**Clinical Study Report Synopsis**

Drug Substance  EMLA cream 5%
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**Lidocaine/prilocaine cream (EMLA®) versus infiltration anaesthesia: a comparison of the analgesic efficacy for punch biopsy and electrocoagulation of genital warts in men**

**Study dates:** Not available from original CSR, which predates ICH-E3 guidance

**Phase of development:** Therapeutic confirmatory (III)

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**Sponsor’s Responsible Medical Officer:** Not available from original CSR, which predates ICH-E3 guidance

This study was performed in compliance with Good Clinical Practice, including the archiving of essential documents.

This submission/document contains trade secrets and confidential commercial information, disclosure of which is prohibited without providing advance notice to AstraZeneca and opportunity to object.
Study centre(s)

This study was conducted at 1 centre in The Netherlands.

Publications


Objectives and criteria for evaluation

Table S1 presents the objectives and outcome variables for this study.

Table S1  Objectives and outcome variables

<table>
<thead>
<tr>
<th>Objectives</th>
<th>Outcome variables</th>
<th>Type</th>
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<tbody>
<tr>
<td>To measure the pain caused by the administration of local anaesthetics,</td>
<td>Degree of pain associated with the injection or application as assessed by the subject on a verbal rating scale (no pain, slight pain [quite tolerable], moderate pain [not quite tolerable], or severe pain [intolerable]), and on a 100-mm horizontal VAS with endpoints of 0 mm (no pain) and 100 mm (intolerable pain).</td>
<td>Efficacy</td>
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<tr>
<td>together with the effectiveness of EMLA, compared to infiltration</td>
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<td>anaesthesia for analgesia in connection with biopsies and electrocoagulation of genital warts.</td>
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<td></td>
<td>Degree of pain during the biopsy/surgery as assessed by the subject on a verbal rating scale (no pain, slight pain [quite tolerable], moderate pain [not quite tolerable], or severe pain [intolerable]), and on a 100-mm horizontal VAS with endpoints of 0 mm (no pain) and 100 mm (intolerable pain).</td>
<td>Efficacy</td>
</tr>
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<td></td>
<td>Local reactions assessed by the subject (eg, burning sensation) and physician (eg, erythema, and oedema) and rated as none, slight, moderate, or profound. The presence of any other reaction was recorded as “yes” or “no”.</td>
<td>Safety</td>
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EMLA Eutectic mixture of local anaesthetics; VAS Visual analogue scale.

Study design

This was an open, randomized, comparative, parallel-group study of analgesia in connection with biopsies and electrocoagulation of genital warts. Subjects were randomized to receive either topical EMLA (eutectic mixture of local anaesthetics) 5% cream or infiltration analgesia with Xylocaine® 1%; subjects were stratified to obtain similar distributions of electrocoagulation and biopsy across the 2 treatment groups.

For subjects in the EMLA group, EMLA 5% cream was applied over the lesions at least 15 minutes and within 30 minutes of the surgical procedure. If the cream was not completely covered by the prepuce, the area was covered with plastic film (GLAD®, West Germany). For subjects in the infiltration anaesthesia group, Xylocaine was injected at the site of the lesion 5 minutes before the surgical procedure. Penile nerve block was not used. The presence of
Analgesia was tested by pin-prick prior to the electrocoagulation/biopsy and local reactions were assessed.

Diagnostic biopsies were taken with a disposable 3- or 4-mm punch (Stiefel). The condylomata were removed with an electrocoagulator (Surgistat™, Valleylab). The degree of pain during the biopsy/surgery was assessed. (If warts in more than 1 location were treated and the pain differed between locations, the worst pain was recorded.) If the procedure was painful, subjects in the EMLA group were given additional cream and subjects in the infiltration analgesia group were given additional Xylocaine. (If surgery was interrupted due to pain, the pain assessment for the initial treatment was made before the administration of additional anaesthesia.)

**Target subject population and sample size**

Males, 18 years of age or older, with warts on the genital mucous membranes and scheduled for electrocoagulation or biopsy were eligible for the study. Those subjects undergoing electrocoagulation were required to have a minimum of 3 warts. Both untreated and previously treated subjects were included; previously treated subjects were not to have received any treatment in the previous 2 weeks. Subjects with an allergy to local anaesthetics of the amide type or having giant condylomata were excluded.

It was assumed that the proportion of subjects feeling slight or no pain (as opposed to those feeling moderate or severe pain) from either administration of anaesthesia or surgical procedure would be 0.9 and 0.5, respectively. Therefore, 30 subjects in each group (60 subjects total) would allow detection of a difference in pain scores between the EMLA and Xylocaine groups with 85% power and a significance level of 0.05.

**Investigational product and comparator(s): dosage, mode of administration and batch numbers**

Commercially available EMLA 5% cream was used in this study. This formulation consisted of lidocaine (25 mg [107 mmol/L]); prilocaine (25 mg [113 mmol/L]); Arlatone® 289 (19 mg); Carbopol® 934 (10 mg); and distilled water (up to 1 g [1 mL]). The total concentration of the active ingredients (lidocaine and prilocaine) was 50 mg/mL; Arlatone (emulsifier) and Carbopol (thickener) were used to obtain a suitable consistency. A layer of cream between 2.5 and 5.0 g (median, 2.5 g) was applied topically to the lesion.

Infiltration anaesthesia was obtained with 0.1 to 4.0 mL (median, 0.7 mL) of Xylocaine 1% (without adrenaline) injected with a 0.5 mm Monoject™ needle.

**Duration of treatment**

Subjects received 1 dose of analgesic treatment prior to electrocoagulation/biopsy.

**Statistical methods**

The statistical analysis evaluated the difference between the 2 groups with regard to pain associated with the anaesthetic procedure ie, application of EMLA cream or infiltration with
Xylocaine (visual analogue scale [VAS] and verbal rating scale), pain associated with the surgical procedure (VAS and verbal rating scale), total pain (sum of VAS from anaesthetic procedure and surgical procedure), and severity of adverse reactions.

These variables were analysed by using the extended Mantel-Haenszel procedure, equal to the stratified Wilcoxon Rank Sum test, which was stratified with respect to surgical procedure. A chi-square approximation to the test statistic was used (SAS version 5.18). The tests were 2-tailed and a p-value <0.05 was considered statistically significant.

**Subject population**

A total of 63 subjects (32 in the EMLA group and 31 in the Xylocaine group) were treated. The groups were comparable in terms of age and location of the treated area. (A 16-year-old subject was erroneously included in the study.)

Of the 63 treated subjects, 3 were excluded from the efficacy pain analyses: 2 subjects in the Xylocaine group had warts on the perigenital skin, not on the mucous membranes, and 1 subject in the Xylocaine group was given EMLA in error. As a result, 31 and 29 subjects in the EMLA and Xylocaine groups, respectively, were evaluated for efficacy.

**Summary of efficacy results**

Biopsies were performed in 18/31 subjects in the EMLA group and 16/29 subjects in the Xylocaine group. The median EMLA cream application time was 25 minutes and the surgical procedure was started within 5 minutes in all but 1 subject (15 minutes). The median duration of surgery was 5 minutes, and the size of the biopsy punches used (3 or 4 mm) was comparable between the groups.

The evaluation of pain due to anaesthetic application as scored by verbal pain assessments showed that topical application of EMLA cream caused less pain than injection of Xylocaine; the difference between the 2 groups was statistically significant ($\chi^2=47.12$, $p<0.001$). No subject felt any discomfort from the application of EMLA whereas the injection of Xylocaine was rated as no pain by 2 subjects, slightly painful by 17 subjects, and moderately painful by 10 subjects. Similarly, a statistically significant difference between groups was observed for application pain as scored by VAS (median VAS score of 0 in the EMLA group versus 13 in the Xylocaine group; $\chi^2=36.26$, $p<0.001$).

The evaluation of pain during surgery or biopsy as scored on verbal pain assessments showed that topical application of EMLA cream resulted in more pain during biopsy/surgery than injection of Xylocaine; the difference between the 2 groups was statistically significant ($\chi^2=11.67$, $p=0.001$). In the EMLA group, 15 subjects reported no pain, and slight, moderate, and severe pain was reported in 10, 5, and 1 subject(s), respectively versus 24 subjects with no pain and 5 subjects with slight pain in the Xylocaine group. No subjects in the Xylocaine group had moderate or severe pain. Similarly, a statistically significant difference between groups was observed for pain during biopsy/surgery as scored by VAS (median VAS score of 3.5 in the EMLA group versus 0 in the Xylocaine; $\chi^2=12.83$, $p<0.001$).
Overall, the total pain scores (VAS scores during EMLA application/Xylocaine injection plus VAS scores during biopsy/surgery) were lower in the EMLA group compared with the Xylocaine group (median VAS total score of 4 and 15, respectively); the difference between the 2 groups was statistically significant ($\chi^2=4.23$, $p=0.04$).

Electrocoagulation tended to be more painful than punch biopsies in both groups. In the Xylocaine group, pain (slight) was only reported for 5 subjects undergoing electrocoagulation. In the EMLA group, 62% (8/13) of electrocoagulations were performed with no (n=4) or slight (n=4) pain, whereas 94% (17/18) of biopsies were taken with no (n=11) or slight (n=6) pain.

**Summary of safety results**

No differences between the 2 treatment groups were observed in the incidence of burning sensation (slight burning reported by 3 and 2 subjects in the EMLA and Xylocaine groups, respectively) or oedema (slight or moderate oedema reported for 6 and 9 subjects in the EMLA and Xylocaine groups, respectively). More subjects in the EMLA group had redness compared with the Xylocaine group (slight or moderate redness in 14 subjects in the EMLA group versus slight redness in 3 subjects in the Xylocaine group; $\chi^2=10.11$, $p=0.001$).

Paleness of the anaesthetized area was observed in 8 subjects in the EMLA group and 1 subject in the Xylocaine group. One subject in the Xylocaine group had a local haematoma. One subject had papules where EMLA had been applied for 30 minutes.

Local reactions from the anaesthetics were transient and necessitated no symptomatic treatment.

**Conclusion(s)**

Pain and discomfort was less during the application of EMLA 5% cream than during the infiltration of Xylocaine. The infiltration of Xylocaine resulted in better surgical anaesthesia than the EMLA cream application. EMLA anaesthesia was satisfactory for 94% of subjects who had biopsies and for 62% of subjects who had electrocoagulations, whereas Xylocaine was effective in all subjects. The results suggest that EMLA may be used as premedication to relieve pain from the local anaesthetic injection before electrocoagulation of genital warts in men.