# CONFIDENTIAL

## A STUDY OF THE USE OF MICRONEEDLE PATCHES TO DELIVER TOPICAL LIDOCAINE IN THE ORAL CAVITY

## Clinical Investigation Plan Number: Innoture/NW-01

## Version 4.0 – 11th April 2018

**Principal Investigator:** Professor N West

**Co-Investigator:** Dr. N Claydon

**Study Site:** Rhiwbina Dental Surgery
25-27 Heol Y Deri
Cardiff
CF14 6HB

**Sponsor:** Innoture Limited
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## Clinical Investigation Plan Agreement

## A STUDY OF THE USE OF MICRONEEDLE PATCHES TO DELIVER TOPICAL LIDOCAINE IN THE ORAL CAVITY

## Clinical Investigation Plan Number: Innoture/NW-01

**Investigator's Agreement Statement:**

I have read, I understand, and I will conduct the study according to this clinical investigation plan and Good Clinical Practices:

Signature: _____ Date: 11/4/18

**Principal Investigator** – Prof N West

Signature: _____ Date: 11/4/18

**Co-Investigator** – Dr. N Claydon

## Clinical Investigation Plan Agreement

# A STUDY OF THE USE OF MICRONEEDLE PATCHES TO DELIVER TOPICAL LIDOCAINE IN THE ORAL CAVITY

## Clinical Investigation Plan Number: Innoture/NW-01

**Signed on behalf of Sponsor Company:**

Signature: _____ Date: 12/04/18

**CEO** – Ken Jones

Signature: _____ Date: 16/04/18

**Medical Advisor** – Dr John Bolodeoku

Signature: _____ Date: 11-APR-2018

**Project Manager** – Jemma Burridge

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## 1.0 SUMMARY OF STUDY

### OBJECTIVES

To look at the effect on patient perceived pain resulting from infiltration injection with local anaesthetic in a dental syringe with prior application of topical anaesthetic to the oral mucosa on a microneedle patch compared to a patch with no microneedles.

To look at the safety of the patches when applied to the oral mucosa.

### STUDY DESIGN

This is a randomised, 2 treatment, double blind design, with respect to the clinical assessor and subject, split mouth, crossover design with a negative control (patch with no microneedles).

Prior to the start of the study, ethical approval by an independent research ethics committee and MHRA approval will be obtained. Potential participants will be invited to attend a screening visit. At this visit participants will be asked to read and sign a Participant Information Sheet and Consent Form prior to any study procedures being performed. They will be given ample time to decide if they wish to participate in the study. All participants will be private dental patients of Rhiwbina Dental.

A dentally qualified clinician will record the participant's demographics, medical history, current/concomitant medications, perform an oral soft tissue examination and ensure the participant fulfils the inclusion and exclusion criteria for the study. Two areas of the mouth will be identified for assessment during the study. The areas of the mouth will be identified as S1 or S2. Site S1 will be left or right palatal mucosa adjacent to the premolar area and S2 will be left or right upper buccal mucosa adjacent to the upper lateral incisor area. Only palatal or buccal aspect will be treated per treatment visit.

Participants who successfully fulfil all the necessary entrance criteria will be provided with training by study staff on how to use a Visual Analogue Scale (VAS) record sheet and randomised to the study to receive treatment combination A or B in a random order. For eligible subjects, the screening visit and first treatment visit will occur at the same visit. The treatment possibilities are outlined below:

**Treatment A** The application of a 5% topical lidocaine gel to one of the identified area within the participants mouth using a microneedle patch. The microneedle patch will be applied to the oral mucosa of the identified site for 3 minutes, followed by infiltration with a local anaesthetic to one of the identified areas within the participants mouth.

**Treatment B** The application of a 5% topical lidocaine gel to one of the identified sites within the participants mouth using a patch with no microneedles. The patch with no microneedles will be applied to the oral mucosa of the identified site for 3 minutes, followed by infiltration with a local anaesthetic to one of the identified areas within the participants mouth.

The chosen sites will be: **S1;** left and right palatal mucosa adjacent to the premolar area or **S2;** left and right upper buccal mucosa adjacent to the upper lateral incisor area. Each participant at the first visit will have either **S1** or **S2** sites allocated for treatment. For example, **Treatment A** will be allocated to **S1 left side** and **Treatment B** to **S1 right side or** vice versa. At the second visit, 2 weeks (+/- 3 days) after the first visit, **Treatment B** will be allocated to **S2 left side** and **Treatment A** to **S2 right side.** After

each treatment to each site participants will be asked to make pain assessments relating to the giving of the local infiltration anaesthetic.

The study consists of 2 visits. At each visit, participants will be assigned to one of the treatment procedures (A or B) according to a predetermined randomisation schedule supplied by the study statistician, see section 8.2.

**Pain Assessment.**
Pain assessments will be performed after application of the topical anaesthetic for 3 minutes. Each test will be performed sequentially i.e. 3 separate needle insertions, with pain assessments recorded by the participant using a Visual Analogue Scale (VAS) and a verbal pain grading after each test. The level of pain at S1 or S2 will be assessed as follows:

**Test I**. A short dental needle, mounted on a dental syringe containing a cartridge of 2% lidocaine hydrochloride and 1:80,000 adrenaline, will be used to penetrate the oral mucosa at the treated site and the patient asked to score the pain using a VAS rating scale and by verbal grading of zero, mild, moderate or severe.

**Test 2.** The same needle will be inserted through the oral mucosa and down to contact bone. Pain will be assessed as in Test 1.

**Test 3.** The same needle will be again inserted through the oral mucosa and the cartridge of local anaesthetic will be injected into the site. Pain will be again assessed as in Test I.

Following enrolment on to the study, participants will be given written and verbal instructions on the VAS and how to complete it. They will be given a test sheet to practice scoring which will be measured and checked by the clinician to ensure the participant understands how to complete the VAS form, see appendix 1.

**STUDY POPULATION**
Healthy participants of either gender aged 18 and over, with no medical or pharmacotherapy history which could compromise the conduct of the study will be recruited. It is envisaged that a sufficient number of healthy subjects will be screened by the study site so that a maximum of 16 who fulfil all the entry criteria will be randomised.

## 2.0 - STUDY FLOW CHART

Obtain NHS Ethical and MHRA Approval
|
Screen Participants
Informed Consent, Medical History, Oral Screening
|
Procedure A or B with pain assessment (Visit 1)
|
Procedure A or B with pain assessment (Visit 2)
|
Analysis of data
|
Final Report written

## 2.1 – STUDY TIMELINES

Start date June 2018
End date December 2018
Study duration 7 months

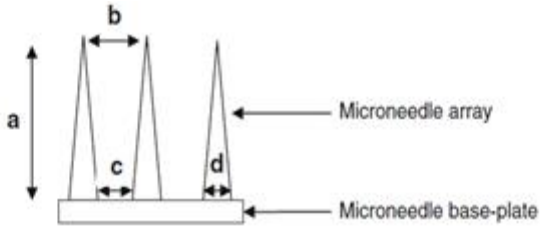
## 3.0 INTRODUCTION AND RATIONALE

Topical anaesthetic agents are often applied to skin and mucosae to reduce the discomfort of the patient to the subsequent use of a needle to inject the same or other drug. In dentistry, the most common use of topical anaesthetics is prior to the injection of a local anaesthetic. Topical lidocaine is perhaps the best known and most frequently used topical anaesthetic in dentistry, which dates back several decades. The British National Formulary (BNF) (1) states that lidocaine applied topically is absorbed through the oral mucosae and can be used up to a concentration of 10%. Side effects, including drug interactions are stated to be much less likely when lidocaine is applied topically (2), appendix 3.

From clinical experience, the benefits of topical anaesthetics in dentistry to reduce pain associated with the subsequent injection is variable and dependent on several factors ranging from the apprehension of the patient to the site of the planned injection. What is generally accepted is that, topical anaesthetics alone do not provide sufficient anaesthesia for most operative procedures to the gingivae, oral mucosa, bone and teeth. These limitations in part must be related to the amount of lidocaine absorbed through the stratified squamous cell epithelium of the oral mucosa into the underlying connective tissues.

Microneedle patches consist of a 2cm by 2 cm array of 625 needles of 400μm height and diameter of (200-250μm) printed using a UV cure resin onto a flexible backing material. The advantage of these patches is that the needles are designed to puncture the outer surface of the epithelium (approximately 150-250μm penetration under normal pressure when tested *in vitro* on pig skin), thus creating minute channels through which a topically applied drug can pass. This method allows a wider range of drugs to be introduced to the site of action while still providing the benefit of by passing first-pass metabolism and thereby improving bioavailability. One key advantage for patients is that use of the microneedle patches does not induce a pain response because they do not penetrate to the dermal layer of the skin which is where the nerve cells and capillaries are located.

a = 400µm, b = 800µm, c = ~450/500µm, d = ~250-350µm




Diagrammatic representation of a microneedle array and its geometrical parameters: (a) height of MNs in array (b) interspacing of MN tips (c) interspacing of MN bases and (d) width of MN at base.

Preliminary in vitro studies using human skin of the rate of permeation of two medicinal products (lidocaine and inulin) with microneedle patches showed that microneedle treatment increased the skin permeation of both compounds assessed. In addition, the permeation of lidocaine also showed a large reduction in lag time which would hasten the onset of local anaesthesia (Ref 3-4). Based on the biological principles of microneedles, they offer the possibility, if not potential, of improving the degree and depth of anaesthesia of topically applied anaesthetics in dentistry.

The aim of this study is to look at the effect on patient perceived pain resulting from infiltration injection with local anaesthetic in a dental syringe with prior application of topical anaesthetic to the oral mucosa on microneedle patch compared to a patch with no microneedles. The oral sites chosen for the study are the upper palatal area and the upper anterior buccal sulcus. These sites represent two areas, which from clinical experience, are difficult to provide pain free dental injections even with prior application of topical anaesthetics. In addition, the safety of the microneedle needle patches will also be considered through the visual oral soft tissue examination performed by the dentist at each visit and the recording of adverse events.

Current standard clinical practice for the application of oral topical anaesthetic is to extrude the gel directly onto a cotton wool roll then rub into the oral mucosa to be treated. For this study, the topical anaesthetic gel will be dispensed onto patches, with or without microneedles, then applied directly to the oral mucosa to be tested. The topical anaesthetic application method being investigated in this study is the patch containing microneedles. It was decided that the most relevant clinical comparator/control application method was to use a patch again, but with no microneedles. The use of cotton wool was not deemed a relevant control as the amount of topical anaesthetic applied to the oral mucosa could not be easily controlled. This is due to a degree of absorption of the gel into the cotton wool thus reducing the amount available for application to the mucosa. This does not happen with the use of the patch thus all topical anaesthetic dispensed is applied to the treatment area.

## 4.0 METHOD AND MATERIALS

### 4.1 PARTICIPANT RECRUITMENT

Prior to the study NHS Ethics and MHRA approvals will be obtained. Potential participants will be sought from private dental patients of Rhiwbina Dental Surgery.

## 4.2 STUDY DESIGN

This is a randomised, 2 treatment, double blind design, with respect to the clinical assessor and subject, split mouth, crossover design with a negative control (patch with no microneedles).

Potential participants will be invited to attend a screening visit. At this visit participants will be asked to read and sign a Participant Information Sheet and Consent Form prior to any study procedures being performed. They will be given ample time to decide if they wish to participate in the study. All participants will be private dental patients of Rhiwbina Dental.

A dentally qualified clinician will record the participant's demographics, medical history, current/concomitant medications, perform an oral soft tissue examination and ensure the participant fulfils the inclusion and exclusion criteria for the study. Two areas of the mouth will be identified for assessment during the study. The areas of the mouth will be identified as S1 or S2. Site S1 will be left or right palatal mucosa adjacent to the premolar area and S2 will be left or right upper buccal mucosa adjacent to the upper lateral incisor area.

Participants who successfully fulfil all the necessary entrance criteria will be provided with training by study staff on how to use a VAS record sheet and randomised on to the study to receive treatment combination A or B at in a random order according to a predetermined randomisation schedule supplied by the study statistician. The screening visit and first treatment visit will occur at the same visit. The treatment possibilities are outlined below:

**Treatment A** The application of a 5% topical lidocaine gel to one of the identified areas within the participants mouth using a microneedle patch. The microneedle patch will be applied to the oral mucosa of the identified site for 3 minutes, followed by infiltration with local anaesthetic to one of the identified areas within the participants mouth.

**Treatment B** The application of a 5% topical lidocaine gel to one of the identified sites within the participants mouth using a patch with no microneedles. The patch with no microneedles will be applied to the oral mucosa of the identified site for 3 minutes, followed by infiltration with local anaesthetic to one of the identified areas within the participants mouth.

The chosen sites will be: **S1;** left and right palatal mucosa adjacent to the premolar area or **S2;** left and right upper buccal mucosa adjacent to the upper lateral incisor area. Each participant at the first visit will have either **S1** or **S2** sites allocated for treatment. For example, **Treatment A** will be allocated to **S1 left side** and **Treatment B** to **S1 right side or** vice versa. At the second visit, 2 weeks (+/- 3 days) after the first visit, **Treatment B** will be allocated to **S2 left side** and **Treatment A** to **S2 right side.** Both sides of the mouth for S1 or S2 will be treated at the same. After each treatment participants will be asked to make pain assessments relating to needle insertion into the oral mucosa and the giving of the local infiltration anaesthetic.

### 4.3 STUDY POPULATION

It is envisaged that a sufficient number of potential participants will be screened in order to randomise 16 onto the study. The dental practice will display a poster informing private patients of Rhiwbina Dental Surgery that a new trial is taking place and details of the study coordinator if they require more details.

### 4.4 ASSESSMENT METHODS

**Three minutes post-topical anaesthetic application:**
**Pain Assessment.**
Pain assessments will be performed after application of the topical anaesthetic for 3 minutes. Each test will be performed sequentially i.e. 3 separate needle insertions, with pain assessments recorded by the participant using a Visual Analogue Scale (VAS) and a verbal pain grading after each test. The level of pain at S1 or S2 will be assessed as follows:

**Test I**. A short dental needle, mounted on a dental syringe containing a cartridge of 2% lidocaine hydrochloride and 1:80,000 adrenaline, will be used to penetrate the oral mucosa at the treated site and the patient asked to score the pain using a VAS rating scale and by verbal grading of zero, mild, moderate or severe.

**Test 2.** The same needle will be inserted through the oral mucosa and down to contact bone. Pain will be assessed as in Test 1.

**Test 3.** The same needle will be again inserted through the oral mucosa and the cartridge of local anaesthetic will be injected into the site. Pain will be again assessed as in Test I.

Following enrolment on to the study, participants will be given written and verbal instructions on the VAS and how to complete it. They will be given a test sheet to practice scoring which will be measured and checked by the clinician to ensure the participant understands how to complete the VAS form, see appendix 1.

## 5.0 OBJECTIVES

### 5.1 PRIMARY OBJECTIVE

To compare the level of perceived pain in healthy participants, when a proprietary topical 5% lidocaine dental gel is applied to the oral mucosa with a microneedle patch and a patch with no microneedles, prior to infiltration with local anaesthesia.

### 5.2 SECONDARY OBJECTIVE

To assess the safety of the patches when applied to the oral mucosa.

## 6.0 STUDY PERSONNEL AND RESPONSIBILITIES

**PRINCIPAL INVESTIGATOR:**

| | |
|---|---|
| Name: | Prof N West |
| Address: | Department of Oral and Dental Science<br>University of Bristol Dental School<br>Lower Maudlin Street<br>Bristol BS1 2LY |
| Tel: | 0117 342 9368 |
| Fax: | 0117 342 4100 |

**CO-INVESTIGATOR:**

| | |
|---|---|
| Name: | Dr N. Claydon |
| Address: | Rhiwbina Dental<br>25 Heol-Y-Deri<br>Rhiwbina<br>Cardiff<br>South Glamorgan<br>CF14 6HB |

**CLINICIAN / STUDY DENTIST:**

| | |
|---|---|
| Name: | Dr N. Claydon/Dr S Daley |

**STUDY MEDICAL STATISTICIAN:**

| | |
|---|---|
| Name: | Robert G. Newcombe PhD CStat FFPH<br>Emeritus Professor of Biostatistics<br>Cardiff University |
| Address: | 21 King George V Drive West<br>Cardiff<br>CF14 4EE |
| Tel: | 029 2075 6723 |

**STUDY SPONSOR:**

| | |
|---|---|
| Name: | Innoture Limited |
| Address | 2nd Floor, 58 Davies Street, Mayfair, London, W1K 5FJ |

**STUDY SITE:** Rhiwbina Dental
25 Heol-Y-Deri
Rhiwbina
Cardiff
South Glamorgan
CF14 6HB

## 7.0 INCLUSION AND EXCLUSION CRITERIA FOR SELECTION OF PARTICIPANTS

### 7.1 Inclusion Criteria

To be included in the study, subjects must:

1. be aged 18 years and over, of either gender and in good health;
2. be willing and physically able to carry out all study procedures;
3. be willing and able to give Informed Consent and provide details of any medical history;
4. be available for all of the study dates
5. have a good standard of oral hygiene and gingival health
6. must have 1 premolar or canine in each quadrant that has no/minimal restorations

### 7.2 Exclusion Criteria

Individuals with the following conditions will not be eligible for participation in the study:

1. presence of soft tissue oral pathology;
2. presence of advanced periodontal disease;
3. Individuals with any serious health conditions, that would preclude participation, in the professional judgement of the Study Dentist;
4. individuals with known allergies or sensitivities to local anaesthetics
5. have participated in another clinical trial in the last 30 days
6. in the opinion of the investigator unable to comply fully with the trial requirements.
7. the subject is an employee of the Sponsor or the site conducting the study.

### 7.3 Withdrawal of Participants from the Clinical Trial

Participants will be advised at the start of the study that they may withdraw from the study at any time, without giving a reason. Participants will be told that they may be removed from the study by the Study Dentist without prior notice for medical reasons (see above), and also if the participant fails to report to the study site when scheduled, unless suitable alternative arrangements can be made (subject to the discretion of the Investigator).

The Investigator will be responsible for documenting all cases of withdrawals. The Investigator will also make every reasonable effort to ascertain the reason for withdrawal.

### 7.4 Participant Remuneration

The participants that complete the study will receive £50 which relates to £25 per visit completed. If for any reason, the study should be terminated before its expected completion date, participants will be reimbursed in full as will participants who are withdrawn due to an adverse event. If participants do not complete the whole study, they will be paid on a pro rata basis at the discretion of the Investigator.

## 8.0 TREATMENT PLAN AND METHODS

### 8.1 Study Schedule and Administration

The 2 treatment procedures to be undertaken over 2 visits are:

A. Microneedle patches with topical anaesthetic to assess patient perceived pain at chosen buccal and palatal oral mucosa sites and following insertion of a needle into the oral mucosa and administration local anaesthetic using infiltration injection.

B. Patches with no microneedles with topical anaesthetic to assess patient perceived pain at chosen buccal and palatal oral mucosa sites and following insertion of a needle into the oral mucosa and administration of local anaesthetic using infiltration injection.

0.5g of the topical anaesthetic gel will be dispensed to the microneedle patch and patch with no microneedles prior to application of the patch to the oral mucosa. The topical anaesthetic gel will contain 5% lidocaine with 0.15 g of cetrimide/100g.

### 8.2 Allocation of Treatments and Randomisation Procedures

Eligible, consenting participants will be randomised equally to one of four possible treatment groups (1-4) for the 2 treatment procedures being assessed as shown below:

| | **Visit 1** | | | | **2 weeks ± 3 days** | **Visit 2** | | | |
|---|---|---|---|---|---|---|---|---|---|
| | **Left Side** | | **Right Side** | | | **Left Side** | | **Right Side** | |
| Treatment group | Palatal mucosa | Buccal mucosa | Palatal mucosa | Buccal mucosa | | Palatal mucosa | Buccal mucosa | Palatal mucosa | Buccal mucosa |
| 1 | A | | B | | | | B | | A |
| 2 | B | | A | | | | A | | B |
| 3 | | A | | B | | B | | A | |
| 4 | | B | | A | | A | | B | |

### 8.3 Participant Restrictions/Concurrent Treatments

There are no restrictions placed on the participants during this study, other than those stated in the exclusion criteria.

### 8.4 Screening and Enrolment Procedures

At the first visit to the study site, participants will be given time to read the Informed Consent Form/Information Sheet and given the opportunity to ask questions about the study. They will then be asked to sign the form and to complete a Medical History Questionnaire.

The clinician will check the documents to assess if all the Medical History eligibility criteria are met. They will then carry out an oral examination and check that all the other eligibility criteria are met. Participants who are suitable for the study will be invited to participate in the study and the first procedure will commence.

The participants GDP (dentist) will be notified of their participation in the study (participant consent given). Study Staff will treat all study documentation as strictly confidential.

### 8.5 Assessments for Efficacy

Data recorded at the screening visit will be recorded into paper CRFs. The clinician and Scribes will initial and date the CRFs. All data must be recorded directly, promptly and legibly in black ink. Any corrections must be made in such a way that the correction does not obscure the original entry.

Data will be transcribed into an excel spreadsheet and transferred to the study statistician in this form.

Mandatory cross-infection control procedures and GCP will be followed.

### 8.6 Assessments for Safety

The clinician will carry out an oral soft tissue examination at the screening visit and at all the assessment visits, both before and after treatment with the patches. Any findings (deviations from normal) will be recorded as adverse events on the Case Report Form provided and will be signed and dated by the clinician. In addition, participants will be asked to report any observations made in connection with using the study regimen (see also Adverse Events).

### 8.7 Compliance Checks

All participants will be asked at each visit as to their adherence to the clinical investigation plan. All answers will be recorded in their Case Report Form.

## 9.0 STUDY MATERIALS

### 9.1 Test Products and Dosage

The products used in the study will be as follows:

1. Microneedle patch
   (Innoture Ltd, London)

2. Patch with no microneedles
   (Innoture Ltd, London)

3. Lidocaine topical dental gel: 5% lidocaine with 0.15 g of cetrimide/100 g
   (Septodont Ltd, Maidstone, Kent, ME16 0JZ)

4. Infiltration anesthesia - 2% lidocaine hydrochloride + 1 in 80,000 adrenaline
   (Septodont Ltd, Maidstone, Kent, ME16 0JZ).

**Microneedle Patch**

A 2.4x2.4cm square patch containing a microneedle array of 2x2cm to the center, 400 microns height with an 800 micron pitch.

This will be provided in its standard packaging to the study site by the sponsor. It will be labeled appropriately, with clinical investigation plan number, expiry date, manufacture date and lot number.

**Patch with no Microneedles**

2.4x2.4cm square patch with no microneedles to the centre.

This will be provided in its standard packaging to the study site by the sponsor. It will be labeled appropriately, with clinical investigation plan number, expiry date, manufacture date and lot number.

The manufacturer's expiry dates for the test products, as appears on each product, will be documented in the study file.

**Lidocaine topical dental gel:**

This will be provided in its standard packaging by the study site. 0.5g of lidocaine gel will be dispensed directly to the centre of either the microneedle patch or patch with no microneedles (this will be

confirmed by weighing the lidocaine and patch). The patches will then be applied directly to the area of the mouth to be tested. The patches should be pressed to the area, then released slightly and then pressed again and held in place for 3 minutes, so that the whole patch area receives pressure. After this time, the patches will be removed, and the pain assessments will be conducted.

**Infiltration anesthesia:**
This will be provided in its standard packaging by the study site. A standard dental syringe and short needle will be used. Infiltration anesthesia will be injected down to the bone of the area of the mouth being tested following the pain assessment tests 1-2.

### 9.2 Storage and Disposition of Test Products
The microneedle patches, patches with no microneedles, lidocaine topical gel and the infiltration anaesthetic will be stored at room temperature in a locked area in the clinical unit at the study site which is not accessible to people outside the study team. Following use, the products will be disposed of as sharps clinical waste. Patches not used after completion of the study will be accounted for and returned to Innoture Ltd. Lidocaine topical gel and the infiltration anaesthetic not used after completion of the study will be accounted for and disposed of.

### 9.3 Precautions/Overdosage
The test products will only be used in the clinical unit under the supervision of study staff.

### 9.4 Other Study Supplies
The Informed Consent forms, Medical History, CRF's, Subject Withdrawal and Adverse Event forms will be supplied by the Study Site Team.

## 10.0 ADVERSE EVENTS

### *10.1 Adverse Event and Medical Device Adverse Effects*
An adverse event (AE) is any untoward medical occurrence in a subject whether or not related to study product or the study procedures. Adverse events include any occurrence that is new in onset, an exacerbation of a pre-existing condition and clinically significant laboratory values.

A Medical Device Adverse Effect (MDAE) is any untoward medical occurrence in a subject which is related to the study product. Medical Device Adverse Effects also include any adverse events resulting from insufficient or inadequate instructions for use (IFUs) and any event resulting from use error or from intentional misuse of the medical device.

No significant adverse effects or medical device adverse effects are expected during the study. AEs and MDAEs will be monitored and recorded throughout the study.

### 10.1.1 Exceptions
The following medical occurrences will not be reported as AEs in any study sponsored by Innoture;

- Pre-treatment Adverse Events; Any medical occurrence that occurs after informed consent, but before first administration of study product or first study procedure is considered as medical history and only recorded as an AE if it worsens during the study.

- Pre-existing medical condition; Events that occur with comparable frequency and severity to the subject's baseline condition are reported as medical history, not AEs.
- Pregnancy; This is not an AE however the PI must report any pregnancies to Innoture for advice regarding the appropriate course of action.
- Overdose; If the amount of study product that is taken or applied is higher than that stated in this clinical investigation plan, this is not an AE. However, any clinical sequalae (signs or symptoms) of the overdose must be reported as an AE. A MDAE must be recorded if the subject is assigned to the investigational product.

### *10.2 Serious Adverse Event*

A serious adverse event (SAE) is an AE that results in any of the following outcomes: death; a life-threatening event; in-patient hospitalisation; prolongation of existing hospitalisation; a persistent or significant disability/incapacity; a congenital anomaly or birth defect. Any other important medical event may be considered a SAE when the event may jeopardise the subject and may require medical or surgical intervention to prevent one of the outcomes listed previously. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, or convulsions that do not result in in-patient hospitalisation. Just as a stable pre-existing condition is not an AE, hospitalisation for elective treatment (e.g. cosmetic or dental procedure) of a pre-existing condition that did not worsen from baseline is not an SAE.

### *10.3 Severity and Relatedness of Adverse Events*

An AE will be recorded only once, with the most extreme severity. Severities are defined as:

| | |
|---|---|
| **Mild** | Awareness of symptoms which require minimal or no treatment and do not interfere with daily activity |
| **Moderate** | Discomfort or low level of interference which is enough to interfere with but not prevent daily activity |
| **Severe** | Interrupted or unable to perform usual daily activity and usually requires treatment. |

The likelihood that the AE was related to the study product or study procedure is defined as;

| | |
|---|---|
| **Not Related** | The AE is clearly due to an alternative cause, even if this cannot be definitely identified. Alternative causes include disease or environmental factors. |
| **Unlikely** | A connection between the AE and the study product or procedure is unlikely.<br>• The AE has a relationship in time to the study product or procedure<br>• An alternative cause (e.g. disease or environmental factors) is the most likely explanation, even if this cannot be identified. |
| **Possibly** | A connection between the AE and the study product or procedure cannot be ruled out with certainty.<br>• The AE has a relationship in time to the study product or procedure<br>• An alternative cause (e.g. disease or environmental factors) seems likely or possible or there is significant uncertainty about the cause of the AE. |

| | |
|---|---|
| **Probably** | There is a high degree of certainty that the AE is related to the study product or procedure.<br>• The AE has a relationship in time to the study product or procedure<br>• A possible alternative cause may be present.<br>• AE disappears or decreases on withdrawal or reduction of study product or procedure (if performed). |
| **Definitely** | The AE is clearly related to the study product or procedure.<br>• There is a strong relationship in time<br>• An alternative cause is unlikely<br>• AE disappears or decreases on withdrawal or reduction of study product or procedure (if performed) |

### *10.4 Reporting of Adverse Events*

All minor adverse events (AEs) will be recorded in the Case Report Form (CRF) and submitted to Innoture. The site staff must maintain source documents to fully record all AEs.

Additionally, Serious Adverse Events (SAEs) and AEs that may affect the safety or continued participation of subjects on the study must be reported immediately. A SAE must be reported to Innoture within 24 hours of the site staff becoming aware of the event. The contact details for reporting any expedited AE are given in the Contacts section of this clinical investigation plan.

### *10.5 Follow-up of Adverse Events*

If an AE is ongoing at the end of the study, follow-up will be performed until the AE has resolved, unless the PI and the Innoture contact named in the clinical investigation plan agree that no further follow up is necessary. Follow-up may take the form of subject visits, a referral to another specialist, site telephone calls to the subject or letters from the treating physician. For expedited AEs, if applicable, the PI will submit follow up reports on additional expedited report forms.

The PI or designee must comply with the specific reporting requirement(s) of the ethics committee, reporting as a minimum any Serious Unexpected Suspected Adverse Reaction (SUSAR) which is an unexpected SAE that may be related to study product or procedure.

### *10.6 Pregnancy Testing*

There is no known risk to the foetus associated with the use of the study products and/or procedures in this study. It is not required to take any additional contraceptive precautions or perform any pregnancy testing prior to inclusion of females of child bearing potential into this study.

### 10.7 Serious Adverse Event Reporting

The investigator shall immediately after awareness (and in any event, not later than 24 hours) inform the sponsor of all SAE's occurring in the study using the following contact details:

SAEreporting@innoture.co

**At the end of the study, the investigator has to inform the sponsor details of all adverse events that occurred.**

## 11.0 DATA MANAGEMENT AND STATISTICAL ANALYSES

### 11.1 Rationale for Sample Size

This study with 16 volunteers has 80% power to detect a difference in analgesia efficacy between microneedle administration and administration without microneedles at the conventional 5% two-sided alpha level provided this difference is at least 0.7 times the standard deviation representing the variation of this difference between different volunteers.

### 11.2 Data Capture and Data Management

There will be a CRF for each subject randomised into the study. It is the responsibility of the PI to ensure the completeness and accuracy of the CRF and to authorise only trained members of staff to complete the CRF.

The CRF will include:

- Demographics
- Inclusion/Exclusion criteria assessment
- Soft tissue pathology CRF
- VAS training
- VAS pain assessment
- Adverse events

The CRF must be completed legibly, using a black ballpoint pen. Erroneous values and/or text must not be obliterated. Instead, the error must be crossed out with a single line, the correct value/text added, and the correction signed or initialled and dated.

There will be study specific records to record the identification of any data to be recorded directly on the CRFs or other written or electronic record of data, and to be considered to be source data.

All site staff must ensure that the subject's anonymity will be maintained. On all documents that are to be submitted to Innoture, subjects must be identified only by an identification code and not by their names. The PI or designee must keep a separate confidential enrolment log that matches identifying codes with the subject's names and addresses. The PI or designee must maintain these documents at the site.

It is the responsibility of the PI or designee to maintain adequate clinical study records. Copies of all clinical study material must be archived for a period of at least 15 years after the end of the study (or more as legally required) or until informed by Innoture that the documents can be destroyed. All documents must be archived in a secure place and treated as confidential material.

The Investigator will keep the CRF's securely in a lockable cupboard or filing cabinet. All CRF's will be maintained in an up-to-date condition at all times.

### 11.3 Statistical Analyses

Two sites per subject will be studied, so the 16 subjects will provide 32 treatment site analysis points. Separate statistical analyses will be performed for each outcome measure for the results from palatal sites and the results from buccal sites, for the three challenges (tests 1, 2 & 3) described in section 4.4. Summary statistics, based on all 16 volunteers, will be calculated for each outcome measure for scores

immediately post-treatment, for administration to the mucosa and to the bone, for each of the following series of results:

Sites with microneedle use.
Sites with no microneedle use.

Paired differences in scores, microneedle minus no microneedle use.

The statistical significance of the microneedle minus comparator differences will be assessed by the Hills-Armitage method: right minus left differences will be calculated for each subject, and compared between subjects who have microneedles used on the right side of the mouth and those who have microneedles used on the left side using a 2-sample t-test. Estimated differences between treatments will be reported, with 95% confidence intervals, in addition to p-values. In the event of substantial departure from Gaussian distributional form, analogous non-parametric analyses will also be considered.

All adverse events will be listed in the Clinical Investigation Report.

## 12.0 ETHICAL CONSIDERATIONS

### Ethics Committee Review

NHS ethical approval and MHRA approval will be obtained prior to the start of the study.
The PI or designee must submit a copy of the clinical investigation plan, subject information sheet and consent form to an Independent Ethics Committee or Institutional Review Board who must provide written approval before study specific procedures commence. The IEC/IRB must also approve any other information that is given to subjects such as advertisements and may require other documents such as study product documentation.

Any modification to the agreed clinical investigation plan must be agreed by both Innoture and the PI and approved in writing by the IEC/IRB. Written approval must be obtained from the IEC/IRB before any amendment is implemented, unless immediate change is required to eliminate hazards to the subjects or when the change(s) involves only logistical or administrative aspects of the study (e.g., change of monitor(s), telephone number(s)).

The PI or designee must obtain informed consent from each subject participating in the study, after explanation of the aims, methods, benefits and potential hazards of the study. The consent must be obtained before any study-specific procedures are performed. It must be made completely and unambiguously clear to each subject that they are free to refuse to participate in the study, or that they can withdraw their consent at any time and for any reason, without incurring any penalty or withholding of treatment. The subject must be given their own copy of the information sheet and signed consent form. The original signed informed consent must be kept on file by the PI or designee.

## 13.0 REGULATORY REQUIREMENTS AND INVESTIGATOR OBLIGATIONS

### 13.1 GCP Statement

It is the responsibility of the PI to ensure that the study is conducted in accordance with the principles of Good Clinical Practice, the latest ratified version of the Declaration of Helsinki and according to applicable local laws and regulations concerning studies conducted on human subjects which are outside of the definition of a medicinal product or medical device.

Quality assurance audits may be performed by the University, the sponsor or any ethics committee or regulatory authority during the course of the study or after study completion.

### 13.2 Premature Termination of the Study

If the study must be terminated before the scheduled end (e.g. because of serious adverse events) the Investigator will notify the Ethics Committee in writing.

### 13.3 Clinical Study Report

The Investigator will provide a final study report. This must include:

-the number of subjects enrolled into and completing the study,
-subjects dropped out or withdrawn (stating reasons)
-a report of all adverse events
- clinical investigation plan deviations or violations
-results and conclusions

The Statistician will be responsible for the provision of the statistical analysis for the final report.

### 13.4 Monitoring

The study monitoring will be done by the sponsor according to the sponsors internal SOP's.
Given adequate supervision and guarantee of confidentiality, the investigator will allow the monitor to check the CRFs for completeness and consistency and to check the informed consent forms in order to verify observance to the clinical investigation plan.

### 13.5 Compensation for Medicine-Induced Injury and Indemnification Requirements

All participants will be insured against any injury caused by the study products by the sponsor according to legal requirements. The participants will be informed about the insurance and requirements on their part.

### 13.6 Publication Policy

The results of this study will be published externally in a peer reviewed scientific journal subject to the contractual arrangements agreed with the sponsor.

## 14.0 REFERENCES

(1). Lidocaine in: British National Formulary (BNF); pp714-715
BMJ Group and RPS publishing, London

(2). Lidocaine (interactions) in: British National Formulary (BNF); p766

(3) Dabboue H, Builles N, Frouin E, Scott D, Ramos J, Marti-Mestres G. Assessing the impact of mechanical damage on full thickness porcine and human skin using an in vitro approach. BioMed Research International 2015; 434623, 10 pages

(4). Assessment of the performance of prototype microneedles 1: evaluation of permeation of radiolabelled lidocaine and inulin through human skin in vitro with and without microneedles and pressure. (Study report No: F01/01/05)

## Appendix 1: Investigator/Designee Instructions for VAS Training Exercise

Participants will be given instructions for using the VAS and asked to complete the VAS line scale training exercise form. The investigator or designee should read the instructions aloud while the participant reads along. Participants will be permitted to ask questions. However, most questions should be answered by rereading the appropriate section of the instructions. The investigator, or designee, will then determine whether the participant understands how to use the VAS based on the line scale training exercise answers and the criteria below.

### Interpretation of the VAS Training Exercise

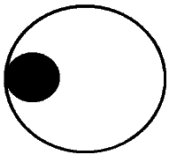
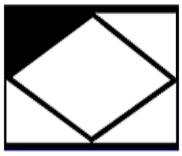
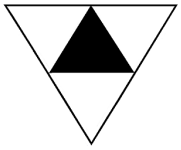
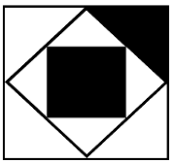
The objective of this exercise is not to determine whether the participant can get the exact answers, but to determine whether they understand the concept. Therefore, the following general criteria are suggested:

- Are the majority of the marks within ±10 mm of the correct value?
- Are the marks generally toward the correct side of the scale? In particular, is the first mark toward the left end, the second toward the right end and the third in the middle? Do the last three responses form a monotonically increasing sequence across the middle of the scale? Is item 4 ≥ item 1? Is item 5 ≥ item 8?

If participants appear unable to interpret the level of shading, the investigator or designee should talk them through the first three figures using questions such as, “is it more or less than half shaded?” and “is it a lot more or a lot less than half shaded?” If the marks are generally correctly ordered, but far from their true positions, the investigator or designee should try to get the participant to verbalize why they placed the marks as they did. However, the investigator or designee should be careful not to pressure the participant to change their responses. One approach would be for the investigator or designee to start with an item that the participant did well, ask about that and then continue by asking about one that seems off.

If participants are not able to deal with the concept of proportions as presented in the exercise, it is unlikely that they will provide useful responses on the subjective and clinical response questionnaires. These participants should be disqualified.

# Answer Key

| | | |
|---|---|---|
| No Shading — Complete Shading |  | 10 |
| No Shading — Complete Shading |  | 90 |
| No Shading — Complete Shading |  | 50 |
| No Shading — Complete Shading |  | 13 |
| No Shading — Complete Shading |  | 75 |
| No Shading — Complete Shading |  | 25 |
| No Shading — Complete Shading |  | 38 |
| No Shading — Complete Shading |  | 67 |

## Appendix 2: Participant Instructions for VAS Training Exercise

We will be asking you to rate your oral health using a line scale such as the one below. You should respond by making a single vertical mark on the line.

NO PAIN _____ WORST PAIN IMAGINABLE

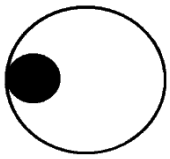
If you experience no pain or discomfort, you should make your mark at the left end of the line ("No Pain"). If you couldn't imagine the pain being any worse, you should make your mark at the right end of the line ("Worst Pain Imaginable"). If your discomfort pain falls somewhere between these two extremes, you should mark a point on the line that represents how bad the pain is relative to these to end-points. If you think that it is half-way between No Pain and the Worst Pain Imaginable, then you would mark the middle of the line.

When we test your teeth, it is important to distinguish between sensation ("I feel something") and discomfort or pain ("It hurts"). A sensation that does not hurt should be rated as "No pain."

In all the evaluations, there are no right or wrong answers; only your opinion counts. Answer carefully, but keep in mind that first impressions are often the most accurate.

In order to give you some practice with this scale, we would like you to complete the exercise on the next page. In this exercise you will be estimating how much of the total area of a series of shapes has been shaded. If none of the figure has been shaded, you should mark the left end of the line. If the figure has been completely shaded, you should mark the right end of the line. If only part of the figure has been shaded, you should make a vertical mark at the appropriate point on the line. For example, if half of the figure has been shaded, you should make your mark in middle of the line. If a quarter of the figure has been shaded, you should make your mark one quarter of the distance from the left end of the scale, etc. Please remember, we are asking you to estimate the area shaded and then to estimate the position of your mark on the line.

Please make a single vertical mark at the point on the line that best represents the degree to which the figure is shaded.

| | |
|---|---|
| No Shading ——— Complete Shading |  |
| No Shading ——— Complete Shading |  |
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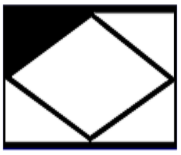
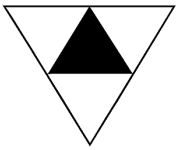
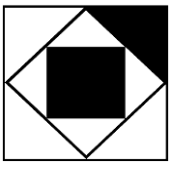
| No Shading ——— Complete Shading |  |
| No Shading ——— Complete Shading |  |
| No Shading ——— Complete Shading |  |
| No Shading ——— Complete Shading |  |
| No Shading ——— Complete Shading |  |

## APPENDIX 3a – Topical Anaesthetic

# Xylonor Gel

### Qualitative and quantitative composition

Lidocaine ..... 5 %
Cetrimide ..... 0.15 %

For excipients, see List of excipients.

### Pharmaceutical form

Gingival gel.

### Therapeutic indications

XYLONOR GEL is indicated for the production of topical anaesthesia in the buccal cavity, especially in the following procedures:

- Anaesthesia of the mucous membrane before injection, lancing of abscesses, or scaling.
- Surface anaesthesia for the extraction of mobile, deciduous or permanent teeth.
- Prevention of gagging during impression taking.

XYLONOR GEL is indicated in adults, and in children and adolescents aged 4 to 18 years of age.

### Posology and method of administration

Topical use only. Gingival route.

**Recommended doses:**

To be used only once from 0.1 to 0.5 g by topical local application with a cotton pellet.

**Dosage schedule:**

Under aseptic conditions, extrude about 2 mm (equivalent to approximately 0.1 g) of gel from the tube onto a cotton pellet. Then massage previously dried mucosa. Removal of excess saliva with cotton rolls or saliva ejector minimises dilution of the gel and permits maximum penetration.

Depending upon the surface to be anaesthetized and the status of the patient (age, physical condition), the dose of the gel used may be increased, up to 0.5 g.

Do not use in children under 4 years of age.

### Contraindications

XYLONOR GEL is contraindicated in patients with history of hypersensitivity to local anaesthetics of the amide type, to cetrimide or to other components of the gel.

### Special warnings and precautions for use

The safety and effectiveness of lidocaine depend on proper dosage, correct technique, adequate precautions and readiness for emergencies. The lowest dose that results in effective anaesthesia should be used to avoid high plasma levels and serious adverse effects. Debilitated, elderly patients, acutely ill patients and children should be given reduced doses commensurate with their age and physical status.

XYLONOR GEL should be used with caution if there is sepsis or extremely traumatised mucosa in the area of application, since under such conditions, there is potential for rapid systemic absorption of both lidocaine and cetrimide.

It should be used with caution in persons with known drug sensitivities.

There is a risk of anesthesiophagia leading to bites (lips, jaws, tongue): patients should be advised to avoid chewing-gum or any type of food as long as the anesthesia persists. It is recommended that the patient does not take any food before he has recovered sensitivity.

There is a possibility of positive results on doping tests perfomed on sportsmen.

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## Interaction with other medicaments and other forms of interactions

Soaps and anionic surfactants are known to decrease the bactericidal activity of cetrimide.

## Pregnancy and lactation

**Pregnancy**

Reproductive studies have been performed in rats and rabbits without evidence of harm to the animal foetus. However, the safe use of lidocaine in humans has not been established with respect to possible adverse effects upon foetal development. Careful consideration should be given to this fact before administering this drug to women of childbearing potential, particularly during early pregnancy.

**Breast-feeding**

Problems in humans have not been documented. However, risk-benefit must be considered.

## Effects on ability to drive and use machines

Not applicable.

## Undesirable effects

Systemic adverse reactions are extremely rare with lidocaine ointments. However, as with any local anaesthetic, adverse reactions may result from high plasma levels due to excessive dosage, or rapid absorption, or may result from hypersensitivity, idiosyncrasy or diminished tolerance.

**- Central nervous system reactions**

CNS reactions are excitatory and/or depressant, and may be characterized by nervousness, dizziness, blurred vision and tremors, followed by drowsiness, convulsions, unconsciousness, and possibly, respiratory arrest. The excitatory reactions may be very brief or may not occur at all, in which case the first manifestations of toxicity may be drowsiness, merging into unconsciousness and respiratory arrest.

**- Cardiovascular system reactions**

Cardiovascular reactions are depressant and may be characterized by hypotension, myocardial depression, bradycardia, and possibly, cardiac arrest.

**- Allergic reactions**

Allergic reactions may occur as a result of sensitivity to local anaesthetics. Anaphylactoid type symptomatology and reactions, characterized by cutaneous lesions, urticaria, and edema, should be managed by conventional means. The detection of potential sensitivity by skin testing is of limited value.

At the concentrations used on the skin and mucous membranes (0.1 - 1%), cetrimide does not generally cause irritation, but some patients become hypersensitive to cetrimide after repeated applications.

## Overdose

The normal application of XYLONOR GEL according to its directions for use is very unlikely to result in an overdose. However, in the improbable case that symptoms of an overdose do occur, the procedure for treatment is described below.

Treatment of a patient with toxic manifestations consists of assuring and maintaining a patent airway, supporting ventilation with oxygen, and assisted or controlled ventilation (respiration) as required. This usually will be sufficient in the management of most reactions. Should a convulsion persist despite ventilatory therapy, small increments of anticonvulsive agents may be given intravenously. Examples of such agents include benzodiazepine (eg., diazepam), ultrashort acting barbiturates (eg., thiopental or thiamylal), or a short acting barbiturate (eg., pentobarbital or secobarbital). Cardiovascular depression may require circulatory assistance with intravenous fluids and/or vasopressors (eg., ephedrine) as dictated by the clinical situation.

## Pharmacodynamic properties

Anaesthetics for dental use.

ATC code: N (Central Nervous System).

XYLONOR GEL contains two therapeutic agents:
1. Lidocaine stabilises the neuronal membranes and prevents the initiation and conduction of nerve impulses, thereby effecting local anaesthetic action. It does not contain a paramino group.

2. Cetrimide is an antiseptic of the quaternary ammonium group with both bactericidal and detergent properties.

It has bactericidal activity against gram-positive organisms but is less effective against some gram-negative organisms; strains of Pseudomonas aeruginosa are particularly resistant.
XYLONOR GEL combines both these ingredients in a non-irritant, water miscible excipient. This gel effects local topical anaesthesia. The onset of action is 2 - 5 minutes.
The duration of anaesthesia is 30 - 60 minutes. This anaesthetic effect is complemented by a disinfectant action.

## Pharmacokinetic properties

1. Lidocaine is metabolized mainly in the liver, and excreted via the kidneys. Approximately 90 % of lidocaine administered is excreted unchanged. The primary metabolite in urine is a conjugate of 4-hydroxy-2,6-dimethylaniline.

2. Cetrimide penetrates into the superficial layer of the epidermis.

Absorption through the gastro-intestinal tract is poor, more than 90 % of the dose ingested is excreted in the feces.

## List of excipients

Saccharin, spearmint oil and macrogol.

## Incompatibilities

None stated.

## Shelf life

24 months.

## Special precautions for storage

Store below 25 °C.
Keep tube tightly closed.

## Nature and contents of containers

Aluminium tube with internal epoxy varnish and polyethylene screw cap containing 15 g of gel.

## Special precautions for disposal

Always discard any unused portion taken from the tube. Tightly close after use.

## Marketing authorisation holder

SEPTODONT Ltd.
Units R & S
Orchard Business Centre
St Barnabas Close
Allington, Maidstone, Kent ME16 0JZ
UK

## Marketing authorisation number

PL 08313/0027

## Date of first authorisation/ renewal of the authorisation

12/02/1988 - 12/02/1993 - 20/11/1998

## Date of revision of the text

13/12/2012

SEPTODONT
58, rue du Pont de Créteil
94100 Saint-Maur-des-Fossés - France
Tel.: 33 (0) 1 49 76 70 00

# Xylonor gel

## Gingival gel
**Lidocaine and cetrimide**

**PATIENT INFORMATION LEAFLET**

Read all of this leaflet carefully before you start using this medicine.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your dentist.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your dentist, doctor or pharmacist.

**In this leaflet:**


### 1. What XYLONOR GEL is and what it is used for

XYLONOR GEL is used to obtain a local anaesthesia of the lining of the inside of the mouth (buccal mucosa) before performing dental procedures.
It contains two active ingredients:
- lidocaine, a local anaesthetic, which numbs the painful area temporarily,
- cetrimide, an antiseptics, which kills any microorganisms that are present.

XYLONOR GEL is for children over 4 years old and adults.
Only a dentist can administer this product.

### 2. Before you use XYLONOR GEL

**Do not use XYLONOR GEL**
- if you are allergic (hypersensitive) to one of the active ingredients (lidocaine or cetrimide) or to any of the other ingredients (refer to section 6).
- if you are allergic to local anaesthetics called amide type anaesthetics.
- in children under 4 years old.

**Take special care with XYLONOR GEL**
- Soaps should be used with caution when you receive XYLONOR GEL, as they can decrease the efficiency of the active substance cetrimide.
- If you have a severe infection or an inflammation in the area to be treated.
- Avoid chewing gums or any type of food as long as the anaesthesia persists, as there is a risk of biting.
- The dentist will adapt the dosage to your age and general condition.
- The dentist should have available resuscitation equipment for effects on heart.

**Using other medicines**
Please tell your dentist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription.

**Pregnancy and breast-feeding**
Ask your dentist for advice before taking any medicine.

**Using XYLONOR GEL and sport**
There is a possibility of positive results on doping tests performed on sportsmen.

### 3. How to use XYLONOR GEL

Your dentist will explain to you why you are being treated with XYLONOR GEL.
He or she will adjust the dosage depending on the treatment you are having.
The usual dose of XYLONOR GEL is 100 to 500 mg (about 2 to 10 mm of gel).
Your dentist will apply it with a cotton pellet to the buccal mucosa.
A lower dose than usual may be used in patients who are ill or weak and in children or the elderly.

**If your dentist uses more XYLONOR GEL than he or she should**
If you swallow a lot of gel, or if you think your child has swallowed any of the gel, tell your dentist.

### 4. Possible side effects

Like all medicine, XYLONOR GEL can cause side effects, although not everybody gets them.
While you are in your dentist's office, your dentist will carefully follow the effects of XYLONOR GEL.

Administration of XYLONOR GEL may cause high plasma levels in active substances (lidocaine and/or cetrimide), especially excessive dosage or rapid absorption. Symptoms include: effects on your senses (hearing, sight, behaviour), effects on your heart and blood vessels, effects on your immune defences (diminished tolerance).

Allergic (hypersensitivity) reactions may occur when using this medicine. Symptoms of these reactions might include: rash, itching, swelling of the throat and difficulty breathing. Inform your dentist, doctor or pharmacist immediately if one of these effects applies to you.

You may develop more severe reactions such as convulsions and reduced level of consciousness with possible arrest of breathing or heart. Emergency medical help should immediately be called.

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**The following very rare side effects affect 1 of 10,000 patients treated:**

- **Effects on your heart and blood vessels:** low blood pressure, slow or irregular heartbeats, which may lead to cardiac arrest,
- **Effects on your lungs:** abnormally slow and shallow respiration, which may lead to respiratory arrest,
- **General effects:** unconsciousness, convulsions, dizziness, drowsiness, feeling nervous,
- **Effects on your senses:** blurred vision, trembling
- **Effects on your skin:** - severe allergic reactions (anaphylactoid reactions) characterized by swelling of the face, lips and/or tongue, difficulty breathing.
  - skin rash, hives or itching in the mouth, skin irritation and occasionally sensitisation.

**If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your dentist, doctor or pharmacist.**

## 5. How to store XYLONOR GEL

Keep out of the reach and sight of children.
It is most unlikely that you will be asked to look after this medicine.
Your dentist will not use this medicine after the expiry date which is stated on the package. The expiry date refers to the last day of that month.
Your dentist will keep it up to 25°C in a dry place, and tightly closed after use.

## 6. Further information

**What XYLONOR GEL contains**

- Active substances: 100 g of gel contains 5 g of lidocaine and 0.15 g of cetrimide.
- The other ingredients are: spearmint oil, saccharin and macrogol.

**What XYLONOR GEL looks like and content of the pack**
It is a white clear gel with an odour of mint.
XYLONOR GEL is available in tube of 15 g.

**Marketing authorisation holder**
Septodont Ltd, Units R & S
Orchard Business Centre
St Barnabas Close
Allington, Maidstone
Kent ME16 0JZ - UK

**Manufacturer**
Septodont
58, rue du Pont de Créteil
94100 Saint-Maur-des-Fossés
France

This leaflet was last approved on: 13/12/2012.

**If more PILs are necessary, call free number 0800435155.**

SEPTODONT
58, rue du Pont de Créteil
94100 Saint-Maur-des-Fossés - France

# Appendix 3b – Infiltration Anaesthetic



**Lignospan Special**
**Utilycaine – Lignokent – Eurocaine 2% - Rexocaine**

**Solution for injection**
**Lidocaine hydrochloride and adrenaline**

**PATIENT INFORMATION LEAFLET**

Read all of this leaflet carefully before you start using this medicine.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your dentist.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your dentist, doctor or pharmacist.

**In this leaflet:**


**1.What LIGNOSPAN SPECIAL is and what it is used for**
LIGNOSPAN SPECIAL is given by injection to cause loss of feeling before and during dental procedures.
It contains two active ingredients:
- lidocaine hydrochloride, a local anaesthetic, which prevents pain,
- adrenaline tartrate, a vasoconstrictor which makes the effect last longer. Adrenaline narrows the blood vessels at the site of injection, which keeps the anaesthetic where needed for a longer time. It also controls the bleeding during the surgery.

LIGNOSPAN SPECIAL is for adults, children and adolescents.

Only a dentist can administer this product.

**2.Before you use LIGNOSPAN SPECIAL**
**Do not use LIGNOSPAN SPECIAL**
- if you are allergic (hypersensitive) to one of the active ingredients (lidocaine hydrochloride or adrenaline tartrate) or to any of the other ingredients (refer to section 6)
- if you are allergic to local anaesthetics called amide type anaesthetics,
- if you are asthmatic or have suffered difficulty with your breathing as a result of taking medicines which contain ingredients called sulphites or metabisulphites,
- if you have a high blood pressure (arterial hypertension),
- if you have particular heart or blood vessels disease (coronary or valvular cardiac disease),
- if you are taking or have taken medicines for depression in the last two weeks,

**Take special care with LIGNOSPAN SPECIAL**
Before receiving this medicine, tell your dentist if:
- you have problems with your heart or blood vessels,
- you have problems with your liver,
- you have a severe infection or an inflammation in the area where the injection will be done.
- the child being treated is under 4 years old

**Using other medicines**
Please tell your dentist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription.
- Do not use LIGNOSPAN SPECIAL if you are taking or have taken medicines for depression in the last two weeks.

Your dentist should take special attention if you are taking the following medicines:
- medicines used to reduce your blood pressure (e.g. betablockers like propranolol or vasopressor drugs like dihydroergotamine),
- medicines used to reduce patient apprehension (e.g. sedatives). In this case, the dosage of anaesthetic should be reduced.

**Pregnancy and breast-feeding**
Ask your doctor or pharmacist for advice before taking any medicine.

**Driving and using machines**
If you experience side effects, including dizziness or blurred vision, you should not drive or operate machinery until these effects have disappeared.

**Important information about some ingredients of LIGNOSPAN SPECIAL**
LIGNOSPAN SPECIAL contains
- less than less than 1 mmol (23mg) sodium per cartridge, i.e. essentially "sodium free".
- potassium metabisulphite: it may rarely cause severe allergic reactions and difficulty in breathing (bronchospasm).

**3.How to use LIGNOSPAN SPECIAL**
Your dentist will explain to you why you are being treated with LIGNOSPAN SPECIAL. He or she will adjust the dosage according to your age, your health and the dental procedure.
One cartridge is usually sufficient but your dentist may give you a greater quantity. LIGNOSPAN SPECIAL is injected between two teeth.

**If your dentist uses more LIGNOSPAN SPECIAL than he or she should**
If you think you may have been given too much of this injection and feel unwell (see section 4. Possible side effects), tell your dentist.

**4. Possible side effects**
Like all medicines, LIGNOSPAN SPECIAL can cause side effects, although not everybody gets them. While you are in your dentist's office, your dentist will carefully follow the effects of LIGNOSPAN SPECIAL.

Administration of LIGNOSPAN SPECIAL may cause high plasma levels in active substances (lidocaine and/or adrenaline), especially overdose or unintended injection. Symptoms include: effects on your senses (hearing, sight, behaviour), effects on your heart and blood vessels, effects on your immune defences (diminished tolerance).

As complications to the manifestations of progressive cerebral hypoxia (decrease below normal levels of oxygen in tissue) and seizure or cardiovascular problem, sweating, feeling of faintness, changes in pulse or sensorium, vasovagal reaction might occur.

Allergic (hypersensitivity) reactions may occur when using this medicine. Symptoms of these reactions might include: rash, itching, swelling of the throat and difficulty breathing. Inform your dentist, doctor or pharmacist immediately if one of these effects applies to you.

**The following common side effects affect between 1 and 10 of every 100 patients treated:**

- failure of cardiac circulation (cardiovascular collapse) which may lead to cardiac arrest, loss or abnormality of rhythm (arrhythmia), conduction disorders, drop in blood pressure (hypotension), convulsions, feeling of well-being commonly exaggerated (euphoria), unconsciousness, malaise, confusion, dizziness, headache, If you are in an upright position, a vasovagal reaction (relating to the action of the nerve upon the blood vessels) may develop, slow or rapid heartbeats (bradycardia or tachycardia), irregular pulsation of heart (palpitations), lightheadedness, feeling nervous (nervousness), apprehension, agitation, drowsiness, buzzing in the ears (tinnitus), blurred or double vision, nausea, vomiting, sensations of heat, cold or numbness, uncontrolled eye movement (twitching), trembling.

**The following very rare side effects affect 1 of 10,000 patients treated:**

- severe allergic reactions (anaphylactoid reactions) characterized by swelling of the face, lips and/or tongue, difficulty breathing.
- allergic reactions characterized by skin rash (cutaneous lesions), eruption of itching wheals (urticaria), swelling (edema)

**If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your dentist, doctor or pharmacist.**

**5. How to store LIGNOSPAN SPECIAL**

Keep out of the reach and sight of children.
It is most unlikely that you will be asked to look after this medicine.
Your dentist will not use this medicine after the expiry date which is stated on the package. The expiry date refers to the last day of that month.
Your dentist will keep it up to 25° C, stored in the original container (protected from light). It should not be frozen.

**6. Further information**

**What LIGNOSPAN SPECIAL contains**

- Active substances: each ml of solution for injection contains:
  - 20 mg of lidocaine hydrochloride,
  - 12.5 micrograms of adrenaline (epinephrine).
- The other ingredients are: potassium metabisulphite (E224), sodium chloride, sodium edetate, sodium hydroxide solution and water for injection.

**What LIGNOSPAN SPECIAL looks like and content of the pack**

It is a solution for injection.
LIGNOSPAN SPECIAL is available in boxes containing 50 cartridges of 1.8 ml or of 2.2 ml.

**Marketing authorisation holder**
Septodont Ltd, Units R & S
Orchard Business Centre
St Barnabas Close
Allington, Maidstone
Kent ME16 0JZ - UK

**Manufacturer**
Septodont
58 rue du Pont de Créteil
94100 Saint-Maur-des-Fossés
France

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**If more PILs are necessary, call free number 0800435155.**