CBG MEB

PUBLIC ASSESSMENT REPORT of the Medicines Evaluation Board in the Netherlands

LONCARTI 40/0.005 mg/ml and LONCARTI 40/0.01 mg/ml, solution for injection
Laboratorios Inibsa, S.A., Spain

articaine (as hydrochloride)
epinephrine (as tartrate)

EU-procedure number: NL/H/1492/001-002/DC
Registration number in the Netherlands: RVG 102889,102892

2 February 2010

Pharmacotherapeutic group:	amides; articaine, combinations
ATC code:	N01BB58
Route of administration:	oromucosal
Therapeutic indication:	Local anaesthesia (infiltration and nerve-block anaesthesia) in dentistry in adults, adolescents and children above 4 years of age.
Prescription status:	prescription only
Date of authorisation in NL:	12 November 2009
Concerned Member States:	Decentralised procedure with BE, BG, CY, DK, EE, EL, FI, LT, LU, LV, NO, PL, RO
Application type/legal basis:	Directive 2001/83/EC, Article 10a

For product information for healthcare professionals and users, including information on pack sizes and presentations, see Summary of Product Characteristics (SPC), package leaflet and labelling.

I INTRODUCTION

Based on the review of the quality, safety and efficacy data, the member states have granted a marketing authorisation for LONCARTI 40/0.005 mg/ml and LONCARTI 40/0.01 mg/ml, solution for injection from Laboratorios Inibsa, S.A. The date of authorisation was on 12 November 2009 in the Netherlands.

LONCARTI 40/0.005 mg/ml is indicated for local anaesthesia (infiltration and nerve-block anaesthesia) in dentistry during minor procedures.

LONCARTI 40/0.01 mg/ml is indicated for local anaesthesia (infiltration and nerve-block anaesthesia) in dentistry, especially for complicated procedures requiring prolonged anaesthesia.

Both formulations are indicated for use in adults, adolescents and children above 4 years of age.

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

The marketing authorisation is granted based on article 10(a) (well-established medicinal use) of Directive 2001/83/EC.
The products at issue contain two known active substances, i.e. articaine and epinephrine (adrenaline). Articaine is used in 57 countries and it is estimated that around 100 million patients are treated with articaine every year (source report Danish Medicines Agency). It is the most widely used local anaesthetic in dentistry in a number of European countries (Hornke et al., 1984; Uihlein M., 1974) and Canada (Vree B., 2005).

LONCARTI contains articaine which is a local anaesthetic of the amide type for dentistry and leads to a reversible inhibition of the irritability of vegetative, sensory and motor nerve fibres. The blocking of voltage dependent Na+ channels on the membrane of the nerve fibre is supposed to be the mechanism of effect of articaine.
The rapid onset of anaesthesia - latency period of 1 - 3 minutes -, the reliable effect with strong analgesic effect and good local tolerability are characteristic. The duration of effect of LONCARTI in pulpal anaesthesia lasts at least 45 minutes, and in soft-tissue anaesthesia 120 to 240 minutes.
Epinephrine leads locally to vasoconstriction, whereby the absorption of articaine is delayed. The result is a higher concentration of the local anaesthetic at the site of effect over a longer period, as well as the reduction in the occurrence of systemic adverse side effects.

This application concerns a bibliographical application based on well-established medicinal use of articaine and epinephrine. This type of application does not require submission of the results of pre-clinical tests or clinical trials if the applicant can demonstrate that the active substance of the medicinal product has been in well-established medicinal use within the Community for at least 10 years, with recognised efficacy and an acceptable level of safety. ''Medicinal use'' does not exclusively mean ''use as an authorised medicinal product'', so that the proof of medicinal use may be submitted even in the absence of a marketing authorisation. Well-established use refers to the use for a specific therapeutic use. For this kind of application, a detailed description of the strategy used for the search of published literature and the justification for inclusion of the references in the application has to be provided. The documentation submitted by the applicant should cover all aspects of the assessment and must include a review of the relevant literature, taking into account pre- and post-marketing studies and published scientific literature concerning experience in the form of epidemiological studies and in particular of comparative epidemiological studies.

No new pre-clinical and clinical studies were conducted, which is acceptable for this bibliographical application.

Based on the fact that this product is a watery solution, no bioequivalence studies are required. Considering the broad experience with this product in Europe and the large number of publications on this product (on randomised trials including paediatric populations), it is considered acceptable to waive further studies that would normally be performed for a new application.

No scientific advice has been given to the MAH with respect to these products.

Paediatric data and data for the elderly were sufficiently provided.

II SCIENTIFIC OVERVIEW AND DISCUSSION

II.1 Quality aspects

Compliance with Good Manufacturing Practice
The MEB has been assured that acceptable standards of GMP (see Directive 2003/94/EC) are in place for these product types at all sites responsible for the manufacturing of the active substance as well as for the manufacturing and assembly of this product prior to granting its national authorisation.

Active substance
The active substances are Articaine HCl and Adrenaline tartrate, both established active substances described in the European Pharmacopoeia (Ph.Eur.*). Articaine HCl is freely soluble in water and in alcohol. Adrenaline tartrate is also freely soluble in water. It is slightly soluble in ethanol (96%).

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 suitablity 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 new general monograph, or both. This procedure is meant to ensure that the quality of substances is guaranteed and that these substances comply with the European Pharmacopoeia.

Manufacturing process
Manufacturing and characterisation of the drug substances are covered by the CEPs.

Quality control of drug substances
The drug substance specification for articaine HCl is in line with the Ph.Eur., with additional requirements for microbial load and bacterial endotoxins which are in line with the USP*. The specification is acceptable in view of the route of synthesis and the various European guidelines.
Batch analytical data demonstrating compliance with the articaine HCl specification have been provided for three full-scale batches.

The drug substance specification for adrenaline tartrate is in line with the Ph.Eur., with additional requirements for microbial load, residual solvents and melting point. The specification is acceptable in view of the route of synthesis and the various European guidelines. Batch analytical data demonstrating compliance with the articaine HCl specification have been provided for three full-scale batches.
The MAH committed to submit results of the first three batches of articaine hydrochloride analysed using the microbial load and bacterial endotoxines Ph.Eur. methods.

Stability of drug substances
For articaine HCl stability data on the active substance have been provided for three full-scale batches stored at 25°C/60% RH (24 months), 30°/65% RH (24 months) and 40°C/75% RH (6 months). The batches were adequately stored. No changes were observed and the proposed retest period of 24 months stored in the proposed packaging protected from light could therefore be granted.

Adrenaline tartrate from is stable for 3 years in the proposed packaging with no special storage conditions. Assessment thereof was part of granting the CEP and has been done by the EDQM.

** Ph.Eur. and USP are official handbooks (pharmacopoeias) in which methods of analysis with specifications for substances are laid down by the authorities of the EU and the USA respectively.*

Medicinal Product

Composition
LONCARTI 40/0.005 mg/ml and LONCARTI 40/0.01 mg/ml are clear, non-opalescent, colourless liquids with a pH ranging from 3.0 to 4.3. The osmolality of the solution is approximately 267 mOsm/kg.

The solution for injection is packed in cartridges made of colourless neutral glass I, with a bromobutyl rubber plunger and an aluminium cap with a bromobutyl disc.

The excipients are: sodium metabisulphite (E223), sodium chloride, hydrochloric acid (for pH adjustment), sodium hydroxide (for pH adjustment), water for injections.

Pharmaceutical development
The development of the product has been described, the choice of excipients is justified and their functions explained. Both drug substances are freely soluble in water. The excipients are usual for this type of dosage form. The choice of sodium metabisulphite as antioxidant has been sufficiently discussed. Moreover it has been included in several marketed articaine/adrenaline products. The main development studies performed are: solubility of the drug substance, stability of the drug substances in solution, effect of the pH on the drug substances and adjustment of tonicity. The type of packaging and usage of the packaging is sufficiently discussed. The pharmaceutical development of the product has been adequately performed.

Manufacturing process
The manufacturing process consists of the following steps: preparation of the solution, filtration of the solution and aseptic filling of the cartridges. Adrenaline is sensitive to high temperatures, and the chosen container cannot be sterilized in the standard autoclave method (described in the Ph.Eur.) as heat can cause the elastomeric plunger to move and draw out of the cartridge. The manufacturing process has been adequately validated according to relevant European guidelines. Process validation data on the product has been presented for three production-scale batches. A commitment to validate three full-scale batches post authorisation has been made. The product is manufactured using conventional manufacturing techniques.

Excipients
The excipients comply with the Ph.Eur. These specifications are acceptable.

Quality control of drug product
The product specification includes tests for appearance and color, pH, identification and assay of articaine, adrenaline and sodium metabisulfite, related substances, sulphonated adrenaline, extractable volume, sub-visible particle contamination, sterility and bacterial endotoxins.
The release and shelf-life limits differ for appearance and color, pH, assay of sodium metabisulfite and related substances. The analytical methods have been adequately described and validated. The MAH committed to develop a suitable method to control the D-adrenaline in the drug product.
Batch analytical data from the proposed production site have been provided on three full-scale batches of both strengths and six pilot-scale batches of both strengths, demonstrating compliance with the release specification.

Compatability
In the absence of compatibility studies, LONCARTI 40/0.005 mg/ml and LONCARTI 40/0.01 mg/ml must not be mixed with other medicinal products.

Stability of drug product
Stability data on the product have been provided for three full-scale batches of both strengths stored at 25°C/60% RH (18 months), 30°/65% RH (12 months) and 40°C/75% RH (6 months). Supportive data have been provided for six pilot-scale batches of both strengths stored at 25°C/60% RH (3 months), 30°/65% RH (3 months) and 40°C/75% RH (2 months) and of a comparable formulation. The pilot-scale batches were not evaluated since the data of only one data point beside the initial data point were included. The conditions used in the stability studies are according to the ICH stability guideline. The

batches were stored in colourless glass cartridges closed with a bromobutylrubber stopper and plunger inside a secondary packaging.
For the full-scale batches during accelerated conditions a tendency to decrease was observed for sodium metabisulfite, adrenaline and articaine and an increase in articaine acid and adrenaline sulfonate was observed. At intermediate and long-term conditions a decrease of sodium metabisulfite and an increase in adrenaline sulphonate within the shelf-life specifications were observed. The sensitivity of adrenaline to light is derived from the literature and therefore storing the product protected from light is considered acceptable.
A shelf-life of 18 months, protected from light could be granted. Extrapolation of the data is not considered appropriate in view of observed variability of the outcomes of the test parameters and non-linearity of the observed trends. The storage condition 'Store below 30°C' is acceptable in view of the stability under these conditions.
Several post-approval commitments have been made regarding stability testing. These can be found on page 13 of this report.

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.2 Non clinical aspects

Pharmacology
Articaine hydrochloride is an amide type local anaesthetic with an intermediate duration of action (1.5 more potent than lidocaine and 1.9 more potent than procaine), which is associated with adrenaline and is used in dentistry.
Articaine is a local anaesthetic that binds to the nerve membrane receptor and acts through the sodium channels (Na+), reducing the membrane's permeability and the rapid entry of sodium ions, inhibiting the generation and the conduction of the nerve impulse. Articaine causes a dose-dependent reduction of nerve excitability (increased electrical threshold), leading to an insufficient propagation of the impulse and, in consequence, to a conduction blockade. Articaine binds with greater affinity to Na+ channels when these are in open or inactive state (that is, during the depolarization phase) than when they are in a resting state, in which moment dissociation occurs. Articaine dissociates slowly, whereby its action is favoured when the stimulation frequency is high, because receptors do not have time to recover and to be available (in a resting state).
With regards to adrenaline, its intended effects include prolonging nerve block duration, reducing plasma concentration of local anaesthetics, reducing surgical bleeding, and intensifying anaesthesia and analgesia.

Pharmacokinetics
Absorption and distribution of articaine, like other amide local anaesthetics, varies depending on many factors, such as site and method of administration, blood flow characteristics, plasma protein binding, plasma pH, and the physical properties of the local anaesthetic.
Most articaine binds to plasma proteins, especially to albumin and is rapidly metabolized mainly by the action of plasma esterases to an inactive metabolite, articainic acid; the liver microsome P450 isoenzyme system also metabolizes a small proportion of articaine. Articaine is eliminated in the urine, primarily as articainic acid alone or as a glucuronade compound. Elimination as unchanged drug is very low.
Data obtained from pharmacokinetic studies in animals are confined to two research works carried out in rats and dogs. Results were highly dispersed, because a small number of animals were used, as to be compared with data in humans with much larger numbers.
From a pharmacokinetic viewpoint, the use of adrenaline lays on its capacity to diminish the absorption rate of articaine and the possibility to prolong the action duration of the local anaesthetic.

Toxicology
Symptoms of toxicity after single doses of articaine include trembling, vertigo, and tonoclonic convulsions. The duration and intensity of these symptoms were dose-dependent and at low doses all symptoms dissipated in 5 to 10 minutes. LD50 in mice is reported as 37 mg/kg after IV injection. This was much

higher after SC injection. In dogs after IM administration, the LD50 was 160 mg/kg.
For adrenaline, LD50 values after SC administration were 8.3 mg/kg for rats, and 11.1 mg/kg for mice. The acute toxicity of articaine measured as the LD50 increased 10-fold in mice and 2-fold in rats when combined with adrenaline. In studies with the mouse, rat and dog, the no-observed effect level (NOEL) of a single dose of subcutaneously administered articaine with adrenaline was between 3-fold and 10-fold greater than the maximum recommended dose in man (7 mg/kg).
After repeated dosing, the NOAEL of articaine in dogs was 25 mg/kg after IM injection. For the combination, two four-week studies with SC administration were conducted in rats and beagle dogs. For both rats and dogs, local effects on the skin occurred at all doses (low dose in the rat, 25 mg/kg and in the dog 20 mg/kg).
There is no evidence of any genotoxic potential of articaine or adrenaline. No carcinogenicity studies have been performed with either articaine or adrenaline which is acceptable for this type of product.
Reproductive toxicity has been investigated in a series of studies using the combination of 4% articaine with 1:100.000 adrenaline, at doses of 20, 40 and 80 mg/kg. No effects on male or female fertility were found at doses up to 80 mg/kg. In embryotoxicity studies in rabbits, maternal toxicity was observed at 40 mg/kg, whereas embryotoxicity (skeletal variations) were evident at 80 mg/kg. In rats, no effects on the embryos was found, therefore the NOEAL was 80 mg/kg. In a pre- and postnatal study in rats, effects on the F1 generation was observed at the high dose (increased still births, delayed eye opening, reduced ability to pass the passive avoidance test). No effects were observed in the F2 generation. With studies using adrenaline alone, it was shown to be teratogenic at 25-fold the human dose.
In local tolerance tests, different anesthetic solutions were compared. All solutions showed skin reactions, with no relation between concentration and inflammatory intensity.

Environmental risk assessment
No increase in environmental exposure is expected as the product is likely to substitute similar products already on the market. A formal environmental risk assessment was therefore not deemed necessary.

II.3 Clinical aspects

Pharmacokinetics
The maximum plasma level of articaine from intra-oral injection is achieved approximately after 10 - 15 minutes. The distribution volume is 1.67 l/kg, the elimination half-life is approximately 20 minutes. Articaine is bound up to 95% in the serum to plasma proteins. Articaine is rapidly hydrolysed by plasma cholinesterases to its primary metabolite articainic acid which is further metabolised to articainic acid glucuronide. Articaine and its metabolites are mainly eliminated in urine.
Adrenaline is rapidly metabolized in the liver and other tissues. The metabolites are excreted renally. Accumulation of articaine in patients with renal or hepatic dysfunction seems unlikely, as articaine is metabolised by plasma esterases into inactive metabolites. Only a very limited amount is excreted unchanged into urine.

Pharmacodynamics
Articaine which is a local anaesthetic of the amide type that causes reversible inhibition of the irritability of vegetative, sensory and motor nerve fibres. The mechanism of effect of articaine is supposed to be due to the blocking of voltage dependent Na^+ channels on the membrane of the nerve fiber. Articaine is an amino-amide agent. In comparison to anaesthetics of the ester type, anaesthetics of the amide type have quicker onset, longer duration of effect and they are far less allergenic than ester agents.
Articaine has a thiophene or sulfur-containing ring and an ester side chain (Hawkins et al., 2002). Because of the thiophene ring, articaine is a compound with high lipid solubility, which may improve diffusion through tissues and passage through lipid membranes (Malamed et al., 2000).
Characteristics of articaine are the rapid onset of anaesthesia (latency period of 1 - 3 minutes) and a strong analgesic effect. When regular doses are applied, the duration of effect of the two formulations in pulpal anaesthesia is expected to last at least 45 minutes and in soft-tissue anaesthesia 120 to 240 minutes.

Adrenaline causes local vasoconstriction delaying the absorption of articaine. This leads to a higher concentration of the local anaesthetic at the site of effect over a longer period, as well as the reduction in the occurrence of systemic adverse side effects and reduced bleeding in the operative area.

Clinical efficacy
For clinical efficacy, data of a total of 16 published randomised clinical trials with the local anaesthetic 4% articaine with 1:100,000 or 1:200,000 adrenaline were included in the bibliographic assessment. Among them, 11 studies correspond to clinical trials in adults and the other 5 studies were conducted in paediatric populations.

Adults
In the 11 adult studies, 3 studies compared articaine of two different adrenaline concentrations (1:200,000 and 1:100,000) or adrenaline-free formulations; 8 studies compared articaine + adrenaline to lidocaine. Nine of these studies were double-blind and randomised. In total, 1828 adults were included in the studies. In seven studies elderly were included.

The doses applied in the studies were in line with the dosing recommendations made in the SPC of Dentocaine. No formal dose response studies were submitted. The dose recommendations made in the SPC are based on established use, and in accordance with other articaine containing products that are available on the European market. According to the submitted literature, 7 mg/kg is the maximal recommended dose of articaine for adults (Haas, 2002) and children (Coté et al., 2006).

From the lidocaine-controlled studies it can be concluded that articaine 40 mg/mL (4%) is at least effective as lidocaine 2%, a well-established local anaesthetic agent belonging to the same class of anaesthetics as articaine (amino-amide caines) when used in dental procedures. There was a tendency that articaine had a faster onset of effect than lidocaine in 4 randomised studies (Vähätalo, 1993; Costa, 2005, Sierra Rebolledo, 2007; Berlin, 2005). There was also a tendency that the duration of anaesthetic effect of articaine 4% is longer than lidocaine in several studies, though this difference varied from 1-50 min in different studies (the largest effect was shown in molar extraction study by Sierra Rebolledo). In a large scaled study by Malamed, 2000, the overall effect size in pain reduction was similar for both articaine 4% and lidocaine 2%, both in simple and more complicated dental procedures.

The studies by Moore et al. (2006, 2007) revealed that articaine without adrenaline is less effective in maxillary infiltration, compared to adrenaline containing formulations, and duration of anaesthesia was significantly shorter in adrenaline-free formulation (13.3 ± 6.8 min, $p<0.001$). Adding of adrenaline to the articaine formulation is thus justified.

Articaine with higher adrenaline percentages (1:100,000) showed similar pupal anaesthesia scores compared to the adrenaline 1:200,000 solution, if similar volumes of both formulations were applied. The onset of effect and duration of anaesthesia was similar for both formulations. However, significant less bleeding was observed after the higher adrenaline formulations. These data justify that formulations with the highest adrenaline concentration is indicated for more complicated procedures. (Moore et al., 2006, 2007)

Elderly
Oertel et al. (1999) have shown that the serum concentration-time curve (Tmax) and maximum drug concentration (Cmax) values after subcutaneous application of articaine did not differ in adults (20-37 years old) and elderly (59-68 years old). In a large scaled study by Malamed, no problems were reported in elderly aged 65-80 years compared to younger adults (N=1325).

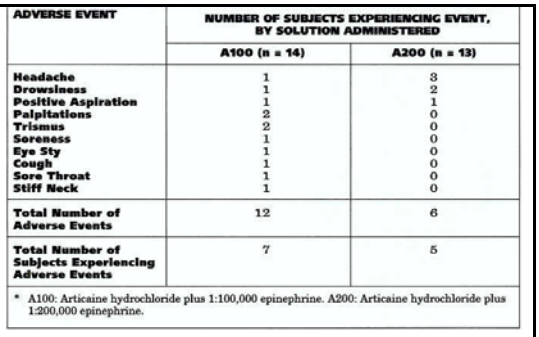
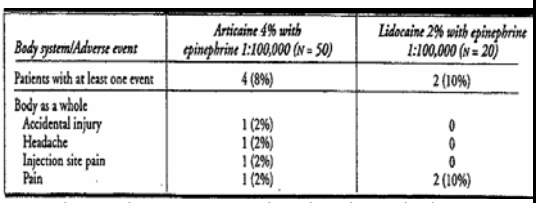
Paediatric data
In the paediatric population, 5 clinical studies were included, three of them are double-blind, randomized – either parallel ((Malamed et al., 2000) or cross-over (Ram and Amir, 2006 and Wright et al., 1991). Additionally, an open study (Dudkiewicz et al., 1991) and a retrospective study (Wright et al., 1989) were performed. As to administered treatments, 2 studies were on articaine with adrenaline (different concentrations), and 3 studies compared articaine + adrenaline with lidocaine and other local anaesthetics.

The paediatric studies included 4 prospective studies with 228 children between 4 and <13 years and a retrospective study (Wright et al., 1989) in 211 children below 4 years of age. The children included in the prospective studies are healthy while in the retrospective study the subjects are mixed: some children were healthy, while the others have pulmonary disturbance (3%), cardiac disorders (5%) and allergies (9%).
In children, the doses of articaine ranged from about 40 to 116.4 mg of articaine and 5 to 29 µg adrenaline.
No significant differences in pain relief between the articaine 4%, lidocaine 2% and prilocaine 4% formulations were observed. In one study, duration of numbness of soft tissues was significantly longer for articaine (3.43 +/- 0.7 h) than for lidocaine (3.0 +/- 0.8 h, p = 0.003). (Ram and Amir, 2006).
In the retrospective study of Wright et. al. (1989,) it was concluded that the results supported the use of articaine in children under 4 years. However, the data are considered too limited to lower the minimal age of 4 years old as recommended in the SPC.

Clinical safety
The MAH presented bibliographic data of a total of 1905 subjects (1540 adults and 365 children) exposed to different dental local anaesthetics: 1008 adults and 345 children received the combination articaine + adrenaline, whereas 564 adults and 54 children received lidocaine + adrenaline, and 45 adults received other anaesthetics.
The most frequently reported adverse events related to articaine use are: paresthesia, hypoesthesia, headache, dizziness, drowsiness, trismus, infection, and pain. The table summarizes adverse events observed with articaine use.

Summary of studies evaluating safety of articaine-adrenaline in dental anaesthesia

<table>
<tr><th>Study / Study design</th><th>Study design</th><th>Treatment</th><th>No. of subjects</th><th>Results/Conclusions</th></tr>
<tr><td colspan="5">Adults</td></tr>
<tr><td>Carrasco et al, 2003</td><td>NR</td><td>4% ART + 1:100,000 ADR
2% LID + 1:100,000 ADR</td><td>86</td><td><table><tr><th></th><th>articaine</th><th>lidocaine</th></tr><tr><td>a. pain injection site</td><td>3 (3.4%)</td><td>2 (2.3%)</td></tr><tr><td>b. headache</td><td>2 (2.3%)</td><td>1 (1.1%)</td></tr><tr><td>c. somnolence</td><td>0</td><td>1 (1.1%)</td></tr><tr><td>d. dizziness</td><td>1 (1.1%)</td><td>0</td></tr></table>Six (2.3%) patients experienced AEs with articaine (ART) and 4 (1.5%) with lidocaine (LID).</td></tr>
<tr><td>Carrera et al. (2000)</td><td>DB</td><td>4% ART + 1:200,000 ADR
3% MEP
3% PRI + 1:1,850,000</td><td>45</td><td>a. heart rate, systolic and diastolic blood pressure and oxygen saturation was more stable with articaine + ADR1:200,000
b. the three studied solutions caused no significant haemodynamic changes with respect to the basal values.</td></tr>
<tr><td>Hersh et al. (2006)</td><td>R, DB, C</td><td>4% ART + 1:200,000 ADR
4% ART + 1:100,000 ADR</td><td>14</td><td></td></tr>
</table>

				 **ADVERSE EVENT** / **NUMBER OF SUBJECTS EXPERIENCING EVENT, BY SOLUTION ADMINISTERED** **A100 (n = 14)** / **A200 (n = 13)** **Headache** 1 / 3 **Drowsiness** 1 / 2 **Positive Aspiration** 1 / 1 **Palpitations** 2 / 0 **Trismus** 2 / 0 **Soreness** 1 / 0 **Eye Sty** 1 / 0 **Cough** 1 / 0 **Sore Throat** 1 / 0 **Stiff Neck** 1 / 0 **Total Number of Adverse Events** 12 / 6 **Total Number of Subjects Experiencing Adverse Events** 7 / 5 * A100: Articaine hydrochloride plus 1:100,000 epinephrine. A200: Articaine hydrochloride plus 1:200,000 epinephrine. 4% ART with 1:200,000 ADR produces less cardiovascular stimulation than 4% ART with 1:100,000 ADR.
Malamed et al. (2001)	DB, R, P	4% ART +1:100,000 ADR 2% LID + 1:100,000 ADR	1325	The overall incidence of adverse events in the combined studies was 22% for the articaine group and 20% for the lidocaine group. The adverse events most frequently reported with articaine use were paresthesia (0.9%), hypoesthesia (0.7%), headache (0.55%), infection (0.45%), and rash and pain (0.3% each).
Mestre et al. (2001)	DB, P	4% ART + 1:100,000 ADR 2% LID + 1:100,000 ADR 2% MEP + 1:1850,000 FEL	45	None of the local anaesthetics studied exerted significant effects heart rate and oxygen saturation.
Mikesell et al., 2005	DB, R, C	4% ART + 1:100,000 ADR 2% LID + 1:100,000 ADR	57	There were no reports of paresthesias. The most common complaint were trismus (9%), soreness (4-5 %) and swelling (0-2 %) at the injection site. The incidence decreased by day 2 and 3 indicating no lasting tissue-damaging effects. There was no significant difference between the two anaesthetic solutions.
Sack and Kleemann (1992)	R, O	4% ART + 1:200,000 ADR 4% ART + 1:100,000 ADR 2% LID + 1: 80,000 ADR	18	Transient peak concentrations of adrenaline do not lead to significant haemodynamic changes in all the 3 groups.
Vähätalo, et al., 1993	DB, R, C	4% ART + 1:200,000 ADR 2% LID + 1: 80,000 ADR	20	No clinically side effects were observed.
Children				
Dudkiewicz et al, 1987	Open	4% ART + 1:100,000 ADR 4% ART + 1:200,000 ADR	50	No side effects were reported and there was no history of postoperative lip bite or discomfort.
Malamed et al., 2000	DB, R, P	4% ART + 1:100,000 ADR 2% LID + 1:100,000 ADR	50 (**)	 *Body system/Adverse event* / *Articaine 4% with epinephrine 1:100,000 (N = 50)* / *Lidocaine 2% with epinephrine 1:100,000 (N = 20)* Patients with at least one event 4 (8%) / 2 (10%) Body as a whole Accidental injury 1 (2%) / 0 Headache 1 (2%) / 0 Injection site pain 1 (2%) / 0 Pain 1 (2%) / 2 (10%) No serious adverse event related to the articaine occurred. The only adverse event directly related to articaine was accidental lip injury.
Ram and Amir, 2006	R, C	2% LID + 1 : 100,000 ADR 4% ART + 1 : 200,000 ADR	62	

				Adverse effects: Lidocaine 2% / Articaine 4% Accidental lip/cheek injury: 2 / 1 Post-procedural pain: 1 / 3 Haematoma: 1 / 0 Adverse events in the two groups were not significantly different.
Wright et al, 1989	Retrospective survey	4% ART (ADR concentrations were not mentioned)	211	No adverse reactions were noted. The authors advocate a change in the SPC that ART could be used in children younger than 4 years.

DB = Double blind, R = Randomised; C = Cross-over; P = Parallel
ADR = Adrenaline; ART = Articaine; AST= time of anesthesia of the soft tissues; CPA = complete pulpal anesthesia; LID = Lidocaine; MEP =Mepivacaine; PL = period latency ; PA= partial anesthesia; EPT = electric pulp testing; N.R. = Not Reported; VAS = Visual Analogue Scale

The above data demonstrate that articaine is relatively safe as compared to lidocaine. In general, the central side effects are rare and local side effects like allergy and pain in injection site are also rare. In children, the incidence of accidental lip bite/injury was low and comparable to lidocaine.

Safety reports have emerged in the literature reporting that articaine use might be associated with prolonged paresthesia (also called persistent anesthesia, see Haas and Lennon, 1995; Van Eeden and Patel, 2002). However, according to the retrospective study of Haas and Lennon (1995), the overall risk is small. The authors calculated that sensory impairment with articaine in the lower jaw appears in 1 out of 785,000 treated patients. The studies included in this dossier, including the large study of Malamed et al (2001) in 1325 patients, did not document an increased risk of nerve damage with 4% articaine compared to 2% lidocaine.
Triggered by 28 reports on suspected nerve damage after anesthesia with articaine, the Danish Medicines Agency evaluated the use of articaine and risk of prolonged anaesthesia. The reported symptoms included reduced or increased sense of touch, sleeping sensation and pain and/or taste disturbances. Causality of the case reports is however unclear: the prolonged paresthesia may rather be due to the interventions than articaine.

Risk management plan
No Risk Management Plan for articaine and epinephrine has been submitted, as the use of both substances is well-established in the Community and extensive clinical use has confirmed a good safety profile. No product specific pharmacovigilance issues were identified pre- or postauthorisation which are not adequately covered by the current SPC. The MAH has a pharmacovigilance system at their disposal, which is based on the current European legislation. Routine pharmacovigilance activities are sufficient to identify actual or potential risks and a detailed European Risk Management Plan is not necessary for this product.

Product information

Readability test
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 test consisted of a pilot test with 3 participants, followed by two rounds with 10 participants each. The characteristics of the population interviewed in the test rounds was: 50% male, 50% female, age ranged from 19-72, educational level was representative of the general population, all were potential users. The subjects had to answer 15 questions. Fourteen of these questions were aimed to detect potential problems in the key messages for safe use. In the 15th question the subjects were asked for their general opinion on the package leaflet, in particular with regard to lay-out and design.
Results on 'findability' were categorised as follows: (1) found very easily (<30 seconds), (2) found easily (>30 seconds-<120 seconds), and (3) with difficulty (>120 seconds). Category (1) and (2) were considered a positive result.
The actual answer to the questions (understanding/using the information) was either considered right or wrong. A satisfactory test outcome was defined:

1. For each of the questions, 90% of the participants is able to find the information requested within the PIL.
2. For each of the questions, 90% of the participants is able to answer the information requested within the PIL.

No weaknesses were identified in the PIL, neither in the first nor in the second round. Nevertheless some changes in lay-out were made between the first and second round to further improve the finding of particular information. The changes were agreed.
In summary, an adequate readability testing has been documented by this report. The package leaflet is in line with the current readability requirements. The results show that the leaflet is easy to read and understandable.

III OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

LONCARTI 40/0.005 mg/ml and LONCARTI 40/0.01 mg/ml, solution for injection have a proven chemical-pharmaceutical quality.

Pharmacodynamic, pharmacokinetic and toxicological properties of articaine and adrenaline are well known. The non-clinical overview submitted by the MAH provides a good overview of the pharmacodynamics, pharmacokinetics and toxicology of articaine, adrenaline and the combination as it is intended for clinical use.

The MAH submitted detailed clinical information on the pharmacodynamic and pharmacokinetic properties and on the efficacy and safety of the articaine/adrenaline combination. Articaine 4% is at least as effective as lidocaine 2% in pain reduction, and its safety profile is comparable. In children, articaine 4% is equally effective as prilocaine 4%.

The addition of adrenaline is well justified, as in head-to-head comparison adrenaline-containing articaine forms were superior over adrenaline-free formulations regarding pain reduction and duration of anaesthesia.

In some studies, articaine 4% displayed longer duration of anaesthesia than lidocaine. On one hand, this may be considered as beneficial, as this may in principle lead to less need for re-injection and post-operative use of analgetics. On the other hand, prolonged anaesthesia may lead to post-operative numbness, as reported in children. However, the incidence of biting accidents because of numbness was very low in children and similar as lidocaine treatment arm.
Reports have been published about rare cases of nerve damage and persistent anaesthesia after articaine. To date, it is not clear whether these serious AEs are really due to the use of articaine, but rather related to nerve damage caused by the injection or procedure itself. Appropriate warnings are included in the SPC.

There was a non-significant trend observed that duration of anaesthesia was slightly prolonged in formulations with higher adrenaline content (1:100,000) compared to lower adrenaline content (1:500,000). A better efficacy 4% ART + 1: 100,000 than 4% ART + 1: 200,000 regarding bleeding in the operative field. It is therefore supported that the higher adrenaline formulation is rather indicated for more complicated dentistry interventions.

In summary, the bibliographic review submitted by the MAH has convincingly shown the clinical efficacy and safety of 4% ART + 1: 100,000 and 4% ART + 1: 200,000. In addition, their well-established use has also been sufficiently substantiated.

The MAH has provided written confirmation that systems and services are in place to ensure compliance with their pharmacovigilance obligations. One post-approval commitment remains, see below.

The SPC, package leaflet and labelling are in the agreed templates and include all important information and warnings.

The decentralised procedure was started on 26 July 2008. 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 the benefit/risk for LONCARTI 40/0.005 mg/ml and LONCARTI 40/0.01 mg/ml is positive for the proposed indications, and have therefore granted a marketing authorisation. The decentralised procedure was finished on 16 June 2009. LONCARTI 40/0.005 mg/ml and LONCARTI 40/0.01 mg/ml, solution for injection were authorised in the Netherlands on 12 November 2009.

A European harmonised birth date has been allocated (29 April 1975) and subsequently the first data lock point for articaine + adrenaline is April 2012. The first PSUR will cover the period from June 2009 to April 2012, after which the PSUR submission cycle is 3 years.

The date for the first renewal will be: 16 June 2014.

The following post-approval commitments have been made during the procedure:

Quality - active substance

- The MAH committed to submit results of the first three batches of articaine hydrochloride analysed using the microbial load and bacterial endotoxines Ph.Eur. methods.

Quality - medicinal product

- The MAH committed to validate the full-scale batch size for the proposed formulation and to submit the obtained results when available.
- The MAH committed to develop a suitable method to control the D-adrenaline in the drug product.
- The MAH committed to revise the specification limits for the pH after finalisation of the stability studies.
- The MAH committed to provide stability data of production-scale batches when available.
- The MAH committed to finish the accelerated, intermediate and long term stability studies which are currently ongoing in order to firmly establish the shelf-life of the products. Once the results covering the complete shelf-life are available, they will be submitted to the Competent Authorities.

Pharmacovigilance system

- The MAH should confirm within 1 month following finalisation of this procedure that the curriculum vitae of the deputy QPPV is available on request.

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List of abbreviations

ASMF	Active Substance Master File
ATC	Anatomical Therapeutic Chemical classification
AUC	Area Under the Curve
BP	British Pharmacopoeia
CEP	Certificate of Suitability to the monographs of the European Pharmacopoeia
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence Interval
C_{max}	Maximum plasma concentration
CMD(h)	Coordination group for Mutual recognition and Decentralised procedure for human medicinal products
CV	Coefficient of Variation
EDMF	European Drug Master File
EDQM	European Directorate for the Quality of Medicines
EU	European Union
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
HCl	Hydrochloride
ICH	International Conference of Harmonisation
MAH	Marketing Authorisation Holder
MEB	Medicines Evaluation Board in the Netherlands
OTC	Over The Counter (to be supplied without prescription)
PAR	Public Assessment Report
Ph.Eur.	European Pharmacopoeia
PIL	Package Leaflet
PSUR	Periodic Safety Update Report
QPPV	Qualified Person for Pharmacovigilance
SD	Standard Deviation
SPC	Summary of Product Characteristics
$t_{½}$	Half-life
t_{max}	Time for maximum concentration
TSE	Transmissible Spongiform Encephalopathy
USP	Pharmacopoeia in the United States

STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

Scope	Procedure number	Type of modification	Date of start of the procedure	Date of end of the procedure	Approval/ non approval	Assessment report attached