# SUMMARY OF PRODUCT CHARACTERISTICS

## 1 NAME OF THE MEDICINAL PRODUCT

Nulbia 5% cream

## 2 QUALITATIVE AND QUANTITATIVE COMPOSITION

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

Excipient(s) with known effect:
Castor oil polyoxyl hydrogenated 19 mg per 1 gram of cream
For the full list of excipients, see section 6.1

## 3 PHARMACEUTICAL FORM

Cream

Nulbia is a white soft cream.

## 4 CLINICAL PARTICULARS

### 4.1 Therapeutic indications

Nulbia is indicated for:

- Topical anaesthesia of the skin in connection with:
  - needle insertion, e.g. intravenous catheters or blood sampling;
  - superficial surgical procedures;

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

Administration of Nulbia on genital mucosa, genital skin or leg ulcers should only be performed by a healthcare professional.

**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 localized lesions. | 2 g (approximately half a 5 g tube) or approximately 1.5 g / 10 $cm^2$ for 1 to 5 hours[1)] |
| Dermal procedures on newly shaven skin of large body areas, e.g. laser hair removal (self-application by patient) | Maximum recommended dose: 60 g. Maximum recommended treated area; 600 $cm^2$ for a minimum of 1 hour, maximum 5 hours[1)]. |
| Dermal surgical procedures on larger areas in a hospital setting, e.g. split-skin grafting. | Approximately 1.5-2 g / 10 $cm^2$ for 2 to 5 hours[1)]. |
| Skin of male genital organs<br>Prior to injection of local anaesthetics<br>Skin of female genital organs<br>Prior to injection of local anaesthetics[2)] | <br>1 g / 10 $cm^2$ for 15 minutes<br><br>1-2 g / 10 $cm^2$ for 60 minutes |
| **Genital mucosa** | |

| | |
|---|---|
| Surgical treatment of localized lesions, e.g. removal of genital warts (condylomata acuminata) and prior to injection of local anaesthetics | Approximately 5-10 g of cream for 5-10 minutes[1)3)4)]. |
| Prior to cervical curettage | 10 g of cream should be administered in the lateral vaginal fornices for 10 minutes. |
| **Leg ulcer(s)** | |
| Adults only<br>Mechanical cleansing/debridement | Approximately 1-2 g/10 $cm^2$ up to a total of 10 g to the leg ulcer(s)[3)5)].<br>Application time: 30-60 minutes |

[1)] After a longer application time anaesthesia decreases.

[2)] On female genital skin, Nulbia alone applied for 60 or 90 minutes does not provide sufficient anaesthesia for thermocautery or diathermy of genital warts.

[3)] Plasma concentrations 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 Nulbia on genital mucosa should be proportionally reduced.

[5)] Nulbia 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 localized lesions. | Approximately 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[1)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 below 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 section 4.4 and 4.8.
[2)] Nulbia 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)] Nulbia 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 $cm^2$.
[6)] After longer application times anaesthesia decreases.

Safety and efficacy for the use of Nulbia 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 Nulbia 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 (i.e., 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 Nulbia 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 Nulbia should be applied under an occlusive dressing.
Cleansing should start without delay after removal of the cream.

The Nulbia 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 special precautions for use

Patients with defective glucose-6-phosphate dehydrogenase, hereditary or idiopathic methaemoglobinaemia are more susceptible to active-substance-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 Nulbia should not be applied to open wounds (excluding leg ulcers).

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

Care should be taken when applying Nulbia 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 petechia and purpura (see Section 4.8). 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, Nulbia should be used with particular care since it may cause eye irritation and chemical burns to the eyes (see section 4.8). 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.

When Nulbia is used in children at any site of the body, children should be carefully watched to prevent them from accidental self-administration of Nulbia in their eyes.

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

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

Lidocaine and prilocaine have bactericidal 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 Nulbia is used prior to BCG vaccination, the results of intracutaneous injections of live vaccines should be monitored.

Nulbia contains castor oil polyoxyl hydrogenated which may cause skin reactions.

*Paediatric population*

Studies have been unable to demonstrate the efficacy of Nulbia for heel lancing in newborn infants.

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

Nulbia should not be used

- in newborn infants/infants up to 12 months of age receiving concomitant treatment with methaemoglobin-inducing agents.

- in pre-term 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 Nulbia 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, phenytoin, phenobarbital). This list is not exhaustive.

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

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

Medicinal products that reduce the clearance of lidocaine (e.g., 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 Nulbia in pregnant women should be undertaken with care because insufficient data are available concerning the use of Nulbia 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.

Nulbia 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

Nulbia has no or negligible influence on the ability to drive and use 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 application site), reported as common.

*Tabulated list of adverse reactions*

The incidences of the Adverse Drug Reactions (ADRs) associated with Nulbia 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 (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100), rare (≥1/10,000 to <1/1,000), very rare (<1/10,000) and not known (cannot be estimated from available data). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Table 3. Adverse reactions

| System Organ Class | Common | Uncommon | Rare | Not known |
|---|---|---|---|---|
| Blood and lymphatic system disorders | | | Methaemoglobinaemia[1] | |

| | | | | |
|---|---|---|---|---|
| Immune system disorders | | | Hypersensitivity[1, 2, 3] | |
| Injury, poisoning and procedural complications | | | | Chemical burns to eyes (see section 4.4) |
| 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]<br>Application site pruritus[2, 3]<br>Application site erythema[1, 2, 3]<br>Application site oedema[1, 2, 3]<br>Application site warmth[2, 3]<br>Application site pallor[1, 2, 3] | Burning sensation[1]<br>Application site irritation[3]<br>Application site pruritus[1]<br>Application site paraesthesia[2] such as tingling<br>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 (see Section 4.9), in newborn infants and infants aged 0 to 12 months.

Reporting of suspected adverse reactions

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 the Yellow Card Scheme Website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

## 4.9 Overdose

Rare cases of clinically significant methaemoglobinaemia have been reported. Prilocaine in high doses may cause an increase in 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. sulfonamides, nitrofurantoin, 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 (see also section 4.4).

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: anaesthetics, local, amides
ATC Code: N01B B20

Mechanism of action
Nulbia provides dermal anaesthesia 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**

Nulbia 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 Nulbia for 1 to 2 hours is at least 2 hours after removal of the dressing, except in the face where the duration is shorter. Nulbia 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 Lidocaine/Prilocaine 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.

Lidocaine/Prilocaine cream produces a biphasic vascular response involving an initial vasoconstriction followed by vasodilatation at the application site (see section 4.8). Irrespective of the vascular response, Lidocaine/Prilocaine cream 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). Nulbia 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 biopsy punch (4mm diameter) to a depth of 2 mm after 60 minutes and 3 mm after 120 minutes Nulbia treatment.

The use of Lidocaine/Prilocaine cream 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 Lidocaine/Prilocaine 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 variation 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. Lidocaine/Prilocaine cream reduces the postoperative pain for up to 4 hours after debridement. Lidocaine/Prilocaine cream 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, s.c. and i.m. vaccinations, lumbar puncture), laser treatment of vascular lesions, and curettage of molluscum contagiosum. Lidocaine/Prilocaine 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 minutes. There was no benefit of Lidocaine/Prilocaine cream versus placebo for liquid nitrogen cryotherapy of common warts. No adequate efficacy for circumcision could be demonstrated.

Eleven clinical studies in newborn infants and infants showed that peak methaemoglobin concentrations occur about 8 hours after epicutaneous Lidocaine/Prilocaine cream 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 Lidocaine/Prilocaine cream.

The use of Lidocaine/Prilocaine 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

The systemic absorption of lidocaine and prilocaine from Lidocaine/Prilocaine Cream is dependent upon the dose, area of application and application time. Additional factors include thickness of the skin (which varies in 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 concentration after treatment with Lidocaine/Prilocaine 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 Lidocaine/Prilocaine cream 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 Lidocaine/Prilocaine cream, 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*

Following application to the thigh in adults (60 g cream/400 $cm^2$ 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 application.

The extent of systemic absorption was approximately 10% following application to the face (10 g/100 $cm^2$ for 2 hours). Maximum plasma concentrations (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 $cm^2$ 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 Lidocaine/Prilocaine cream for 10 minutes to vaginal mucosa, maximum plasma concentrations of lidocaine and prilocaine (mean 0.18 μg/mL and 0.15 μg/mL respectively) were reached after 20-45 minutes.

*Leg ulcer*
Following a single application of 5 to 10 g of Lidocaine/Prilocaine cream to leg ulcers with an area of up to 64 $cm^2$ 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 $cm^2$, 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 2-4 hours.

Following repeated application of 2-10 g Lidocaine/Prilocaine cream to leg ulcers with an area of up to 62 $cm^2$ 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 monoglycinexylidide and 2,6-xylidine or of prilocaine and its metabolite ortho-toluidine. The maximum observed plasma concentration for lidocaine, monoglycinexylidide 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 Lidocaine/Prilocaine cream to chronic leg ulcers with an area between 62-160 $cm^2$ 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 $cm^2$ results in an

increased $C_{max}$ for the sum of lidocaine and prilocaine concentrations of 7.2ng/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 applications of Lidocaine/Prilocaine 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 Lidocaine/Prilocaine 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 Lidocaine/Prilocaine Cream 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 embryo fetal 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 Nulbia. 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

Castor oil polyoxyl hydrogenated
Carbomer 974P
Sodium hydroxide (for pH adjustment)
Water purified.

## 6.2 Incompatibilities

Not applicable

## 6.3 Shelf life

36 months

After first opening: 6 months

## 6.4 Special precautions for storage

Store below 30 °C. Do not refrigerate or freeze.

## 6.5 Nature and contents of container

Aluminium tube internally varnished with an epoxy phenolic resin, sealed with a latex sealant and closed with a polypropylene screw cap. The dressing is a polyurethane film with acrylate adhesive.

Pack sizes:

1 x 30g tube

1 x 5g tube

1 x 5g tube with 2 dressings

1 x 5g tube with 3 dressings

5 x 5g tubes

5 x 5g tubes with 12 dressings

Not all pack sizes may be marketed.

### 6.6 Special precautions for disposal

*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

Glenmark Pharmaceuticals Europe Limited
Laxmi House
2B Draycott Avenue
Kenton, Middlesex
HA3 0BU
United Kingdom

## 8 MARKETING AUTHORISATION NUMBER(S)

PL 25258/0225

## 9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

30/06/2021

## 10 DATE OF REVISION OF THE TEXT

03/10/2025