LEDAGA® (Chlormethine) 160 mcg/g Topical Gel

1. NAME OF THE MEDICINAL PRODUCT

Ledaga 160 micrograms/g gel

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each gram of gel contains chlormethine hydrochloride equivalent to 160 micrograms of chlormethine.

Excipients with known effect

Each tube contains 10.5 grams of propylene glycol and 6 micrograms of butylhydroxytoluene.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Gel.

Clear, colourless gel.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Ledaga is indicated for the topical treatment of mycosis fungoides-type cutaneous T-cell lymphoma (MF-type CTCL) in adult patients (see section 5.1).

4.2 Posology and method of administration

Treatment with Ledaga should be initiated by an appropriately experienced physician.

Posology

A thin film of Ledaga should be applied once daily to affected areas of the skin.

Treatment with Ledaga should be stopped for any grade of skin ulceration or blistering, or moderately severe or severe dermatitis (e.g., marked skin redness with oedema). Upon improvement, treatment with Ledaga can be restarted at a reduced frequency of once every 3 days. If reintroduction of treatment is tolerated for at least 1 week, the frequency of application can be increased to every other day for at least 1 week and then to once-daily application if tolerated.

Elderly

The dosing recommendation for elderly patients (≥ 65 years old) is the same as for younger adult patients (see section 4.8).

Paediatric population

The safety and efficacy of Ledaga in children aged 0 to 18 years have not been established. No data are available.

Method of administration

Ledaga is for topical application to the skin.

The following instructions should be followed by patients or caregivers when applying Ledaga:

- Patients must wash hands thoroughly with soap and water immediately after handling or applying Ledaga. Patients should apply Ledaga to affected areas of the skin. In case of Ledaga exposure to non-affected areas of the skin, patients should wash the exposed area with soap and water.
- Caregivers must wear disposable nitrile gloves when applying Ledaga to patients. Caregivers should remove gloves carefully (turning them inside out during the removal to avoid contact with Ledaga) and wash hands thoroughly with soap and water after removal of gloves. If there is accidental skin exposure to Ledaga, caregivers must immediately wash exposed areas thoroughly with soap and water for at least 15 minutes. Remove and wash contaminated clothing.
- The opening of the tube is covered with a foil safety seal. The cap should be used to puncture the seal. The tube should not be used and the pharmacist should be contacted if the seal is missing, punctured, or lifted.
- Ledaga should be applied immediately or within 30 minutes after removal from the refrigerator. The tube should be returned to the refrigerator immediately after each use. With clean hands, the tube should be placed back into the original box and the box should be placed in the supplied transparent, sealable, plastic bag for storage in the refrigerator.
- Ledaga should be applied to completely dry skin at least 4 hours before or 30 minutes after showering or washing. The patient should allow treated areas to dry for 5 to 10 minutes after application before covering with clothing. Occlusive (air- or water-tight) dressings should not be used on areas of the skin where Ledaga was applied.
- Emollients (moisturisers) or other topical products may be applied to the treated areas 2 hours before or 2 hours after application of Ledaga.
- Fire, flame, and smoking must be avoided until Ledaga has dried.

4.3 Contraindications

Hypersensitivity to chlormethine or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Mucosal or eye exposure

Contact with mucous membranes, especially those of the eyes, must be avoided. Exposure of mucous membranes such as the oral mucosa or nasal mucosa causes pain, redness, and ulceration, and these may be severe. Exposure of the eyes to chlormethine causes pain, burns, inflammation, photophobia, and blurred vision. Blindness and severe irreversible anterior eye injury may occur.

Patients should be advised that if any mucous membrane exposure occurs:

- irrigation should be performed immediately for at least 15 minutes with copious amounts of water (or sodium chloride 9 mg/ml (0.9%) solution for injection, or a balanced salt ophthalmic irrigating solution may be used if there is eye exposure), and
- medical care should be obtained immediately (including ophthalmological consultation if there is eye exposure).

Local skin reactions

Patients should be assessed during treatment for skin reactions such as dermatitis (e.g., redness, swelling, inflammation), pruritus, blisters, ulceration, and skin infections. The face, genitalia, anus, and intertriginous skin are at increased risk of skin reactions to topical chlormethine.

For dose modification information in case of skin reactions, see section 4.2.

Hypersensitivity

Hypersensitivity reactions, including isolated cases of anaphylaxis, have been reported in the literature after the use of topical formulations of chlormethine (see sections 4.3 and 4.8).

Skin cancer

Skin-directed therapies for MF-type CTCL have been associated with secondary skin cancers, although the specific contribution of chlormethine has not been established. Patients should be monitored for development of skin cancers during and after discontinuation of treatment with chlormethine.

Secondary exposure to Ledaga

Direct skin contact with Ledaga should be avoided in individuals other than the patient. Risks of secondary exposure may include skin reactions, mucosal injury, and skin cancers. Recommended application instructions should be followed to prevent secondary exposure (see section 4.2).

Excipients

This medicinal product contains propylene glycol and butylhydroxytoluene.

Propylene glycol may cause skin irritation.

Butylhydroxytoluene may cause local skin reactions (e.g. contact dermatitis), or irritation to the eyes and mucous membranes.

4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential

Ledaga is not recommended in women of childbearing potential not using contraception.

Pregnancy

There are limited data from the use of chlormethine in pregnant women.

Studies in animals have shown reproductive toxicity after systemic administration (see section 5.3).

Ledaga is not recommended during pregnancy.

Breast-feeding

It is unknown whether chlormethine is excreted in human milk.

A risk to newborns/infants cannot be excluded due to the potential for topical or systemic exposure of the breast-feeding child to chlormethine through contact with the mother’s skin.

A decision must be made whether to discontinue breast-feeding or to discontinue Ledaga therapy, taking into account the benefit of breast-feeding for the child and the benefit of therapy for the breast-feeding mother.

Fertility

In animals, adverse effects of chlormethine on male fertility after systemic administration have been documented (see section 5.3). The relevance to humans receiving topical chlormethine is unknown.

4.7 Effects on ability to drive and use machines

Ledaga has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

Summary of the safety profile

In a randomised-controlled trial (n=128 exposed to Ledaga for a median duration of 52 weeks), the most frequent adverse reactions to Ledaga were skin related: dermatitis (54.7%; e.g., skin irritation, erythema, rash, urticaria, skin-burning sensation, pain of the skin), pruritus (20.3%), skin infections (11.7%), skin ulceration and blistering (6.3%), and skin hyperpigmentation (5.5%). Cutaneous hypersensitivity reactions were reported in 2.3% of the treated patients.

Tabulated list of adverse reactions

Adverse reactions reported with Ledaga in an active-controlled trial in patients with MF-type CTCL are shown below. Frequencies were defined using the following convention: 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); not known (cannot be estimated from the available data). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Immune system disorders	
Common	Hypersensitivity
Skin and subcutaneous tissue disorders	
Very common	Dermatitis, skin infections, pruritus
Common	Skin ulceration and blistering, skin hyperpigmentation

Elderly population

In the controlled clinical trial, 31% (79/255) of the study population were aged 65 years or older. The safety profile observed in elderly patients was consistent with that in the overall patient population.

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 national reporting system.

4.9 Overdose

No cases of overdose after cutaneous use of Ledaga were reported during the clinical development programme or post-marketing period. Management of overdose should consist of washing the exposed area with water.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antineoplastic agents, nitrogen mustard analogues, ATC code: L01AA05.

Mechanism of action

Chlormethine is a bifunctional alkylating agent that inhibits rapidly proliferating cells.

Clinical efficacy and safety

The efficacy and safety of Ledaga were assessed in a randomised, multicentre, observer-blinded, active-controlled, non-inferiority clinical trial (Study 201) of 260 adult patients with Stage IA (141), IB (115), and IIA (4) MF-type CTCL who had received at least one prior skin-directed therapy. Qualifying prior therapies included topical corticosteroids, phototherapy, topical bexarotene, and topical nitrogen mustard. Patients were not required to be refractory to or intolerant of prior therapies. Patients were stratified based on stage (IA vs IB and IIA) and then randomised to receive either Ledaga (equivalent to 0.02% chlormethine HCl) or the comparator (a petroleum-based 0.02% chlormethine HCl ointment).

Study medicinal product was to be applied topically once daily for 12 months. Dosing could be suspended or continued at reduced frequency in the case of skin reactions. The median daily usage of Ledaga was 1.8 g. The maximum individual daily usage in the trial was 10.5 g of gel (i.e., 2.1 mg of chlormethine HCl).

The primary efficacy endpoint in Study 201 was the Composite Assessment of Index Lesion Severity (CAILS) response rate. Assessment was undertaken by a blinded observer. A response was defined as an at least 50% improvement in the baseline CAILS score, confirmed at a subsequent visit at least 4 weeks later. A complete response was defined as a confirmed CAILS score of 0. A partial response was defined as an at least 50% reduction in the baseline CAILS score. Non-inferiority was considered to have been demonstrated if the lower bound of the 95% confidence interval around the ratio of response rates (Ledaga/comparator) was greater than or equal to 0.75. The CAILS score was adjusted by removal of the pigmentation score and simplification of the plaque elevation scale.

As the main secondary endpoint, patients were also evaluated using the Severity Weighted Assessment Tool (SWAT), which was based on an assessment of all lesions. The response criteria were the same as for CAILS.

Efficacy was evaluated in the Efficacy Evaluable (EE) population, which included all 185 patients who were treated for at least 6 months with no major protocol deviations [Table 1], and in the Intent-To-Treat (ITT) population, which included all 260 randomised patients.

Table 1 CAILS and SWAT-confirmed response rates by 12 months in Study 201 (efficacy evaluable population)

	Response rates (%)			
	Ledaga N=90	**Comparator N=95**	**Ratio**	**95% CI**
CAILS Overall Response (CR+PR)	**76.7%**	**58.9%**	**1.301**	**1.065–1.609**
Complete Response (CR)	18.9%	14.7%		
Partial Response (PR)	57.8%	44.2%		
SWAT Overall Response (CR+PR)	**63.3%**	**55.8%**	**1.135**	**0.893–1.448**
Complete Response (CR)	8.9%	4.2%		
Partial Response (PR)	54.4%	51.6%		

CAILS = Composite Assessment of Index Lesion Severity; CI = confidence interval; CR = Complete Response; PR = Partial Response; SWAT = Severity Weighted Assessment Tool.

The ratio of response and the 95% confidence interval in the ITT population were 1.226 (0.974–1.552) for CAILS and 1.017 (0.783–1.321) for SWAT and therefore consistent with those in the EE population for both the overall CAILS and SWAT responses.

Reductions in mean CAILS scores were observed as early as at 4 weeks, with further reductions observed with continuing therapy.

In the EE population, the percentage of patients who achieved a confirmed response by CAILS was similar between disease stages IA (79.6 %) and IB–IIA (73.2%).

Results in other secondary endpoints (response in percentage of body surface area affected, time to first confirmed CAILS response, duration of first confirmed CAILS response and time to disease progression) were consistent with those for CAILS and SWAT.

A small number of subjects (6.3%, 8/128) treated with Ledaga utilised topical corticosteroids. Thus, the safety of the concomitant use of Ledaga with topical corticosteroids has not yet been established.

5.2 Pharmacokinetic properties

Patients who received Ledaga in Study 201 had no measurable concentrations of chlormethine in blood collected 1, 3 and 6 hours post-application on Day 1, and at the first month visit.

Similarly, patients who received chlormethine gel 0.04% in a follow-up study (Study 202) had no measurable concentrations of chlormethine or its degradation product (half-mustard) in blood collected 1 hour post-application on Day 1 or after 2, 4, or 6 months of treatment.

5.3 Preclinical safety data

Chlormethine was shown to be genotoxic in bacterial, plant, and mammalian cells. Chlormethine was carcinogenic in rat and mouse carcinogenicity studies after subcutaneous and intravenous administration.

Dermal application of chlormethine to mice at a dose of 15 mg/kg for up to 33 weeks resulted in skin tumours (squamous cell carcinomas and skin papilloma). There were no reports of systemic tumours after topical administration of chlormethine.

Intravenously administered chlormethine impaired male fertility in rats at a dose of ≥ 0.25 mg/kg once every 2 weeks for 24 weeks. No dedicated animal studies on the effects of chlormethine on female fertility have been reported in the literature.

Chlormethine caused foetal malformations in mice and rats when given as single injections of 1–2.5 mg/kg. Other findings in animals included embryo-lethality and growth retardation when administered as a single injection.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Diethylene glycol monoethyl ether
Propylene glycol (E 1520)
Isopropyl alcohol
Glycerol (E 422)
Lactic acid (E 270)

Hydroxypropylcellulose (E 463)
Sodium chloride
Menthol racemic
Disodium edetate
Butylhydroxytoluene (E 321)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

Frozen tube
4 years in the freezer (–15 °C to –25 °C).

After defrosting
60 days in the refrigerator (+2 °C to +8 °C).

Ledaga should be removed from the refrigerator just prior to application and returned to the refrigerator immediately after each use in its box inside the child-resistant, transparent, sealable, plastic bag.

6.4 Special precautions for storage

Unopened tube
Store and transport frozen (–15 °C to –25 °C) or refrigerated (+2 °C to +8 °C).

After defrosting
Store and transport refrigerated (+2 °C to +8 °C).

6.5 Nature and contents of container

Ledaga is provided in a white aluminium tube with an inner lacquer and an aluminium seal and a white polypropylene screw cap. Each tube contains 60 g of gel.

6.6 Special precautions for disposal and other handling

Ledaga is a cytotoxic medicinal product.

Caregivers must wear nitrile gloves when handling Ledaga. Patients and caregivers must wash hands after handling Ledaga.

Ledaga is an alcohol-based product and is flammable. The recommended application instructions should be followed (see section 4.2).

Unused refrigerated Ledaga should be discarded after 60 days, together with the plastic bag.

Any unused medicinal product or waste material, including the plastic bag and the nitrile gloves used for application, must be disposed of in accordance with local requirements.

7. MANUFACTURER

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8. PRODUCT REGISTRATION HOLDER

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9. DATE OF REVISION OF THE TEXT

9 December 2023

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