

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Denela 5% Cream

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

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

Excipient with known effect: macrogolglycerol hydroxystearate. Each gram of cream contains 19 mg of macrogolglycerol hydroxystearate (hydrogenated polyoxyl castor oil)
For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Cream
White soft cream.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

- Denela 5% Cream is indicated for:
- Topical anaesthesia of the skin in connection with:
 - needle insertion and injections eg. intravenous catheters, blood sampling or vaccination;
 - superficial surgical procedures, e.g.laser treatment and hair removal
 - in adults and in the paediatric population.
 - Topical anaesthesia of the genital mucosa, e.g. prior to superficial surgical procedures or infiltration anaesthesia in adults and adolescents ≥ 12 years.
 - Topical anaesthesia of leg ulcers to facilitate mechanical cleansing/debridement in adults only.

4.2 Posology and method of administration

Posology

Adults and adolescents

The details of the Indications or Procedures for use, with Dosage and Application Time are provided in Tables 1 and 2.

For further guidance on the appropriate use of the product in such procedures, please refer to *Method of administration*.

Table 1 Adults and adolescents 12 years of age and above

Indication/Procedure	Dosage and Application Time
Skin	
Minor procedures e.g. needle insertion and surgical treatment of localised lesions.	2 g (approx. half a 5 g tube) or approx. 1.5g/10cm ² for 1 to 5 hours ¹⁾
Dermal surgical procedures on larger areas in a hospital setting e.g. split skin grafting.	Approx. 1.5-2 g/10 cm ² for 2 to 5 hours ¹⁾
Dermal procedures on newly shaven skin of large	Maximum recommended dose: 60g.

body areas e.g. laser hair removal (self-application by patient)	Maximum recommended treated area: 600 cm ² for a minimum of 1 hour, maximum 5 hours. ¹⁾
Skin of male genital organs Prior to injection of local anaesthetics Skin of female genital organs Prior to injection of local anaesthetics ²⁾	1 g/10 cm ² for 15 minutes 1-2 g/10 cm ² for 60 minutes
Genital mucosa	
Surgical treatment of localised lesions, e.g. removal of genital warts (condylomata accuminata) and prior to injection of local anaesthetics.	Approx. 5-10 g Denela for 5-10 minutes. ^{1) 3) 4)}
Prior to cervical curettage	10 g of cream should be administered in lateral vaginal fornices for 10 minutes.
Leg ulcer(s)	
Adults only Mechanical cleansing /debridement	Approx. 1-2 g/10 cm ² up to a total of 10 g to the leg ulcer(s). ^{3) 5)} Application time: 30 to 60 minutes.

- 1) After a longer application time anaesthesia decreases.
- 2) On female genital skin, Denela alone applied for 60 or 90 minutes does not provide sufficient anaesthesia for thermocautery or diathermy of genital warts.
- 3) Plasma levels have not been determined in patients treated with doses of >10 g, (See also Section 5.2).
- 4) In adolescents weighing less than 20 kg the maximum dose of Denela on genital mucosa should be proportionally reduced.
- 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.

Paediatric population

Table 2 Paediatric patients 0-11 years of age

Age group	Procedure	Dosage and Application time
-	Minor procedures, e.g. needle insertion and surgical treatment of localised lesions.	Approx. 1g/10 cm ² for one hour (see details below)
Newborn infants and infants 0-2 months ^{1) 2) 3)}	-	Up to 1 g and 10 cm ² for one hour ⁴⁾
Infants 3-11 months ²⁾	-	Up to 2 g and 20 cm ² for one hour ⁵⁾
Toddlers and children 1-5 years	-	Up to 10 g and 100 cm ² for 1-5 hours ⁶⁾
Children 6-11 years	-	Up to 20 g and 200 cm ² for 1-5 hours ⁶⁾
Paediatric patients with atopic dermatitis	Prior to removal of mollusca	Application time: 30 minutes

- 1) 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, see sections 4.4 and 4.8.
- 2) Denela should not be used in infants up to 12 months of age receiving treatment with methaemoglobin-inducing agents, because of safety concerns, see sections 4.4 and 4.8.

- 3) Denela should not be used at less than 37 weeks gestational age, because of safety concerns, see section 4.4.
- 4) Application for > 1 hour has not been documented.
- 5) No clinically significant increase in methaemoglobin levels has been observed after an application time of up to 4 hours on 16 cm².
- 6) After longer application time anaesthesia decreases.

Safety and efficacy for the use of Denela on genital skin and genital mucosa have not been established in children younger than 12 years.

Available paediatric data do not demonstrate adequate efficacy for circumcision.

Elderly

No dose reduction is necessary in elderly patients (see sections 5.1 and 5.2).

Hepatic impairment

A reduction of a single dose is not necessary in patients with impaired hepatic function (see section 5.2).

Renal impairment

A dose reduction is not necessary among patients with restricted renal function.

Method of administration

Cutaneous use

The protective membrane of the tube is perforated by applying the cap.

One gram of Denela pressed out of a tube of 30 g is approximately 3.5 cm. If high levels of accuracy in dosing are required to prevent overdose (ie, at doses approaching the maximum in newborn infants or if two applications may be required in a 24 hour period), a syringe can be used where 1 mL = 1 g.

A thick layer of Denela should be applied to the skin, including genital skin, under an occlusive dressing. For application to larger areas, such as split-skin grafting, an elastic bandage should be applied on top of the occlusive dressing to give an even distribution of cream and protect the area. In the presence of atopic dermatitis, the application time should be reduced.

For procedures related to genital mucosa, no occlusive dressing is required. The procedure should be commenced immediately after removal of the cream.

For procedures related to leg ulcers, a thick layer of Denela should be applied under an occlusive dressing. Cleansing should start without delay after removal of the cream.

The Denela tube is intended for single use when used on leg ulcers: The tube with any remaining contents should be discarded after each occasion that a patient has been treated.

4.3 Contraindications

Hypersensitivity to lidocaine and/or prilocaine or local anaesthetics of the amide type or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Patients with defective glucose-6-phosphate dehydrogenase, hereditary or idiopathic methaemoglobinaemia are more susceptible to drug induced signs of methaemoglobinaemia. In glucose-6-phosphate dehydrogenase deficient patients the antidote methylene blue is ineffective at methaemoglobin reduction, and is capable of oxidising haemoglobin itself, and therefore methylene blue therapy cannot be given.

Due to insufficient data on absorption, 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 dose, area and time of application (see Section 4.2).

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, the eye should immediately be rinsed with water or sodium chloride solution and protected 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.

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 (castor oil polyoxyl hydrogenated), which may cause skin reactions.

Paediatric population

Studies have been unable to demonstrate the efficacy of Denela for heel lancing in newborn infants. In newborn 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 within the recommended dosing.

If the recommended dose is exceeded the patient should be monitored for system adverse reactions secondary to methaemoglobinaemia (see sections 4.2, 4.8 and 4.9).

Denela should not be used:

- in newborn infants/infants up to 12 months of age receiving concomitant treatment with methaemoglobin-inducing agents.
- in preterm newborn infants with a gestational age less than 37 weeks as they are at risk of developing increased methaemoglobin levels.

Safety and efficacy for the use of Denela on genital skin and genital mucosa have not been established in children younger than 12 years.

Available paediatric data do not demonstrate adequate efficacy for circumcision.

4.5 Interaction with other medicinal products and other forms of interaction

Prilocaine in high doses may cause an increase in methaemoglobin levels particularly in conjunction with methaemoglobin-inducing medicinal products (e.g. sulphonamides, nitrofurantoin, phenobarbital, phenytoin). This list is not exhaustive.

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.

Paediatric population

Specific interaction studies in children have not been performed. Interactions are likely to be similar to the adult population.

4.6 Fertility, pregnancy and lactation

Pregnancy

Although topical application is associated with only a low level of systemic absorption, the use of Denela in pregnant women should be undertaken with care because insufficient data are available concerning the use of Denela in pregnant women. However, animal studies do not indicate any direct or indirect negative effects on pregnancy, embryo-foetal development, parturition or postnatal development. Reproduction toxicity has been shown with subcutaneous/intramuscular administration of high doses of lidocaine or prilocaine much exceeding the exposure from topical application (see section 5.3).

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.

Breastfeeding

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. Denela can be used during breastfeeding if clinically needed.

Fertility

Animal studies have shown no impairment of the fertility of male or female rats (see section 5.3).

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

Summary of the safety profile

The most frequently observed adverse drug reactions (ADRs) are related to administration site conditions (transient local reactions at the application site), reported as common.

Tabulated list of adverse reactions

The incidences of the Adverse Drug Reactions (ADRs) associated with prilocaine/lidocaine therapy is tabulated below. The table is based on adverse events reported during clinical trials, and/or post-marketing use. Their frequency of Adverse Reactions is listed by MedDRA System Organ Class (SOC) and at the preferred term level. Within each System Organ Class, adverse reactions are listed under frequency categories of: very common ($\geq 1/10$), common ($\geq 1/100$ to $< 1/10$), uncommon ($\geq 1/1,000$ to $< 1/100$), rare ($\geq 1/10,000$ to $< 1/1,000$), very rare ($< 1/10,000$). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Table 3 Adverse reactions

System Organ Class	Common	Uncommon	Rare
Blood and lymphatic system disorders			Methaemoglobinaemia ¹
Immune system disorders			Hypersensitivity ^{1, 2, 3}
Eye disorders			Corneal irritation ¹
Skin and subcutaneous tissue disorders			Purpura ¹ , Petechiae ¹ (especially after longer application times in children with atopic dermatitis or mollusca contagiosa)
General disorders and administration site conditions	Burning sensation ^{2,3} Application site pruritus ^{2, 3} Application site erythema ^{1, 2, 3} Application site oedema ^{1, 2, 3} Application site warmth ^{2, 3} Application site pallor ^{1, 2, 3}	Burning sensation ¹ Application site irritation ³ Application site pruritus ¹ Application site paraesthesia ² such as tingling Application site warmth ¹	

- 1) Skin
- 2) Genital Mucosa
- 3) Leg ulcer

*Paediatric population*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 newborn infants and infants aged 0 to 12 months.

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via HPRA Pharmacovigilance, Earlsfort Terrace, IRL – Dublin 2; Tel: +353 1 6764971; Fax: +353 1 6767836. Website: www.hpra.ie; E-mail: medsafety@hpra.ie.

4.9 Overdose

Rare cases of clinically significant methaemoglobinaemia have been reported. Prilocaine in high doses may cause an increase in the methaemoglobin levels, particularly in susceptible individuals (section 4.4), with too frequent dosing in newborn infants and infants below 12 months of age (section 4.2) and in conjunction with methaemoglobin-inducing medicinal products (e.g. sulphonamides, nitrofuradantin, phenytoin and phenobarbital). 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.

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 medicinal products; 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; amides

ATC Code: N01B B20

Mechanism of action

Denela Cream provides dermal analgesia through the release of lidocaine and prilocaine from the cream into the epidermal and dermal layers of the skin and the vicinity of dermal pain receptors and nerve endings. Lidocaine and prilocaine are amide-type local anaesthetics. They both stabilize neuronal membranes by inhibiting the ionic fluxes required for the initiation and conduction of impulses, thereby producing local anaesthesia. The quality of anaesthesia depends upon the application time and the dose.

Skin

Denela is applied to intact skin under an occlusive dressing. The time needed to achieve reliable anaesthesia of intact skin is 1 to 2 hours, depending on the type of procedure. The local anaesthetic effect improves with longer application times from 1 to 2 hours in most parts of the body, with the exception of the skin of the face and the male genitals. Because of thin facial skin and high tissue blood flow, maximal local anaesthetic effect is obtained after 30-60 minutes on the forehead and on the cheeks. Similarly, local anaesthesia of the male genitals is achieved after 15 minutes. The duration of anaesthesia following the application of Denela for 1 to 2 hours is at least 2 hours after removal of the dressing, except in the face where the duration is shorter. Denela is equally effective and has the same anaesthetic onset time across the range of light to dark pigmented skin (skin types I to VI).

In clinical studies of prilocaine/lidocaine cream on intact skin, no differences in safety or efficacy (including anaesthetic onset time) were observed between geriatric patients (aged 65 to 96 years) and younger patients.

Denela produces a biphasic vascular response involving initial vasoconstriction followed by vasodilatation at the application site (see section 4.8). Irrespective of the vascular response, Denela facilitates the needle procedure

compared to placebo cream. 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 4.4). Denela may cause a transient increase in skin thickness, partly caused by hydration of the skin under the occlusive dressing. The skin thickness decreases over the course of 15 minutes air exposure.

The depth of cutaneous anaesthesia increases with application time. In 90% of patients the anaesthesia is sufficient for the insertion of a biopsy punch (4 mm diameter) to a depth of 2 mm after 60 minutes and 3 mm after 120 minutes prilocaine/lidocaine cream treatment.

The use of Denela prior to measles-mumps-rubella or intramuscular diphtheria-pertussis-tetanus-inactivated poliovirus-*Haemophilus influenzae b* or Hepatitis B vaccines does 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.

Genital mucosa

Absorption from the genital mucosa is more rapid and onset time is shorter than after application to the skin. After a 5-10 minute application of prilocaine/lidocaine cream to female genital mucosa the average duration of effective analgesia to an argon laser stimulus, which produced a sharp, pricking pain was 15-20 minutes (individual variations in the range 5-45 minutes).

Leg ulcers

Reliable anaesthesia for the cleansing of leg ulcers is achieved after an application time of 30 minutes in most patients. An application time of 60 minutes may improve the anaesthesia further. The cleansing procedure should start within 10 minutes of removal of the cream. Clinical data from a longer waiting period are not available. Prilocaine/lidocaine cream reduces the postoperative pain for up to 4 hours after debridement. It also reduces the number of cleansing sessions required to achieve a clean ulcer compared to debridement with placebo cream. No negative effects on ulcer healing or bacterial flora have been observed.

Paediatric population

Clinical studies involved more than 2,300 paediatric patients of all age groups and demonstrated efficacy for needle pain (venipuncture, cannulation, sc and im vaccinations, lumbar puncture), laser treatment of vascular lesions, and curettage of molluscum contagiosum. Prilocaine/lidocaine cream diminished the pain of both needle insertion and injection of vaccines. Analgesic efficacy increased from 15 to 90 minutes application on normal skin but on vascular lesions 90 minutes provided no benefit over 60 min. There was no benefit of prilocaine/lidocaine versus placebo for liquid nitrogen cryotherapy of common warts. No adequate efficacy for circumcision could be demonstrated.

Eleven clinical studies in neonates and infants showed that peak methaemoglobin concentrations occur about 8 hours after epicutaneous prilocaine/lidocaine 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. The use of prilocaine/lidocaine cream prior to measles-mumps-rubella or intramuscular diphtheria-pertussis-tetanus-inactivated poliovirus-*Haemophilus influenzae b* or Hepatitis B vaccines 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

Absorption, distribution, biotransformation and elimination

Systemic absorption of lidocaine and prilocaine from Denela Cream is dependent upon the dose, area of application and application time. Additional factors include thickness of the skin (which varies between different areas of the body), other conditions such as skin diseases, and shaving. Following application to leg ulcers, the characteristics of the ulcers may also affect the absorption. Plasma concentrations after treatment with prilocaine/lidocaine cream are 20-60% lower for prilocaine than for lidocaine, because of a larger volume of distribution and more rapid clearance. The major elimination pathway of lidocaine and prilocaine is via hepatic metabolism and metabolites are renally excreted. However, the rate of metabolism and elimination of the local

anaesthetics after topical application of Denela are governed by the rate of absorption. Therefore, a decrease in clearance, such as in patients with severely impaired liver function, has limited effects on the systemic plasma concentrations after a single dose of Denela, and after single doses repeated once daily short term (up to 10 days).

Symptoms of local anaesthetic toxicity become increasingly apparent at increasing plasma concentration from 5 to 10 µg/mL of either active substance. It should be assumed that the toxicity of lidocaine and prilocaine are additive.

Intact skin

After application to the thigh in adults (60 g cream/400 cm² 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 cm² for 2 hours). Maximum plasma levels (mean 0.16 and 0.06 µg/ml) were reached after approximately 1.5-3 hours.

In studies of split-skin grafting in adults application for up to 7 hours 40 minutes to the thigh or upper arm to an area of up to 1,500 cm² resulted in maximum plasma concentrations not exceeding 1.1 µg/mL lidocaine and 0.2 µg/mL prilocaine.

Genital mucosa

After the application of 10 g prilocaine/lidocaine 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.

Leg ulcer

Following a single application of 5 to 10 g of prilocaine/lidocaine cream to leg ulcers with an area of up to 64 cm² for 30 minutes, the maximum plasma concentrations of lidocaine (range 0.05-0.25 µg/mL, one individual value of 0.84 µg/mL) and of prilocaine (0.02-0.08 µg/mL) were reached within 1 to 2.5 hours.

After an application time of 24 hours to leg ulcers with an area of up to 50-100 cm², the maximum plasma concentrations of lidocaine (0.19-0.71 µg/mL) and of prilocaine (0.06-0.28 µg/mL) were usually reached within 2 to 4 hours.

Following repeated application of 2-10 g prilocaine/lidocaine cream to leg ulcers with an area of up to 62 cm² for 30-60 minutes 3-7 times a week for up to 15 doses during a period of one month, there was no apparent accumulation in plasma of lidocaine and its metabolites monoglycine xylidide and 2,6-xylidine or of prilocaine and its metabolite ortho-toluidine. The maximum observed plasma concentration for lidocaine, monoglycine xylidide and 2,6-xylidine were 0.41, 0.03 and 0.01 µg/mL respectively. The maximum observed plasma concentrations for prilocaine and ortho-toluidine were 0.08 µg/mL and 0.01 µg/mL respectively.

Following repeated application of 10 g prilocaine/lidocaine cream to chronic leg ulcers with an area between 62-160 cm for 60 minutes once daily during 10 consecutive days, the mean maximum plasma concentration of the sum of lidocaine and prilocaine concentrations was 0.6 µg/mL. The maximum concentration does not depend on the patient's age but is significantly (p<0.01) related to the size of the ulcer area. Increasing the ulcer area by 1 cm² results in an increased C_{max} for the sum of lidocaine and prilocaine concentrations of 7.2 ng/mL. The sum of the maximum plasma concentrations of lidocaine and prilocaine is less than one-third of those associated with toxic reactions, with no apparent accumulation over 10 days.

Special populations

Elderly patients

Plasma concentrations of lidocaine and prilocaine in both geriatric and non-geriatric patients following application of prilocaine/lidocaine cream to intact skin are very low and well below potentially toxic levels.

Paediatric population

The maximum plasma concentrations of lidocaine and prilocaine after application of prilocaine/lidocaine cream in paediatric patients of different ages were also below potentially toxic levels. See table 4.

Table 4. Plasma concentrations of lidocaine and prilocaine in paediatric age groups from 0 months to 8 years of age

Age	Applied amount of cream	Application time of the cream on the skin	Plasma concentration [ng/ml] Lidocaine/Prilocaine
0 - 3 months	1 g/10 cm ²	1 hour	135/107
3 - 12 months	2 g/16 cm ²	4 hours	155/131
2 - 3 years	10 g/100 cm ²	2 hours	315/215
6 - 8 years	10 - 16 g/100-160 cm ² (1 g/ 10 cm ²)	2 hours	299/110

5.3 Preclinical safety data

In animal studies the toxicity noted after high doses of either lidocaine or prilocaine, alone or in combination, consisted of effects on the central nervous and cardiovascular systems. When lidocaine and prilocaine were combined, only additive effects were seen, with no indication of synergism or unexpected toxicity. Both active substances were shown to have a low oral acute toxicity, providing a good safety margin in the event that it is inadvertently swallowed. In studies on reproduction toxicity, embryotoxic or fetotoxic effects of lidocaine were detected at doses of 25 mg/kg s.c. in the rabbit and for prilocaine starting at doses of 100 mg/kg i.m. in the rat. At doses below the maternal toxic range in the rat, lidocaine has no effect on the postnatal development of the offspring. An impairment of the fertility of male or female rats by lidocaine or prilocaine was not observed. Lidocaine crosses the placental barrier by means of simple diffusion. The ratio of the embryofetal dose to the maternal serum concentration is 0.4 to 1.3.

Neither local anaesthetic showed a genotoxic potential in either in vitro or in vivo genotoxicity tests. Cancer studies have not been performed with either lidocaine or prilocaine alone or in combination, due to the indication and duration of therapeutic use of these active substances.

A metabolite of lidocaine, 2,6-dimethylaniline, and a metabolite of prilocaine, σ-toluidine, showed evidence of genotoxic activity. These metabolites have been shown to have carcinogenicity potential in preclinical toxicological studies evaluating chronic exposure. Risk assessments comparing the calculated maximum human exposure from intermittent use of lidocaine and prilocaine, with the exposure used in preclinical studies, indicate a wide margin of safety for clinical use.

Local tolerance studies using a 1:1 (w/w) mixture of lidocaine and prilocaine as an emulsion, cream or gel indicated that these formulations are well tolerated by intact and damaged skin and mucosal membranes.

A marked irritative reaction was seen after single ocular administration of a 50 mg/g lidocaine + prilocaine 1:1 (w/w) emulsion, in an animal study. This is the same concentration of local anaesthetics and a similar formulation as for Denela. This ocular reaction may have been influenced by the high pH of the formulation of the emulsion (approximately 9), but is probably also partly a result of the irritative potential of the local anaesthetics themselves.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Macrogolglycerol hydroxystearate (hydrogenated polyoxyl castor oil)
Carbomer (974P)
Sodium hydroxide
Purified water

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years
Shelf life after first opening the tube: 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.

5 g Packs:

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

30g Packs:

- 30 g tube with a wooden spatula

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Precautions to be taken before handling or administering the medicinal product

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

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

Teva B.V.
Swensweg 5
2031GA Haarlem
Netherlands

8 MARKETING AUTHORISATION NUMBER

PA1986/059/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of First Authorisation: 3rd May 2013

10 DATE OF REVISION OF THE TEXT

November 2017