is based on up-to-date and adequate scientific literature. The overview justifies why there is no need to generate additional non-clinical pharmacology, pharmacokinetics and toxicology data. Therefore, the member states agreed that no further non-clinical studies are required.
IV. CLINICAL ASPECTS

IV.1 Introduction

Articaine hydrochloride and adrenaline tartrate are well-known active substances with established efficacy and tolerability. A clinical overview has been provided, which is based on scientific literature. The overview justifies why there is no need to generate additional clinical data. Therefore, the member states agreed that no further clinical studies are required.

IV.2 Pharmacokinetics

Articaine hydrochloride/Epinephrine NewLine Pharma 40 mg/ml + 0.01 mg/ml, solution for injection is a parenteral formulation and therefore fulfils the exemption mentioned in the Note for Guidance on bioequivalence “5.1.6 parenteral solutions”, which states that a bioequivalence study is not required if the product is administered as an aqueous intravenous solution containing the same active substance in the same concentration as the currently authorised reference medicinal product (NfG CPMP/EWP/QWP 1401/98). Therefore, it may be considered as therapeutic equivalent, with the same efficacy/safety profile as known for the active substance of the reference medicinal product. The current product can be used instead of its reference product.

IV.3 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 Articaine hydrochloride/Epinephrine NewLine Pharma.

<table>
<thead>
<tr>
<th>Important identified risks</th>
<th>- Allergic reactions</th>
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<td>- Toxic reactions (cardiovascular, respiratory or neurological)</td>
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<tr>
<th>Important potential risks</th>
<th>None</th>
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<tr>
<td>Missing information</td>
<td>- Use in pregnancy</td>
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The member states agreed that routine pharmacovigilance activities and routine risk minimisation measures are sufficient for the risks and areas of missing information.

IV.4 Discussion on the clinical aspects

For this authorisation, reference is made to the clinical studies and experience with the innovator product Articadent. No new clinical studies were conducted. Risk management is
adequately addressed. This generic medicinal product can be used instead of the reference product.

V. USER CONSULTATION

The package leaflet (PL) 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 test consisted of: a pilot test with three participants, followed by two rounds with 10 participants each. The questions covered the following areas sufficiently: traceability, comprehensibility and applicability. The results show that the PL 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

Articaine hydrochloride/Epinephrine NewLine Pharma 40 mg/ml + 0.01 mg/ml, solution for injection has a proven chemical-pharmaceutical quality and is a generic form of Articadent 1/100,000, solution injectable à usage dentaire. Articadent is a well-known medicinal product with an established favourable efficacy and safety profile.

Since both the reference and current product are intended for parenteral use, no bioequivalence study is deemed necessary. A biowaiver has been granted.

The Board followed the advice of the assessors.

There was no discussion in the CMD(h). Agreement between member states was reached during a written procedure. The member states, on the basis of the data submitted, considered that essential similarity has been demonstrated for Articaine hydrochloride/Epinephrine NewLine Pharma with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 6 September 2018.
### STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

<table>
<thead>
<tr>
<th>Procedure number*</th>
<th>Scope</th>
<th>Product Information affected</th>
<th>Date of end of procedure</th>
<th>Approval/ non approval</th>
<th>Summary/ Justification for refuse</th>
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