SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Lidocaine/Prilocaine 5 % cutaneous patch

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

1 g of emulsion for a cutaneous patch of 10 cm^2 contains;

Lidocaine 0.0250 g

Prilocaine 0.0250 g

Excipient(s) with known effect:

1 g of emulsion for a cutaneous patch of 10 cm^2 contains 0.0200 g castor oil.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Cutaneous Patch.

Cutaneous patch consisting of an absorbent disc of approximately 10 cm^2 impregnated with 1 gram of an emulsion containing the eutectic mixture (1:1) of the two anaesthetics lidocaine (2.5%) and prilocaine (2.5%), surrounded by an adhesive foam ring, with the entire unit adherent to a laminated backing foil acting as an occlusive dressing.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Topical anaesthesia of the skin prior to:

- Needle insertion (sub-cutaneous or iv),
- Superficial, instrumental and laser beam surgical intervention.

4.2 Posology and method of administration

- **Posology**

Surface/ Age	Intervention	Application
Skin	Minor procedures, e.g. needle insertion and surgical treatment of localised lesions	The patch is applied to the skin area selected
Adults and adolescents 12 years and above		One or two patches to be applied at least 1 hour before intervention, Application time: 1 – 5 hours [1)]
Newborn infants and infants (0-2 months)[2,3,4,7)]		No more than one patch**.** Application time: up to 1 hour [5)]
Infants (3-11 months) [2, 3,)]		Up to 2 patches. Application time: up to 1 hour[6)]
Toddlers & Children (1-5 years)		Up to 10 patches Application time: 1 – 5 hours[1)]
Children (6-11 years)		Up to 20 patches Application time: 1 – 5 hours[1)]
Children with atopic dermatitis	Prior to curettage of mollusca	Application time: 30 minutes

1) The anaesthetic effect is reduced 5 hours after application.

2) 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 sections 4.4 and 4.8.

3) Until further clinical data is available, Lidocaine/Prilocaine 5 % should not be used in infants between 0-12 months of age receiving treatment with methaemoglobin - inducing agents, because of safety concerns, see sections 4.4 and 4.8.

4) Until further clinical data is available, Lidocaine/Prilocaine 5 % should not be used in preterm infants with a gestational age less than 37 weeks.

5) A longer application time than 1 hour has not been documented.

6) No clinically significant increase in methaemoglobin levels has been observed after an application time of up to 4 hours on 16 cm^2

7) Due to its size, the use of the patch should be avoided for some part of the bodies for new born and neonates (0-2 months).

Method of administration

For cutaneous use.

The cutaneous patch must be applied at least one hour before the intervention.

Make sure that the cutaneous surface to anesthetize is clean and dry.

To open the patch, take the aluminium corner for this purpose.

The white part of the cutaneous patch contains the anaesthetic, do not touch it.

Apply the cutaneous patch so that the white disc covers the area to be anesthetized.

Do not press the central part of the patch, to prevent leakage under the adhesive.

To ensure a good adhesion of the cutaneous patch, apply firmly around the edge.

Indicate the time of application on the cutaneous patch.

4.3 Contraindications

- Hypersensitivity to the active substances, the amide-type local aneasthetics or to any of the excipients listed in 6.1;
- Patients with congenital or idiopathic methaemoglobinaemia;
- Porphyria;
- Children/neonates younger than 3 months with a G6PD deficiency or suspected.

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. Lidocaine/prilocaine patches should not be used in children/neonates younger than 3 months with a G6PD deficiency or suspected. 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.

- Lidocaine/prilocaine patches should not be applied to damaged skin or open wounds (excluding leg ulcers) because the data on the absorption of the active substances are not sufficient.
- The efficacy of lidocaine/prilocaine during the capillary samples in the heel has not been clinically demonstrated.
- Care should be taken when applying lidocaine/prilocaine patches 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 patches for 30 minutes.

- When applied in the vicinity of the eyes, lidocaine/prilocaine patches should be used with particular care since it may cause eye irritation (see section 5.3). 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.
- In children/neonates younger than 3 months a transient, clinically insignificant increase in methaemoglobin plasma levels is commonly observed up to 12 hours after an application of lidocaine/prilocaine patches within the recommended dosing.
- Patients treated with antiarrhythmic class III drugs (e.g. 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 immunisation response is not affected when lidocaine/prilocaine patches are used prior to BCG vaccination, the results of intracutaneous injections of live vaccines should be monitored.

Paediatric population

Studies have been unable to demonstrate the efficacy of lidocaine/prilocaine for heel lancing in newborn infants. 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).

Until further clinical data is available, lidocaine/prilocaine should not be used in the following cases:

- in infants between 0 and 12 months of age receiving treatment with methaemoglobin inducing agents;
- in preterm infants with a gestational age less than 37 weeks;

- This product contains hydrogenated castor oil, which can cause skin reactions.
- Due to the presence of castor oil, there is a risk of sensitization, especially in children under 3 years.
- Athletes must be aware that this product contains an active substance that may lead to a positive result in case of anti-doping controls.

Precautions for use

- In young children, a special monitoring is recommended to maintain the cutaneous patch and to prevent a possible risk of ingestion or contact with the eyes, secondary to a manipulation of the patch by the child.
- In case of use of lidocaine/prilocaine prior to a regional anaesthetic, the quantities of local anaesthetics administered by transcutaneous route should be considered.

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 agents (e.g. sulphonamides, nitrofurantoin, phenytoin, phenobarbital). This list is not exhaustive.

The following combinations should be taken into account:

Other local anaesthetics

With large doses of lidocaine/prilocaine, 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 toxic effects are additive.

Methaemoglobin-inducing agents (sulfamides, dapsone, metoclopramide, flutamide, sodium nitroprussiate, injectable and local anaesthetics containing prilocaine), in particular in children/neonates younger than 3 months: risk of addition of methaemoglobin effects**.**

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).

Drugs that reduce the clearance of lidocaine (e.g. cimetidine or beta blockers) 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 (e.g. lidocaine/prilocaine patches) at recommended doses.

Paediatric population

Specific interaction studies in children have not been performed, but interactions are probably similar to the one observed in adults.

4.6 Fertility, pregnancy and lactation

Pregnancy

Although topical application is associated with only a low level of systemic absorption, the use of Lidocaine/Prilocaine 5% cutaneous patch in pregnant women should be undertaken with care because insufficient data are available concerning the use of Lidocaine/Prilocaine 5% cutaneous patch in pregnant women. However, animal studies do not indicate any direct or indirect harmful effects on pregnancy, embryo-fetal 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.

Breast-Feeding

Lidocaine and, in all probability, prilocaine are excreted into breast milk, but in such small quantities that there is generally no risk of the child being affected at therapeutic dose levels. Lidocaine/Prilocaine 5% cutaneous patch can be used during breast-feeding 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

Lidocaine/Prilocaine has no influence on the ability to drive and use machines at the recommended dosage.

4.8 Undesirable effects

Adverse reactions are divided into groups according to the MedDRA convention frequencies: 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), unknown (cannot be estimated with the available data).

System Organ Class	Uncommon	Rare
Blood and lymphatic system disorders		Methaemoglobinaemia
Immune system disorders		Hypersensitivity
Eye disorders		Corneal irritation after accidental eye exposure.
Skin and subcutaneous tissue disorders		Rare cases of discrete local lesions at site of administration such as Purpura, Petechiae (especially after longer application times in children with atopic dermatitis or mollusca contagiosa)
General disorders and administration site conditions	Burning sensation, itching sensation or warmth at the application site. Transient local reactions at the application site such as paleness, erythema (redness) and oedema	In rare cases, local anaesthetic preparations have been associated with allergic reactions (in the most severe cases anaphylactic shock).

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 at: 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 increase in the methaemoglobin plasma 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, 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.

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.

The application of massive doses of the combination lidocaine and prilocaine may lead to overdose; in this case, a monitoring in specialized environment should be maintained for several hours after the removal of the cutaneous patches, due to the delayed absorption of the two local anesthetics.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Local amide-type anaesthetic, ATC code: N01BB20.

Lidocaine/Prilocaine 5 % cutaneous patch contains 2 amide-type local anaesthetics: lidocaine and prilocaine.

Lidocaine/prilocaine is an oil-in-water emulsion, in which the oil phase consists of a eutectic mixture of lidocaine and prilocaine in the ratio 1:1. The emulsion of this oil in the water allows crossing the cutaneous barrier to get an efficient analgesia of the skin. Local anaesthetics acts directly on the nerves by blocking in a reversible, total and specific manner the nerve conduction. The molecular mass of lidocaine base is 234; the one of prilocaine base is 220. Their pKa is 7.7. and pH is 9.2.

Mechanism of action:

Lidocaine/prilocaine, applied on intact skin, provides dermal anaesthesia through the release of lidocaine and prilocaine from the cream into the epidermal and dermal layers of the skin and the accumulation of lidocaine and prilocaine in the vicinity of dermal pain receptors and nerve endings. Lidocaine and prilocaine are amide-type local anaesthetics.

Both substances stabilize the membrane of the nerve cells by inhibiting the flow of ions necessary for impulse conduction, and thereby induce local analgesia.

The quality of analgesia is dependent on application time and dose. The time needed to achieve reliable anaesthesia of intact skin is at least 1 hour.

Clinical efficacy and safety:

In clinical studies of lidocaine/prilocaine 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.

Pharmacodynamic effects:

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 lidocaine/prilocaine treatment.

Lidocaine/prilocaine is equally effective and has the same anaesthetic onset time across the range of light to dark pigmented skin (skin types I to VI).

The use of lidocaine/prilocaine prior to measles-mumps-rubella or intramuscular diphtheria-pertussis-tetanus-inactivated poliovirus-Haemophilus influenza 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 immunisation, as compared to placebo treated patients.

Lidocaine/prilocaine produces a biphasic vascular response involving initial vasoconstriction followed by vasodilatation at the application site (see section 4.8). Irrespective of the vascular response, lidocaine/prilocaine 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).

5.2 Pharmacokinetic properties

The available pharmacokinetic data are obtained from lidocaine/prilocaine cream 5% applied to intact skin.

Absorption

The systemic absorption of lidocaine and prilocaine from patches appears to depend on dose, area of application, time of application, the thickness of the skin at the site of application and other characteristics of the skin.

Intact skin

Approx. 5% of the lidocaine and prilocaine is absorbed by adults following application of lidocaine/prilocaine (60 g patches/400 cm^2 for 3 hours). The maximum plasma concentration (average 0.12 and 0.07 μg/ml for lidocaine and prilocaine respectively) is attained 2-6 hours after application.

Following application to facial skin (10 g/100 cm^2 for 2 hours) systemic absorption was approx.10 %. The maximum plasma concentration (average 0.16 and 0.06 μg/ml for lidocaine and prilocaine respectively) is attained 1.5-3 hours after application.

The plasma level of lidocaine and prilocaine is very low in both elderly and non-elderly patients following application to intact skin and far below the potentially toxic level.

Paediatric population

In children under 3 months the maximum plasma concentration of lidocaine and prilocaine was 0.135 μg/ml and 0.107 μg/ml respectively after application of 1 g lidocaine/prilocaine cream to 10 cm^2 over 1 hour. In 3-12 month old children 0.155 μg/ml and 0.131 μg/ml respectively was found following application of 2 g of lidocaine/prilocaine cream to 16 cm^2 over 4 hours. Approximately the same result was seen in children aged between 2 and 3 years old (0.315 μg/ml and 0,215 μg/ml after 10 g lidocaine/prilocaine cream to 100 cm^2 over 2 hours and finally 0.299 μg/ml and 0.110 μg/ml respectively in children aged 6-8 years after application of 10-16 g lidocaine/prilocaine cream to 100-160 cm^2 over 2 hours).

5.3 Preclinical safety data

The toxicity observed in animal studies at high doses of lidocaine and prilocaine either alone or in combination was: effects on the central nervous system and cardiovascular system.

The combination lidocaine and prilocaine caused only additive effects with no sign of synergy or unexpected toxicity. Both substances have a low oral acute toxicity and hence a good safety margin in the event of lidocaine/prilocaine being ingested by mistake.

In studies on reproduction toxicity, embryo-toxic or feto-toxic 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 mutagenic potential in either *in vitro* or *in vivo* mutagenicity 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 lignocaine, 2, 6-dimethylaniline, and a metabolite of prilocaine, *o*-toluidine, showed evidence of mutagenic 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 lignocaine 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.

•Preclinical studies on the adhesive used in the patch did not raise any concerns.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Laminated backing foil (aluminium foil with plastic film), absorbent disc (cellulose),

adhesive foam tape (polyethylene coated ring with acrylate adhesive),

macrogolglycerol hydroxystearate (hydrogenated castor oil),

carbomers,

sodium hydroxide,

purified water.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years

6.4 Special precautions for storage

Do not store above 25°C.

Do not refrigerate. Do not freeze.

6.5 Nature and contents of container

Lidocaine/Prilocaine patches consists of an occlusive dressing (user part) and a protective liner (closure part). The user part is composed of an aluminium/plastic backing laminate, an absorbent cellulose disc and a foam tape ring. The tape is polyethylene foam coated with acrylate adhesive. The closure part is an aluminium/plastic laminate. A peel-off seal between the backing and closure laminates encloses the disc, which is impregnated with lidocaine/prilocaine emulsion. Pack of 1 or 20.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Morningside Healthcare Ltd

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Leicester, LE19 1WP, UK

8 MARKETING AUTHORISATION NUMBER(S)

PL 20117/0291

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