1. Name of Finished Pharmaceutical Product

Topocain-LP Cream (Lidocaine 2.5% w/w and Prilocaine 2.5% w/w Cream)

2. Qualitative and quantitative composition

Each gram cream contains:
Lidocaine Ph. Eur. 25 mg
Prilocaine Ph. Eur. 25 mg

For excipients see List of excipients

3. Pharmaceutical Form

White homogenous cream

4. Clinical particulars

4.1 Therapeutic indications

Surface anaesthesia of the skin in connection with needle insertion and for superficial surgical procedures.

Surface anaesthesia of leg ulcers prior to cleaning and superficial surgical procedures, e.g. removal of fibrin, pus and necroses.

Surface anaesthesia of the genital mucosa.

4.2 Posology and method of administration

Adults

Intact skin:

	Dose and administration	**Application time**
For needle insertion e.g. insertion of intravenous cannula, taking of blood samples	Approx. 2 g per 10 cm^2. A thick layer of cream is applied to the skin and covered with an occlusive dressing.	1 hours; Maximum 5 hours
For minor superficial surgical procedures, e.g. removal of warts	1.5-2 g per 10 cm^2. A thick layer of cream is applied to the skin and covered with an occlusive dressing.	1 hours; Maximum 5 hours
For more extensive superficial surgical procedures in a hospital setting, e.g. split skin grafting	1.5-2 g per 10 cm^2. A thick layer of cream is applied to the skin and covered with an occlusive dressing.	2 hours; Maximum 5 hours

Leg Ulcers:
For cleaning of leg ulcers: approx. 1-2 g per 10 cm^2. The cream is applied in a thick layer to the surface of the ulcer, but not more than 10 g per treatment occasion. Cover the ulcer surface with an occlusive dressing.

An opened tube is intended for single use, and left-over cream should therefore be discarded after each treatment occasion.
Application time: at least 30 minutes.
For leg ulcers with tissue that is especially difficult to penetrate, the application time may be extended to 60 minutes. Cleaning of the ulcer should be begun within 10 minutes after removal of the cream.
TOPOCAIN-LP Cream has been used on up to 15 treatment occasions during a 1-2-month period without a reduction in effect or increase in the number of local reactions.

Genital use:
Skin*:*
Use before injection of local anaesthetics:
Men: 1 g per 10 cm^2. A thick layer of cream is applied to the skin.
Application time: 15 minutes.

Women: 1-2 g per 10 cm^2. A thick layer of cream is applied to the skin.
Application time: 60 minutes.

Mucosa:
For removal of condylomata or before injection of local anaesthetics: approx. 5-10 g, depending on the area treated. The whole surface including mucous membrane folds must be covered. Occlusion is not necessary.
Application time: 5-10 minutes.
The surgery may be begun immediately after removal of the cream.

Children

For needle insertion, removal of mollusca and other minor superficial surgical procedures:
1 g per 10 cm^2. A thick layer of cream is applied to the skin and covered with an occlusive dressing.
The dose should not exceed 1 gram per 10 cm^2 and should be adjusted according to the application area.

Age	**Application area**	**Application time**
0 – 3 months	maximum 10 cm^2 (total of 1 g) (maximum daily dose)	1 hour (note: not longer)
3 – 12 months	maximum 20 cm^2 (total of 2 g)	1 hour
1 – 6 years	maximum 100 cm^2 (total of 10 g)	1 hour; maximum 5 hours
6 – 12 years	maximum 200 cm^2 (total of 20 g)	1 hours; maximum 5 hours

Children with atopic dermatitis: reduced application time to 30 minutes.

4.3 Contraindication

Known hypersensitivity to local anaesthetics of the amide type or to any of the excipients.

4.4 Warnings and Precautions

Patients with glucose-6-phosphate dehydrogenase deficiency or congenital or idiopathic methaemoglobinaemia are more susceptible to drug-induced methaemoglobinaemia.

Due to insufficient data on absorption, TOPOCAIN-LP Cream should not be applied to open wounds other than leg ulcers.

Studies have been unable to demonstrate the efficacy of TOPOCAIN-LP Cream for heel lancing in neonates.

Care should be taken when applying TOPOCAIN-LP Cream to patients with atopic dermatitis. A shorter application time, 15-30 minutes, may be sufficient (see Pharmacodynamic properties).

Prior to curettage of mollusca in children with atopic dermatitis, an application time of 30 minutes is recommended.

TOPOCAIN-LP Cream should not be applied to the genital mucosa of children owing to insufficient data on absorption. However, when used in neonates for circumcision, a dose of 1.0 g lidocaine and prilocaine cream on the prepuce has proven to be safe.

Care should be taken not to allow TOPOCAIN-LP Cream to come in contact with the eyes as 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 in water or sodium chloride solution and protect it until sensation returns.

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

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

Patients treated with anti-arrhythmic drugs class III (e.g., amiodarone) should be under close surveillance and ECG monitoring considered, since 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 is not affected when lidocaine and prilocaine cream is used prior to BCG vaccination, the results of intra cutaneous injections of live vaccines should be monitored.

Until further clinical data are available, TOPOCAIN-LP Cream should not be used in the following cases:

(a) in infants between 0 and 12 months of age receiving treatment with methaemoglobin-inducing agents.

(b) in preterm infants with a gestational age less than 37 weeks.

4.5 Interactions with other medicines and other forms of interactions

Prilocaine in high doses may cause an increase in the methaemoglobin level particularly in conjunction with methaemoglobin-inducing agents (e.g., sulphonamides).

With large doses of TOPOCAIN-LP Cream, 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 (e.g., amiodarone) have not been performed, but caution is advised (see also Warnings and precautions).

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., TOPOCAIN-LP Cream) at recommended doses.

4.6 Fertility, pregnancy and lactation

Pregnancy

Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryonal/foetal development, parturition or postnatal development.

In both animal and humans, 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 potential. 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 Effect on ability to drive and use machines

Not applicable at the recommended dosage.

4.8 Undesirable effects

FREQUENCY OF ADVERSE EVENTS

Intact skin	
Common Events (>1%)	Skin: Transient local reactions at the application site such as paleness, erythema (redness) and oedema.
Uncommon Events (>0.1% and <1%)	Skin: Skin sensations (an initial mild burning or itching sensation at the application site).
Rare Events (<0.1%)	General: Methaemoglobinaemia (see Interactions with other medicines and other forms of interactions and Overdose). Rare cases of discrete local lesions at the application site, described as purpuric or petechial, have been reported, especially after longer

	application times in children with atopic dermatitis or mollusca contagiosa. Corneal irritation after accidental eye exposure. In rare cases, local anaesthetic preparations have been associated with allergic reactions (in the most severe instances anaphylactic shock).
Genital mucosa	
Common Events (>1%)	Application site: Transient local reactions such as erythema (redness), oedema and paleness. Local sensations (an initial, usually mild, burning sensation, itch or warmth at the application site).
Uncommon Events (>0.1% and <1%)	Application site: Local paraesthesia such as tingling.
Rare Events (<0.1%)	General: In rare cases, local anaesthetic preparations have been associated with allergic reactions (in the most severe instances anaphylactic shock).
Leg Ulcer	
Common Events (>1%)	Skin: Transient local reactions at the application site such as paleness, erythema (redness) and oedema. Skin sensations (an initial, usually mild burning sensation, itch or warmth at the application site).
Uncommon Events (>0.1% and <1%)	Skin: Skin irritation (at the application site).
Rare Events (<0.1%)	General: In rare cases, local anaesthetic preparations have been associated with allergic reactions (in the most severe instances anaphylactic shock).

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product

4.9 Overdose

Rare cases of clinically significant methaemoglobinaemia have been reported. Prilocaine in high doses may cause an increase in the methaemoglobin level 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. 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.

5. Pharmacological properties

5.1 Pharmacodynamics properties

Pharmacotherapeutic group: Local anaesthetics of the amide-type, ATC code: N01B B20

TOPOCAIN-LP Cream 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 anaesthetic agents. 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.

TOPOCAIN-LP Cream is applied to **intact skin** under an occlusive dressing. The time needed to achieve reliable anaesthesia of intact skin is 1-2 hours, depending on the type of procedure.

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

The duration of anaesthesia following the application of TOPOCAIN-LP Cream for 1-2 hours is at least 2 hours after removal of the dressing.

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 min and 3 mm after 120 min TOPOCAIN-LP Cream treatment. TOPOCAIN-LP Cream 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 TOPOCAIN-LP 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.

Absorption from the **genital mucosa** is more rapid and onset time is shorter than after application to the skin.

After a 5-10 min application of TOPOCAIN-LP 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 min (individual variations in the range 5-45 min).

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. TOPOCAIN-LP Cream reduces the postoperative pain for up to 4 hours after debridement. TOPOCAIN-LP 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.

TOPOCAIN-LP Cream produces a biphasic vascular response involving initial vasoconstriction followed by vasodilatation at the application site (see Undesirable effects). Irrespective of the

vascular response, TOPOCAIN-LP 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 Warnings and precautions).

5.2 Pharmacokinetics Properties

The systemic absorption of lidocaine and prilocaine from TOPOCAIN-LP 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.

Intact skin: Following application to the thigh in adults (60 g cream/400 cm^2 for 3 hours), the extent of absorption was approx 5% of lidocaine and prilocaine. Maximum plasma concentrations (mean 0.12 and 0.07 µg/ml) were reached approx 2-6 hours after application.

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

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

Children: Following the application of 1.0 g lidocaine and prilocaine cream in neonates below 3 months of age, to approx 10 cm^2 for one hour, the maximum plasma concentrations of lidocaine and prilocaine were 0.135 µg/ml and 0.107 µg/ml respectively. Following the application of 2.0 g lidocaine and prilocaine cream in infants between 3 and 12 months of age, to approx. 16 cm^2 for four hours, the maximum plasma concentrations of lidocaine and prilocaine were 0.155 µg/ml and 0.131 µg/ml respectively. Following the application of 10.0 g of lidocaine and prilocaine cream in children between 2 and 3 years of age, to approx 100 cm^2 for two hours, the maximum plasma concentrations of lidocaine and prilocaine were 0.315 µg/ml and 0.215 µg/ml respectively. Following the application of 10.0-16.0 g lidocaine and prilocaine cream in children between 6 and 8 years of age, to approx 100-160 cm^2 for two hours, the maximum plasma concentrations of lidocaine and prilocaine were 0.299 µg/ml and 0.110 µg/ml respectively.

Genital mucosa: After the application of 10 g lidocaine and 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 and prilocaine cream to leg ulcers with an area of up to 64 cm^2 for 30 minutes, the maximum plasma levels 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 1-2.5 hours.

After an application time of 24 hours to leg ulcers with an area of up to 50-100 cm^2, the maximum plasma levels 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 and 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 levels for lidocaine, monoglycinexylidide and 2,6-xylidine were 0.41, 0.03 and 0.01 µg/ml respectively. The maximum observed plasma levels for prilocaine and ortho-toluidine were 0.08 µg/ml and 0.01 µg/ml respectively.

6. Pharmaceutical particulars

6.1 List of excipients

Sr. No.	Name of Ingredients
1	Croduret 60- SO (SG)
2	Carbomer 934 P
3	Sodium hydroxide
4	Purified water

6.2 Incompatibilities

Not applicable

6.3 Shelf life

Please refer to the expiry date on the packaging.

6.4 Special precautions for storage

Store below 30°C. Do not freeze. Keep out of the reach of children.

6.5 Nature and contents of container

1 x 5 gm, 1x10 gm & 1x30 gm aluminium tube with HDPE screw-on cap and one pack insert placed inside a carton.

Manufactured in India by:

GRACURE PHARMACEUTICALS LIMITED.
E 1105 Industrial Area, Phase 3, Bhiwadi, 301019, India

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