

## **SUMMARY OF PRODUCT CHARACTERISTICS**

### **1 NAME OF THE MEDICINAL PRODUCT**

Denela 5% Cream

### **2 QUALITATIVE AND QUANTITATIVE COMPOSITION**

Lidocaine 2.5% w/w (25 mg/g)

Prilocaine 2.5% w/w (25 mg/g)

For a full list of excipients, see section 6.1.

### **3 PHARMACEUTICAL FORM**

Cream

White soft cream.

### **4 CLINICAL PARTICULARS**

#### **4.1 Therapeutic indications**

Topical anaesthesia of the skin in connection with:

- Intact 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.
- Dermal procedures on newly shaven skin of large body areas e.g. laser hair removal
- Topical anaesthesia of the genital mucosa, e.g. prior to superficial surgical procedures or prior to infiltration anaesthesia of mucosa.
- Topical anaesthesia of leg ulcers to facilitate mechanical cleansing/debridement.

In term newborn infants and children under the age of 18 years, Denela is indicated for local anaesthesia on intact skin prior to minor dermatological procedures. Studies have failed to demonstrate efficacy of Denela for heel lancing in newborn infants.

## 4.2 Posology and method of administration

Surface/ Age	Procedure	Application
<b>Skin</b>		Apply a thick layer of cream on the skin and cover it with occlusive dressing.
Adults		Approx. 1.5 g/10 cm <sup>2</sup>
	Minor procedures e.g. needle insertion and surgical treatment of localised lesions.	2 g (approx. half a 5 g tube) for 1 to 5 hours <sup>1)</sup>
	Dermal surgical procedures on larger areas in a hospital setting e.g. split skin grafting.	Approx. 1.5-2 g/10 cm <sup>2</sup> for 2 to 5 hours <sup>1)</sup>
	Dermal procedures on newly shaven skin of large body areas e.g. laser hair removal (self-application by patient)	Maximum recommended dose: 60g. Maximum recommended treated area: 600 cm <sup>2</sup> for a minimum of 1 hour, maximum 5 hours. <sup>1)</sup>
Children	Minor procedures, e.g. needle insertion and surgical treatment of localised lesions	Approx. 1.0 g/10 cm <sup>2</sup> for 1 hour (see details below)
Neonates 0-2 months <sup>3)</sup>		Up to 1.0 g and 10 cm <sup>2</sup> <sup>2)</sup>
Infants 3-11 months <sup>3)</sup>		Up to 2.0 g and 20 cm <sup>2</sup> <sup>4)</sup>
Children 1-5 years		Up to 10.0 g and 100 cm <sup>2</sup> for 1-5 hours <sup>1)</sup>
Children 6-11 years		Up to 20.0 g and 200 cm <sup>2</sup> for 1-5 hours <sup>1)</sup>
Children with atopic dermatitis	Prior to removal of mollusca.	Application time: 30 minutes
<b>Genital mucosa</b>	Surgical treatment of	Approx. 5-10 g Denela for 5-10

Adults	localised lesions, e.g. removal of genital warts (condylomata accuminata) and prior to injection of local anaesthetics.  Prior to cervical curettage.	minutes <sup>1)</sup> . No occlusive dressing is required. Commence the procedure immediately after removal of cream.  Administer 10 g of cream in lateral vaginal fornices for 10 minutes.
<b>Skin of male genital organs</b> Adults	Prior to injection of local anaesthetics	Apply a thick layer of Denela cream (1 g/10cm <sup>2</sup> ) with occlusive dressing for 15 minutes
<b>Skin of female genital organs</b> Adults	Prior to injection of local anaesthetics <sup>7)</sup>	Apply a thick layer of Denela cream (1-2 g/10cm <sup>2</sup> ) with occlusive dressing for 60 minutes
<b>Leg ulcer</b> Adults	Mechanical cleansing /debridement of leg ulcer(s).	Apply a thick layer of the cream, approx. 1-2 g/10 cm <sup>2</sup> up to a total of 10 g to the leg ulcer(s). <sup>5, 6)</sup> Cover with an occlusive dressing.  Application time: 30 to 60 minutes.  Cleansing should start without delay after removal of the cream.

- 1) After > 5 hours application time anaesthesia decreases.
- 2) Application for >1 hour has not been documented.
- 3) Until further clinical data are available, Denela should not be used in infants up to 12 months of age receiving treatment with methaemoglobin-inducing agents.
- 4) No clinically significant increase in plasma methaemoglobin levels has been observed after an application time of up to 4 hours on 16 cm<sup>2</sup>.
- 5) Denela has been used for the treatment of leg ulcers up to 15 times over a period of 1-2 months without loss of efficacy or increased number or severity of adverse events.
- 6) Plasma levels have not been determined in patients treated with doses of >10 g, (See also Section 5.2).
- 7) On female genital skin, Denela alone applied for 60 or 90 min does not provide sufficient anaesthesia for thermocautery or diathermy of genital warts.

One gram of Denela cream pressed out of a tube of 30 g is approximately 3.5 cm.

Persons frequently applying or removing cream should ensure that contact is avoided in order to prevent the development of hypersensitivity.

### **Paediatric population**

#### Adolescents $\geq 12$ years:

As for adults (approximately 2 g Denela applied under an occlusive dressing for a minimum of 60 minutes, maximum 5 hours).

#### Term newborn infants, infants and children $\leq 11$ years:

In term newborn infants and infants < 3 months, only one single dose should be applied in any 24 hour period.

For children aged 3 months and above, a maximum of 2 doses, separated by at least 12 hours can be given within any 24 hour period. If, based on clinical need, a decision is nevertheless taken to use two applications in children under the age of 3 months, see sections 4.4 and 4.8.

The safety of Denela in pre-term newborn infants has not been established. Use of Denela is not recommended in pre-term infants.

Use of Denela is not recommended in infants less than 3 months of age receiving treatment with methaemoglobin-inducing drugs (see section 4.4).

For all age groups analgesic efficacy may decline if the skin application time is more than 5 hours. Procedures on intact skin should begin soon after the occlusive dressing is removed.

On the genital mucosa analgesic efficacy declines after 10-15 minutes and therefore the procedure should be commenced immediately.

### **Methods of dose estimation**

Denela is available in 5 g and 30 g tubes. To dispense 1 g of Denela from either tube size, apply the cream to a circular area with a diameter of approx. 18 mm (a 1 pence coin) and depth of approx. 4 to 5 mm.

If high levels of accuracy in dosing are required to prevent overdose (i.e. at doses approaching the maximum in neonates or if two applications may be required in a 24 h period), a syringe can be used where 1 ml = 1 g.

A string of cream can be used to define the quantity of Denela administered from the 30 g tube where 1 g = 3.5 cm; however, a string of cream may not be appropriate for all application needs, e.g. when administering a low dose to small surface areas.

### **4.3 Contraindications**

Hypersensitivity to the amide-type local anaesthetics or to any other component of the product.

### **4.4 Special warnings and precautions for use**

Denela should not be used in the following cases:

- (a) in pre-term neonates i.e. gestational age less than 37 weeks.
- (b) in infants/neonates between 0 and 12 months of age receiving treatment with methaemoglobin-inducing agents due to the possible additive effects.

In infants/neonates younger than 3 months a transient, clinically insignificant increase in methaemoglobin level is commonly observed up to 12 hours after an application of Denela.

Patients with defective glucose-6-phosphate dehydrogenase, hereditary or idiopathic methaemoglobinaemia are more susceptible to drug induced signs of methaemoglobinaemia.

In term newborn infants, infants and children, Denela should only be used on intact skin and should not be applied to genital mucosa.

In term neonates and infants < 3 months, only one single dose should be applied in any 24 hour period. If, based on clinical need, a decision is nevertheless taken to use two applications in children under the age of 3 months, the child should be clinically monitored for systemic adverse reactions (see sections 4.8 and 4.9).

Consideration should be given to the fact that pulse oximeter values may overestimate the actual oxygen saturation in case of increased methaemoglobin fraction; therefore, in cases of suspected methaemoglobinaemia, it may be more helpful to monitor oxygen saturation by co-oximetry.

Care must be taken to limit the dose and area of application and to prevent accidental ingestion.

Due to insufficient data on absorption of active substances, Denela should not be applied to open wounds (excluding leg ulcers).

Due to the potentially enhanced absorption on newly shaven skin, it is important to adhere to the recommended dosage, area and time of application (see Section 4.2).

Studies have been unable to demonstrate the efficacy of Denela for heel lancing in neonates.

Denela should not be applied to the genital mucosa of children owing to insufficient data on absorption of active substances. However, when used in neonates for circumcision, a dose of 1.0 g Denela on the prepuce has been proven to be safe.

Care should be taken when applying Denela to patients with atopic dermatitis. A shorter application time, 15-30 minutes, may be sufficient (see Section 5.1). Application times of longer than 30 minutes in patients with atopic dermatitis may result in an increased incidence of local vascular reactions, particularly application site redness and in some cases petechiae and purpura (see Section 4.8 Undesirable effects). Prior to removal of mollusca in children with atopic dermatitis, it is recommended to apply cream for 30 minutes.

When applied in the vicinity of the eyes, Denela cream should be used with particular care since it may cause eye irritation. Also the loss of protective reflexes may allow corneal irritation and potential abrasion. If eye contact occurs, immediately rinse the eye with water or sodium chloride solution and protect the eye until sensation returns.

Denela should not be applied to an impaired tympanic membrane. Tests on laboratory animals have shown that Denela cream has an ototoxic effect when instilled into the middle ear. Animals with an intact tympanic membrane, however, show no abnormality when exposed to Denela cream in the external auditory canal.

Although the systemic availability of prilocaine by percutaneous absorption of Denela is low, caution should be exercised in patients with anaemia, congenital or acquired methaemoglobinaemia or patients on concomitant therapy known to produce such conditions.

Patients treated with anti-arrhythmic drugs class III (eg, amiodarone) should be carefully monitored and ECG monitoring considered as cardiac effects may be additive.

Lidocaine and prilocaine have bacteriocidal and antiviral properties in concentrations above 0.5 – 2%. For this reason, although one clinical study suggests that the

immunization response, as assessed by local wheal formation, is not affected when Denela Cream is used prior to BCG vaccination, the results of intracutaneous injections of live vaccines should be monitored.

Denela 5% Cream contains macrogolglycerol hydroxystearate (hydrogenated polyoxyl castor oil) which may cause skin reactions.

#### **4.5 Interaction with other medicinal products and other forms of interaction**

Methaemoglobinaemia may be accentuated in patients already taking drugs known to induce the condition, e.g. sulphonamides, acetanilid, aniline dyes, benzocaine, chloroquine, dapsone, metoclopramide, naphthalene, nitrates and nitrites, nitrofurantoin, nitroglycerin, nitroprusside, pamaquine, para-aminosalicylic acid, phenacetin, phenobarbital, phenytoin, primaquine, quinine.

With large doses of Denela, consideration should be given to the risk of additional systemic toxicity in patients receiving other local anaesthetics or agents structurally related to local anaesthetics, since the toxic effects are additive.

Specific interaction studies with lidocaine/prilocaine and anti-arrhythmic drugs class III (eg, amiodarone) have not been performed, but caution is advised (see also Section 4.4).

Drugs that reduce the clearance of lidocaine (eg, cimetidine or betablockers) may cause potentially toxic plasma concentrations when lidocaine is given in repeated high doses over a long time period. Such interactions should therefore be of no clinical importance following short-term treatment with lidocaine (eg, Denela cream) at recommended doses.

#### **4.6 Fertility, pregnancy and lactation**

Animal studies do not indicate any direct or indirect harmful effects on pregnancy, embryo-foetal development, parturition or postnatal development.

##### Pregnancy

Lidocaine and prilocaine cross the placental barrier and may be absorbed by the foetal tissues. It is reasonable to assume that lidocaine and prilocaine have been used in a large number of pregnant women and women of childbearing age. No specific disturbances to the reproductive process have so far been reported, e.g. an increased incidence of malformations or other directly or indirectly harmful effects on the foetus. However caution should be exercised when used in pregnant women.

## Lactation

Lidocaine and, in all probability, prilocaine are excreted in breast milk, but in such small quantities that there is generally no risk of the child being affected at therapeutic dose levels.

### **4.7 Effects on ability to drive and use machines**

Denela has no influence on driving ability and the ability to operate machines when used at the recommended doses.

### **4.8 Undesirable effects**

Common (>1/100)	Skin	Transient local reactions at the application site such as paleness, erythema (redness) and oedema. <sup>1,2,3)</sup>  An initial and usually mild sensation of burning, itching or warmth at the application site <sup>2,3)</sup>
Uncommon (1/1000 to 1/100)	Skin	An initial mild burning, itching sensation or warmth at the application site <sup>1)</sup>  Local paresthesia at the application site, e.g. tingling sensation <sup>2)</sup>  Skin irritation at the application site <sup>3)</sup>
Rare (<1/1000)	General	Methaemoglobinaemia. <sup>1)</sup>  Rare cases of discrete local lesions at site of administration such as purpuric or petechial, especially at longer application time in children with atopic dermatitis or mollusca contagiosa <sup>1)</sup>  Corneal irritation after accidental eye exposure <sup>1)</sup>  In rare cases, local anaesthetic preparations have been associated with allergic reactions (in the most severe cases anaphylactic shock) <sup>1,2,3)</sup>

1) Intact skin

2) Genital Mucosa

3) Leg ulcer

## Paediatric population

In clinical trials 298 neonates and infants aged up to 12 months were treated with Emla Cream (Table 3). A large number of infants and children aged 1 year and older have been treated with Emla in clinical trials and in clinical practice since 1984.

**Table 3. Number of paediatric patients, up to 12 months old, included in clinical studies with Emla, by age group**

Group	Number of patients
Pre-term neonates	21
Age 0–1 months	148
Age 1–3 months	55
Age 3–12 months	74
<b>Total number</b>	<b>298</b>

Frequency, type and severity of adverse reactions are similar in the paediatric and adult age groups, except for methaemoglobinaemia, which is more frequently observed, often in connection with overdose, in neonates and infants aged 0 to 12 months.

Rare cases of clinically significant methaemoglobinaemia in children have been reported in literature. Prilocaine, one of the components of Denela, may in high doses cause an increase in the methaemoglobin level, particularly in susceptible individuals (Section 4.4) and in conjunction with other methaemoglobin-inducing agents. Clinically significant methaemoglobinaemia should be treated with a slow intravenous injection of methylthionium chloride (Section 4.9).

### 4.9 Overdose

Rare cases of clinically significant methaemoglobinaemia have been reported. Prilocaine in high doses may cause an increase in the methaemoglobin plasma levels particularly in conjunction with methaemoglobin-inducing agents (e.g. sulphonamides).

Clinically significant methaemoglobinaemia should be treated with a slow intravenous injection of methylene blue.

Should other symptoms of systemic toxicity occur, the signs are anticipated to be similar in nature to those following the administration of local anaesthetics by other routes of administration. Local anaesthetic toxicity is manifested by symptoms of

nervous system excitation and, in severe cases, central nervous and cardiovascular depression.

Severe neurological symptoms (convulsions, CNS depression) must be treated symptomatically by respiratory support and the administration of anticonvulsive drugs; circulatory signs are treated in line with recommendations for resuscitation.

Since the rate of absorption from intact skin is slow, a patient showing signs of toxicity should be kept under observation for several hours following emergency treatment.

## **5 PHARMACOLOGICAL PROPERTIES**

### **5.1 Pharmacodynamic properties**

Pharmacotherapeutic group: Local anaesthetics

ATC Code: N01B B20

Denela Cream provides dermal analgesia. The depth of analgesia depends upon the application time and the dose. Denela causes transient local peripheral vasoconstriction or vasodilation at the treated area.

In patients with atopic dermatitis, a similar but shorter vascular reaction is seen, with erythema occurring after 30-60 minutes, indicating more rapid absorption through the skin (see section 4.5 Special precautions and special warnings for use).

### **Paediatric population**

#### Clinical safety studies

Methaemoglobin formation after the use of Emla in term infants was studied with the aim to establish the safety of 1 g Emla 5% Cream. Forty-seven neonates and infants, aged 0-3 months, with a post conceptual age of  $\geq 37$  weeks were included in a double blind, randomized, placebo-controlled study. Methaemoglobin concentrations before treatment with Emla and placebo were in the range 0.67-1.57% and 0.50-1.53%, respectively. After treatment with 1 g Emla /placebo for 60-70 min methaemoglobin concentrations were 0.50-2.53% for Emla and 0.50-1.53% for placebo. From 3.5 to 13 h after application the concentrations were significantly higher with Emla than with placebo, but were clinically insignificant. One sample, in the Emla group (2.53%), had a methaemoglobin concentration above the reference value of 2%.

Altogether, data from eleven clinical studies in neonates and infants showed that peak methaemoglobin concentrations occur about 8 hours after epicutaneous Emla administration, are clinically insignificant with recommended dosage, and return to normal values after about 12-13 hours. Methaemoglobin formation is related to the cumulative amount of prilocaine percutaneously absorbed, and may therefore increase with prolonged application times of Denela.

Physiological methaemoglobin concentrations in both paediatric patients and adults are normally maintained below 2%. A major increase in methaemoglobin (to a concentration of 25-30%) will cause signs and symptoms of hypoxaemia. In neonates elevated methaemoglobin levels up to 5–6% are not regarded as clinically significant.

### Circumcision

In two randomized, double-blind, placebo-controlled studies in full-term neonates aged 1 to 4 days Emla Cream (0.5 or 1 g) was applied on the prepuce for one hour before circumcision, covered with an occlusive dressing. In the study using 0.5 g Emla there were no significant differences with placebo in assessment of pain performed by evaluating facial expressions or heart rate, respiratory rate, oxygen saturation, or in general skin colour.

Emla Cream (1 g) significantly reduced the pain during parts of the circumcision procedure, as demonstrated by less facial activity, reduction in duration of cry and lower heart rates. No differences were found for oxygen saturation, respiratory rate and Neonatal Infant Pain Scale (NIPS) – which includes facial expression, cry, breathing pattern and state of arousal.

### Vaccination

Two randomized double-blind, placebo-controlled studies in infants and neonates looked at anaesthetic efficacy of Emla Cream in vaccinations and the effect on the immunogenicity of live vaccines.

The first study used Emla Cream prior to subcutaneous measles-mumps-rubella vaccine, in patients aged 12-15 months, where 1g of cream was applied for 60 – 180 minutes. Emla significantly reduced vaccination pain versus placebo, demonstrated by difference between the pre- and post-vaccination total score on the Modified Behavioural Pain Scale (MBPS - includes measurement of facial expression, cry and body movement). No difference versus placebo was seen with the separate assessment of proportion of patients that cry and duration of cry.

The second used Emla Cream prior to intramuscular diphtheria-pertussis-tetanus-inactivated poliovirus-*Haemophilus influenzae b* or Hepatitis B vaccines in patients aged 0-6 months, where 1 or 2g of cream was applied to patients aged 0-4 and 6 months respectively, for 60-180 minutes. Emla significantly reduced vaccination pain versus placebo, demonstrated as above, for the 6 month-old group, however in the 0-4 month old group there was high variation in treatment response. In the 2 and 4 month-

old groups, Emla gave reduced pain versus placebo, however statistical significance was not shown ( $p=0.120$  and  $0.225$  respectively).

Within both studies, the use of Emla did not affect mean antibody titres, rate of seroconversion, or the proportion of patients achieving protective or positive antibody titres post immunization, as compared to placebo treated patients.

## 5.2 Pharmacokinetic properties

Systemic absorption of lidocaine and prilocaine from Denela Cream is dependent upon the dose, application time, and the thickness of the skin, which varies between different areas of the body.

**Intact skin:** In order to provide reliable dermal analgesia, Denela Cream should be applied under an occlusive dressing for at least 1 hour. The duration of analgesia after an application time of 1-2 hours is at least 2 hours after removal of the dressing.

After the application of Denela Cream to intact male genital skin for 15 minutes (median 1g), plasma concentrations of lidocaine and prilocaine (mean 6.6 nanogram/ml and 4.1 nanogram/ml) were reached after approximately 1.5 hours.

After application to the thigh in adults (60 g cream/400 cm<sup>2</sup> for 3 hours) the extent of absorption was approximately 5% of lidocaine and prilocaine. Maximum plasma concentrations (mean 0.12 and 0.07 µg/ml) were reached approximately 2-6 hours after the application.

The extent of systemic absorption was approximately 10% following application to the face (10 g/100 cm<sup>2</sup> for 2 hours). Maximum plasma levels (mean 0.16 and 0.06 µg/ml) were reached after approximately 1.5-3 hours.

**Genital mucosa:** Absorption from the genital mucosa is more rapid than after application to the skin. After the application of 10 g Emla Cream for 10 minutes to vaginal mucosa maximum plasma concentrations of lidocaine and prilocaine (mean 0.18 micrograms/ml and 0.15 micrograms/ml respectively) were reached after 20-45 minutes.

### Paediatric population

Following the application of 1 g Emla Cream in infants/neonates below 3 months of age, to approx 10 cm<sup>2</sup> for one hour, the maximum plasma concentrations of lidocaine and prilocaine were 0.135 micrograms/ml and 0.107 micrograms/ml respectively.

Following the application of 2 g Emla Cream in infants between 3 and 12 months of age, to approx 16 cm<sup>2</sup> for four hours, the maximum plasma concentrations of

lidocaine and prilocaine were 0.155 micrograms/ml and 0.131 micrograms/ml respectively.

Following the application of 10 g of Emla Cream in children between 2 and 3 years of age, to approx 100 cm<sup>2</sup> for two hours, the maximum plasma concentrations of lidocaine and prilocaine were 0.315 micrograms/ml and 0.215 micrograms/ml respectively.

Following the application of 10-16 g Emla Cream in children between 6 and 8 years of age, to approx 100-160 cm<sup>2</sup> for two hours, the maximum plasma concentrations of lidocaine and prilocaine were 0.299 micrograms/ml and 0.110 micrograms/ml respectively.

### **5.3 Preclinical safety data**

Lidocaine and prilocaine are well established active ingredients.

## **6 PHARMACEUTICAL PARTICULARS**

### **6.1 List of excipients**

Macroglycerol hydroxystearate

Carbomer

Sodium hydroxide

Purified water

### **6.2 Incompatibilities**

None known.

### **6.3 Shelf life**

24 months

In-use shelf life: 3 months

#### **6.4 Special precautions for storage**

Store below 25°C, do not freeze.

#### **6.5 Nature and contents of container**

Collapsible white aluminum 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 by 5 g tubes with 12 occlusive dressings – also referred to as a ‘pre-medication pack’
- 1 by 5 g tube with 2 occlusive dressings
- 1 b 5 g tube

30g Packs:

- 1 by 30 g tube with a sterile wooden spatula – also referred to as a ‘surgical pack’

#### **6.6 Special precautions for disposal**

No special requirements.

### **7 MARKETING AUTHORISATION HOLDER**

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**8      MARKETING AUTHORISATION NUMBER(S)**

PL 17507/0119

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