Public Assessment Report

Decentralised Procedure

DENELA 5% CREAM

(lidocaine and prilocaine)

Procedure No: UK/H/3229/001/DC

UK Licence No: PL 17507/0119

Auden Mckenzie Limited
Lay Summary

On 10 April 2013, Ireland and the UK agreed to grant Marketing Authorisations to Auden Mckenzie Limited for the medicinal product Denela 5% cream (PL 17507/0119; UK/H/3229/001/DC). The licences were granted via the Decentralised Procedure (DCP), with the UK as Reference Member State (RMS). After the national phase, a Marketing Authorisation was granted in the UK on 30 April 2013.

This product is only available from a pharmacy (legal status P). It contains two medicines called lidocaine and prilocaine, which belong to a group of medicines called local anaesthetics. Denela cream works by numbing the surface of the skin for a short time. It is put on the skin before certain medical procedures and helps to stop pain on the skin.

No new or unexpected safety concerns arose from this application and it was therefore judged that the benefits of using Denela 5% cream outweigh the risks; hence, a Marketing Authorisation was granted.
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# Module 1

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<th><strong>Product Name</strong></th>
<th>Denela 5% cream</th>
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<tr>
<td><strong>Type of Application</strong></td>
<td>Hybrid, Article 10(3)</td>
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<tr>
<td><strong>Active Substances</strong></td>
<td>Lidocaine and Prilocaine</td>
</tr>
<tr>
<td><strong>Form</strong></td>
<td>Cream</td>
</tr>
<tr>
<td><strong>Strength</strong></td>
<td>5% cream containing:</td>
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<tr>
<td></td>
<td>Lidocaine 2.5% w/w</td>
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<tr>
<td></td>
<td>Prilocaine 2.5% w/w</td>
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<tr>
<td><strong>MA Holder</strong></td>
<td>Auden Mckenzie (Pharma Division) Ltd, Mckenzie House, Bury Street, Ruislip, Middlesex, HA4 7TL, UK</td>
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<tr>
<td><strong>Reference Member State (RMS)</strong></td>
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</tr>
<tr>
<td><strong>Concerned Member States (CMS)</strong></td>
<td>Ireland</td>
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<td><strong>Procedure Number</strong></td>
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<tr>
<td><strong>Timetable</strong></td>
<td>Day 210 – 10 April 2013</td>
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Module 2
Summary of Product Characteristics

The current approved UK version of the Summary of Product Characteristics (SmPC) for this product is available on the MHRA website.
Module 3
Patient Information Leaflet

The current approved UK version of the Patient Information Leaflet (PIL) for this product is available on the MHRA website.
Module 4
Labelling

30g Tube:

Denela™ 5% Cream
Lidocaine 2.5% & Prilocaine 2.5%

Each gram of cream contains 25 mg of lidocaine and 25 mg of prilocaine.

For topical use as directed by a healthcare professional

Keep out of the sight and reach of children

Store below 25°C and do not freeze

Medicinal product not subject to medical prescription

This medicine should be disposed of 3 months after first opening.

5g Tube:

Denela™ 5% Cream
Lidocaine 2.5% & Prilocaine 2.5%

Each gram of cream contains 25 mg of lidocaine and 25 mg of prilocaine.

For topical use as directed by a healthcare professional

Keep out of the sight and reach of children

Store below 25°C and do not freeze

Medicinal product not subject to medical prescription

This medicine should be disposed of 3 months after first opening.
Carton for 30 g tube with spatula:
Carton for 5g tube & 2 dressings:

Denela 5% cream
Lidocaine 2.5% & Prilocaine 2.5%

Instructions for Application
1. Remove the paper frame using the cut-out. Smooth down the edges of the dressing and frame to ensure the dressing is fully in place for at least 30 minutes.
2. Apply the frame and compress firmly around the dressing.
3. Do not spread the cream.
4. After 60 mins (max) remove the dressing and clean the area with alcohol.
5. The area of application can be covered with the cover frame.
6. Do not spread the cream.

Keep out of the reach of children.

Medical product not for use by the public.
Carton for 5g tube (with no dressings):
Module 5
Scientific discussion during initial procedure

I INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the member states considered that the application for Denela 5% Cream (PL 17507/0119; UK/H/3229/001/DC) could be approved. This application was submitted via the Decentralised Procedure, with the UK as the Reference Member State (RMS), and Ireland as the Concerned Member State (CMS).

The legal status of the product is pharmacy (P) only supply. It is indicated for use for topical anaesthesia of the skin prior to minor dermatological procedures (e.g. needle insertion and surgical treatment of localised lesions) and prior to dermal procedures on larger areas (e.g. split skin grafting); for dermal procedures on newly shaven skin of large body areas (e.g. laser hair removal); for topical anaesthesia of the genital mucosa (e.g. prior to superficial surgical procedures or prior to infiltration anaesthesia of mucosa); and for topical anaesthesia of leg ulcers to facilitate mechanical cleansing/debridement.

In newborn infants and children under the age of 18 years, Denela is indicated for local anaesthesia on intact skin prior to minor dermatological procedures.

This was an application made under the Decentralised Procedure (DCP), according to Article 10(3) of Directive 2001/83/EC, as amended, as a hybrid application. The reference medicinal product for this application is EMLA Cream 5% (PL 00017/0213) which was initially granted a marketing authorisation to Astra Pharmaceuticals Limited in the UK on 28 January 1986. The current marketing authorisation holder is AstraZeneca UK Limited.

The active substances lidocaine and prilocaine are amide-type local anaesthetics. Anaesthesia is achieved by the inhibition of pain signals to the brain. Lidocaine and prilocaine inhibit nerve conduction by interfering with the entry of sodium ions through the nerve cell membrane. With sufficient blockade, the membrane of the postsynaptic neuron fails to depolarise and transmit an action potential.

No new non-clinical studies were conducted, which is acceptable given that this is a hybrid application based on an originator product that has been licensed for over 10 years.

To support the application, the Marketing Authorisation Holder submitted a non-inferiority study comparing the test product Denela 5% Cream (Auden McKenzie) and EMLA 5% Cream (AstraZeneca UK Limited), in healthy male and female volunteers undergoing forearm cannulation. The study was conducted in two parts. Part A was a 2-way, crossover, pilot study in individuals who found peripheral venous cannulation to be painful without the use of topical local anaesthetic cream. EMLA Cream 5% was used in order to estimate the efficacy of EMLA cream in comparison with a placebo cream identical in appearance to EMLA cream and to obtain an estimate of within-subject variability. Part B was a randomised, double-blind, placebo-controlled, 3-way crossover study to demonstrate the therapeutic non-inferiority of Denela 5% cream to the reference EMLA Cream 5%.

The RMS has been assured that acceptable standards of Good Manufacturing Practice are in place at all sites responsible for the manufacture, assembly and batch release of this product.

The RMS and CMS considered that the application could be approved with the end of procedure (Day 210) on 10 April 2013. After a subsequent national phase, a licence was granted in the UK on 30 April 2013.
## II. ABOUT THE PRODUCT

| Name of the product in the Reference Member State | Denela 5% cream |
| Name(s) of the active substance(s) (INN) | Lidocaine and Prilocaine |
| Pharmacotherapeutic classification (ATC code) | Local anaesthetics (N01B B20) |
| Pharmaceutical form and strength(s) | 5% cream containing: Lidocaine 2.5% w/w Prilocaine 2.5% w/w |
| Reference numbers for the Mutual Recognition Procedure | UK/H/3299/01/DC |
| Reference Member State | United Kingdom |
| Member States concerned | Ireland |
| Marketing Authorisation Number(s) | PL 17507/0119 |
| Name and address of the authorisation holder | Auden Mckenzie (Pharma Division) Ltd Mckenzie House, Bury Street, Ruislip, Middlesex, HA47TL |
III  SCIENTIFIC OVERVIEW AND DISCUSSION
III.1  QUALITY ASPECTS
S.  Active substances – Lidocaine and Prilocaine

rINN: Lidocaine
Chemical Abstracts Service (CAS) Registry Number: 137-58-6
Structure:

Molecular formula: $\text{C}_{14}\text{H}_{22}\text{N}_2\text{O}$
Molecular weight: 234.3
Appearance: White, or almost white, crystalline powder, which is practically insoluble in water and very soluble in ethanol and in methylene chloride.

rINN: Prilocaine
Chemical Abstracts Service (CAS) Registry Number: 721-50-6
Structure:

Molecular formula: $\text{C}_{13}\text{H}_{20}\text{N}_2\text{O}$
Molecular weight: 220.3
Appearance: White, or almost white, crystalline powder, which is slightly soluble in water and very soluble in acetone and in ethanol.

Lidocaine and prilocaine are the subject of European Pharmacopoeia monographs.

All aspects of the manufacture and control of these active substances are covered by a European Directorate for the quality of Medicines (EDQM) Certificate of Suitability (CEP).
P. Medicinal Product

Other Ingredients
Other ingredients consist of the pharmaceutical excipients, namely sodium hydroxide, purified water, macrogolglycerol hydroxystearate and carbomer.

All excipients comply with their respective European Pharmacopoeia monograph.

None of the excipients are sourced from animal or human origin. No genetically modified organisms (GMO) have been used in the preparation of this product.

Pharmaceutical Development
The objective of the development programme was to formulate a stable product that was comparable in performance to the innovator product EMLA Cream 5% (AstraZeneca UK Limited).

A satisfactory account of the pharmaceutical development has been provided.

Comparative in vitro diffusion and impurity profiles have been provided for the proposed product and its respective innovator product.

Manufacturing Process
Satisfactory batch formulae have been provided for the manufacture of the finished product. The manufacturing process has been validated using three production-scale batches and has shown satisfactory results.

Finished Product Specification
The finished product specification proposed is acceptable. Test methods have been described and have been adequately validated. Batch data have been provided and comply with the release specifications. Certificates of analysis have been provided for all working standards used.

Container-Closure System
The finished product is packaged in collapsible white aluminium tubes, internally coated with an epoxy resin-based lacquer and closed with a white polypropylene cap.

There are four different pack types in total. The 5 g packs are supplied with or without CE marked occlusive dressings for use with the cream. The 30 g packs are supplied with a sterile CE marked wooden spatula, to facilitate the application and spreading of the cream. The pack variants are listed below.

5 g Packs:  
5 x 5 g tubes with 12 occlusive dressings – also referred to as a ‘pre-medication pack’
1 x 5 g tube with 2 occlusive dressings
1 x 5 g tube

30 g Packs:  
1 x 30 g tube with a sterile wooden spatula – also referred to as a ‘surgical pack’

Satisfactory specifications and Certificates of Analysis have been provided for all packaging components. All primary packaging complies with the current European regulations concerning materials in contact with food.

Stability of the product
Stability studies were performed in accordance with current guidelines on batches of finished product packed in the packaging proposed for marketing. The data from these studies support a shelf-life of 24 months (unopened) and an in-use shelf-life of 3 months, with the storage conditions “Store below 25°C, do not freeze.”
Bioequivalence/bioavailability

Bioequivalence studies are not necessary to support this application. For products that are applied locally and are intended to act without systemic absorption, the approach to determine equivalence on systemic measurements is not applicable. The applicant has submitted a non-inferiority study of Denela and EMLA 5% creams, in healthy male and female volunteers undergoing forearm cannulation. This study is discussed in section III.3, Clinical Aspects.

Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and Labels

The SmPC, PIL and labels are pharmaceutically acceptable.

A package leaflet has been submitted to the MHRA along with results of consultations with target patient groups (‘user testing’), in accordance with Article 59 of Council Directive 2001/83/EC, as amended. The results indicate that the package leaflet is well-structured and organised, easy to understand and written in a comprehensive manner. The test shows that the patients/users are able to act upon the information that it contains.

Marketing Authorisation Application (MAA) form

The MAA form is pharmaceutically satisfactory.

Quality Overall Summary (Expert report)

The pharmaceutical expert report has been written by an appropriately qualified person and is a suitable summary of the pharmaceutical dossier.

Conclusion

The grant of a Marketing Authorisation is recommended.

III.2 NON-CLINICAL ASPECTS

As the pharmacodynamic, pharmacokinetic and toxicological properties of lidocaine and prilocaine are well-known, no further non-clinical studies are required and none have been provided.

The applicant’s non-clinical expert report has been written by an appropriately qualified person and is satisfactory, providing an appropriate review of the product’s pharmacology and toxicology.

The applicant has provided an acceptable environmental risk assessment (ERA) for both active substances, in accordance with the Guideline on the Environmental Risk Assessment of Medicinal Products for Human Use (EMEA/CHMP/SWP4447/00).

There are no objections to the approval of this product from a non-clinical viewpoint.
III.3 CLINICAL ASPECTS

Clinical Pharmacology
The clinical pharmacology of lidocaine and prilocaine are well-known. With the exception of the clinical study detailed below, no new data are provided or required for this type of application.

Efficacy
To support the application, the applicant has conducted a non-inferiority study, summarised below.

A Phase I, randomised, double-blind, placebo-controlled, crossover, pilot and therapeutic non-inferiority study of EMLA and Denela in healthy male and female volunteers undergoing forearm cannulation.

Objectives
Part A: To estimate the size effect of the reference product versus placebo and to obtain an estimate of within-subject variability of differences in pain response.
Part B: To investigate therapeutic non-inferiority of Denela to EMLA cream.

Methodology
Part A was a 2-way crossover pilot study. It selected individuals who found peripheral venous cannulation painful (defined as a pain recording of 25mm or greater on a 100 mm visual analog scale (VAS) for pain) when it was performed without the use of topical local anaesthetic cream. EMLA cream 5% was used in order to estimate its efficacy in comparison with a placebo cream (identical in appearance to EMLA cream) and to test the study methodology, i.e. the usefulness of the VAS for pain, in preparation for Part B.

The first dose was administered to the right forearm. Following 2 hours of occlusion with the allocated treatment, the occlusive dressing and treatment were removed and subjects received their first venous cannulation at the treatment site. The remaining treatment was applied to the left forearm not less than 2 hours following fixation of the first cannula into the vein. Following a further 2 hours of occlusion, subjects received their second venous cannulation at the treatment site (left forearm) i.e. there was a minimum interval of 4 hours between successive cannulations. Subjects were asked to record their perceived pain on a VAS, 1 minute following cannulation. The venous cannula was removed after 5 minutes.

Part B was a randomised, double-blind, placebo-controlled, 3-way crossover study to demonstrate the therapeutic non-inferiority of Denela 5% cream to EMLA Cream 5%. Subjects received 2 g of each of the following treatments over the 3 treatment visits:
Treatment A (Reference): EMLA Cream 5% - AstraZeneca UK Limited
Treatment B (Placebo): Test cream product minus anaesthetic constituents identical in appearance to EMLA cream - Auden Mckenzie (Pharma Division) Ltd
Treatment C (Test): Denela 5% cream - Auden Mckenzie (Pharma Division) Ltd

Treatments were separated by an interval of at least 1 week and involved application of the allocated treatment to both forearms for a period of 2 hours. Cannulation was performed on one forearm only (unless there was a failed cannulation attempt in the first instance). Subjects were asked to record their perceived pain on a VAS, 1 minute following cannulation. The venous cannula was removed after 5 minutes. Adverse events and local tolerability were assessed after 5 minutes and 30 minutes of the cannula being removed.
Results
Part A: The mean benefit of EMLA cream compared with placebo was estimated at 30.2 mm (95% confidence interval [CI] 18.5 to 41.9 mm). For Part B of the study, based on clinical judgement of an important difference in effect between the products, a non-inferiority margin of 10 mm was set.

Table 11-3 Summary of pain intensity and within subject change – Part A

<table>
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<tr>
<th>Summary Statistic</th>
<th>Actual</th>
<th>Within Subject Change</th>
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<tbody>
<tr>
<td></td>
<td>Screening</td>
<td>A (Placebo)</td>
</tr>
<tr>
<td>N</td>
<td>12</td>
<td>12</td>
</tr>
<tr>
<td>Mean</td>
<td>51.7</td>
<td>49.8</td>
</tr>
<tr>
<td>SD</td>
<td>13.5</td>
<td>13.0</td>
</tr>
<tr>
<td>Minimum</td>
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<td>21</td>
</tr>
<tr>
<td>Median</td>
<td>52</td>
<td>51</td>
</tr>
<tr>
<td>Maximum</td>
<td>77</td>
<td>75</td>
</tr>
<tr>
<td>LS Mean</td>
<td>49.8</td>
<td>19.6</td>
</tr>
<tr>
<td>LS Mean Difference (95% CI)</td>
<td>-30.2 (-41.9, -18.5)</td>
<td></td>
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</tbody>
</table>

Part B: Denela 5% cream (test cream) was non-inferior to EMLA cream 5% (reference cream). The difference between Denela and EMLA creams (least-squares [LS] mean difference) was 1.4mm (95% CI -3.4 to 6.1). Pain intensity was significantly reduced following application of both Denela and EMLA creams: the difference between Denela cream and placebo (LS mean difference) was -30.6 mm (p<0.0001) and between EMLA cream and placebo -31.9 mm (p<0.0001).

Table 11-4 Summary of pain intensity and within subject change – Part B

<table>
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<tr>
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<th>Actual</th>
<th>Within subject Change</th>
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<tr>
<td></td>
<td>Screening</td>
<td>A (reference)</td>
</tr>
<tr>
<td></td>
<td>B (Placebo)</td>
<td>C (Test)</td>
</tr>
<tr>
<td>N</td>
<td>60</td>
<td>99</td>
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<tr>
<td>Mean</td>
<td>54.4</td>
<td>12.6</td>
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<tr>
<td>SD</td>
<td>18.2</td>
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<td>Minimum</td>
<td>90</td>
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<tr>
<td>Median</td>
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<td>46</td>
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<tr>
<td>Maximum</td>
<td>90</td>
<td>97</td>
</tr>
<tr>
<td>LS Mean</td>
<td>15.0</td>
<td>45.7</td>
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<tr>
<td>LS Mean Difference (95% CI) (p-value)</td>
<td>R-P: -31.9 (p&lt;0.0001)</td>
<td>R-P: -31.9 (p&lt;0.0001)</td>
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</table>

Conclusion
The upper and lower 95% CI for the LS mean difference between the test and reference products were within pre-defined acceptance criteria, therefore therapeutic non-inferiority was established. Furthermore, both Denela 5% cream and EMLA cream 5% were superior to placebo, showing that the VAS was an appropriate measure for this study.

Safety
With the exception of the data submitted during the non-inferiority study, no new safety data were submitted and none were required. No new or unexpected safety issues were raised by the non-inferiority study.

SmPC, PIL and Labels
The SmPC, PIL and labels are medically acceptable. The SmPC is consistent with that for the originator product.
Pharmacovigilance System and Risk Management Plan
The Pharmacovigilance System, as described by the applicant, fulfils the requirements and provides adequate evidence that the applicant has the services of a qualified person responsible for pharmacovigilance, and has the necessary means for the notification of any adverse reaction suspected of occurring either in the Community or in a third country.

Suitable justification has been provided for not submitting a risk management plan for this product.

Clinical Expert Report
The clinical expert report has been written by an appropriately qualified physician and is a suitable summary of the clinical aspects of the dossier.

Conclusion
The grant of a Marketing Authorisation is recommended.
IV OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT
QUALITY
The important quality characteristics of Denela 5% cream are well-defined and controlled. The specifications and batch analytical results indicate consistency from batch to batch. There are no outstanding quality issues that would have a negative impact on the benefit-risk balance.

NON-CLINICAL
No new non-clinical data were submitted and none are required for applications of this type.

CLINICAL
Non-inferiority has been shown between the test product Denela 5% Cream (Auden McKenzie) and EMLA 5% Cream (AstraZeneca UK Limited). These products can be considered interchangeable.

No new or unexpected safety concerns arose from this application.

The SmPC, PIL and labelling are satisfactory and consistent with those for the reference product.

BENEFIT-RISK ASSESSMENT
The quality of the product is acceptable, and no new non-clinical or clinical safety concerns have been identified. The non-inferiority study supports the claim that the applicant’s product and the originator product are therapeutically equivalent. Extensive clinical experience with lidocaine and prilocaine is considered to have demonstrated the therapeutic value of the compound. The benefit-risk is therefore considered to be positive.
Module 6

STEPS TAKEN AFTER INITIAL PROCEDURE - SUMMARY

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<th>Scope</th>
<th>Outcome</th>
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