LEDAGA®

Prescribing Information

1. NAME OF THE MEDICINAL PRODUCT

Ledaga®

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

The active ingredient in LEDAGA is chlormethine. Each tube of LEDAGA contains 60g of 0.016% w/w (160mcg/g) chlormethine clear gel (equivalent to 0.02% chlormethine HCl).

For the full list of excipients, see section 4.8.

3. PHARMACEUTICAL FORM

Gel

4. CLINICAL PARTICULARS

4.1 INDICATIONS AND USAGE

Topical treatment of Stage IA and IB mycosis fungoides-type cutaneous T-cell lymphoma in patients who have received prior skin-directed therapy.

4.2 DOSAGE AND ADMINISTRATION

4.2.1 Dosing and Dose Modification

For Topical Dermatological Use Only

Apply a thin film of LEDAGA gel once daily to affected areas of the skin.

Stop treatment with LEDAGA for any grade of skin ulceration, blistering, or moderately-severe or severe dermatitis (*i.e.*, marked skin redness with edema) [*see Warnings and Precautions (4.4.3)*]. 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 one week, the frequency of application can be increased to every other day for at least one week and then to once daily application if tolerated.

4.2.2 Application Instructions

LEDAGA is a cytotoxic drug. Follow applicable special handling and disposal procedures.

Patients must wash hands thoroughly with soap and water after handling or applying LEDAGA.

Caregivers must wear disposable nitrile gloves when applying LEDAGA to patients 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 and remove contaminated clothing [*see Warnings and Precautions (4.4.2)*].

Patients or caregivers should follow these instructions when applying LEDAGA:

- Apply immediately or within 30 minutes after removal from the refrigerator. Return LEDAGA to the refrigerator immediately after each use.

- Apply to completely dry skin at least 4 hours before or 30 minutes after showering or washing. Allow treated areas to dry for 5 to 10 minutes after application before covering with clothing.
- Emollients (moisturizers) may be applied to the treated areas 2 hours before or 2 hours after application.
- Do not use occlusive dressings on areas of the skin where LEDAGA was applied.
- Avoid fire, flame, and smoking until LEDAGA has dried [*see Warnings and Precautions (4.4.6)*].

4.3 CONTRAINDICATIONS

The use of LEDAGA is contraindicated in patients with known severe hypersensitivity to chlormethine. Hypersensitivity reactions, including anaphylaxis, have occurred with topical formulations of chlormethine.

4.4 WARNINGS AND PRECAUTIONS

4.4.1 Mucosal or Eye Injury

Exposure of the eyes to chlormethine causes pain, burns, inflammation, photophobia, and blurred vision. Blindness and severe irreversible anterior eye injury may occur. Advise patients that if eye exposure occurs, (1) immediately irrigate for at least 15 minutes with copious amounts of water, normal saline, or a balanced salt ophthalmic irrigating solution and (2) obtain immediate medical care (including ophthalmologic consultation).

Exposure of mucous membranes such as the oral mucosa or nasal mucosa causes pain, redness, and ulceration, which may be severe. Should mucosal contact occur, immediately irrigate for at least 15 minutes with copious amounts of water, followed by immediate medical consultation.

4.4.2 Secondary Exposure to LEDAGA

Avoid direct skin contact with LEDAGA in individuals other than the patient. Risks of secondary exposure include dermatitis, mucosal injury, and secondary cancers. Follow recommended application instructions to prevent secondary exposure [*see Dosage and Administration (4.2.2)*].

4.4.3 Dermatitis

The most common adverse reaction was dermatitis, which occurred in 56% of the patients [*see Adverse Reactions (4.5)*]. Dermatitis was moderately severe or severe in 23% of patients. Monitor patients for redness, swelling, inflammation, itchiness, blisters, ulceration, and secondary skin infections. The face, genitalia, anus, and intertriginous skin are at increased risk of dermatitis. Follow dose modification instructions for dermatitis [*see Dosage and Administration (4.2.1)*].

4.4.4 Non-Melanoma Skin Cancer

Four percent (4%, 11/255) of patients developed a non-melanoma skin cancer during the clinical trial or during one year of post-treatment follow-up: 2% (3/128) of patients receiving LEDAGA, and 6% (8/127) of patients receiving the chlormethine ointment comparator. Some of these non-melanoma skin cancers occurred in patients who had received prior therapies known to cause non-melanoma skin

cancer. Monitor patients for non-melanoma skin cancers during and after treatment with LEDAGA. Non-melanoma skin cancer may occur on any area of the skin, including untreated areas.

4.4.5 Embryo-fetal Toxicity

Based on case reports in humans, findings in animal reproduction studies, its mechanism of action, and genotoxicity findings, chlormethine may cause fetal harm There are case reports of children born with malformations in pregnant women systemically administered chlormethine. Chlormethine was teratogenic and embryo-lethal after a single subcutaneous administration to animals. Advise women to avoid becoming pregnant while using LEDAGA. If this drug is used during pregnancy or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to a fetus [*see Use in Specific Populations (4.7.1)*].

4.4.6 Flammable Gel

Alcohol-based products, including LEDAGA, are flammable. Follow recommended application instructions [*see Dosage and Administration (4.2.2)*].

4.5 ADVERSE REACTIONS

The following clinically significant adverse reactions are discussed in greater detail in other sections of the prescribing information:

- Mucosal or eye injury [*see Warnings and Precautions (4.4.1)*]
- Secondary exposure to LEDAGA [*see Warnings and Precautions (4.4.2)*]
- Dermatitis [*see Warnings and Precautions (4.4.3)*]
- Non-melanoma skin cancer [*see Warnings and Precautions (4.4.4)*]

4.5.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared with rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

In a randomized, observer-blinded, controlled trial, LEDAGA 0.016% (equivalent to 0.02% chlormethine HCl) was compared to an Aquaphor®-based chlormethine HCl 0.02% ointment (Comparator) [*see Clinical Studies (5.3)*]. The maximum duration of treatment was 12 months. Sixty-three percent (63%) of patients in the LEDAGA arm and 67% in the comparator arm completed 12 months of treatment.

The body system associated with the most frequent adverse reactions was skin and subcutaneous tissue disorders. The most common adverse reactions (occurring in at least 5% of the patients) are shown in Table 1.

Table 1. Most Commonly Reported (≥5%) Cutaneous Adverse Reactions

	LEDAGA N=128 % of patients		Comparator N=127 % of patients	
	Any Grade	Moderately-Severe or Severe	Any Grade	Moderately-Severe or Severe
Dermatitis	56	23	58	17
Pruritus	20	4	16	2

Bacterial skin infection	11	2	9	2
Skin ulceration or blistering	6	3	5	2
Skin hyperpigmentation	5	0	7	0

In the clinical trial, moderately-severe to severe skin-related adverse events were managed with treatment reduction, suspension, or discontinuation. Discontinuations due to adverse reactions occurred in 22% of patients treated with LEDAGA and 18% of patients treated with the comparator. Sixty-seven percent (67%) of the discontinuations for adverse reactions occurred within the first 90 days of treatment. Temporary treatment suspension occurred in 34% of patients treated with LEDAGA and 20% of patients treated with the comparator. Reductions in dosing frequency occurred in 23% of patients treated with LEDAGA and 12% of patients treated with the comparator.

Reductions in hemoglobin, neutrophil count, or platelet count occurred in 13% of patients treated with LEDAGA and 17% treated with Comparator.

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.

Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form

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(https://sideeffects.health.gov.il)

4.6 DRUG INTERACTIONS

No drug interaction studies have been performed with LEDAGA. Systemic exposure has not been observed with topical administration of LEDAGA; therefore, systemic drug interactions are not likely.

4.7 USE IN SPECIFIC POPULATIONS

4.7.1 Pregnancy

Risk Summary
Based on case reports in humans, findings in animal reproduction studies, its mechanism of action, and genotoxicity findings, mechlorethamine may cause fetal harm.

Available published case reports in pregnant women receiving intravenous mechlorethamine demonstrate that mechlorethamine can cause major birth defects when a pregnant woman is systemically exposed. In animal reproduction studies, subcutaneous administration of mechlorethamine to pregnant rats and ferrets during organogenesis resulted in embryo□fetal mortality, alterations to growth, and structural abnormalities. Based on limited available data with LEDAGA use in pregnant women, if LEDAGA is used during pregnancy or if the patient becomes pregnant while taking this drug, patient should be advised of the potential risk to the fetus.

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In

the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

Data

Human Data

The limited available data with LEDAGA use in pregnant women does not show evidence of congenital malformation in newborns. Cases of newborns with congenital malformations have been reported in women who received systemic mechlorethamine during pregnancy.

Animal Data

Chlormethine caused fetal malformations in the rat and ferret when given as single subcutaneous injections of 1 mg/kg. Other findings in animals included embryo lethality and growth retardation when administered as a single subcutaneous injection.

4.7.2 Lactation

Risk Summary

There are no data on the presence of chlormethine or its metabolites in human milk, the effects of the drug on the breastfed child, or the effects of the drug on milk production. Because of the potential for topical or systemic exposure to LEDAGA through exposure to the mother's skin and the potential for serious adverse reactions in the breastfed child from chlormethine, advise patients not to breastfeed during treatment with LEDAGA.

4.7.3 Females and Males of Reproductive Potential

Contraception

Females

Advise female patients of reproductive potential to use effective contraception during treatment with LEDAGA. A barrier method of contraception should be used to avoid direct exposure of reproductive organs to LEDAGA.

Males

Based on genotoxicity findings, advise males with female partners of reproductive potential to use effective contraception during treatment with LEDAGA [*see Nonclinical Toxicology (5.2)*]. A barrier method of contraception should be used to avoid direct exposure of reproductive organs to LEDAGA.

Infertility

Based on animal data, chlormethine may impair fertility in males and females [*see Nonclinical Toxicology (5.2)*]. The reversibility of the effect on fertility is unknown.

4.7.4 Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

4.7.5 Geriatric Use

A total of 79 patients age 65 and older (31% of the clinical trial population) were treated with either LEDAGA or the comparator in the clinical trial. Forty-four percent (44%) of patients age 65 or older treated with LEDAGA

achieved a CAILS response compared to 66% of patients below the age of 65. Seventy percent (70%) of patients age 65 and older experienced cutaneous adverse reactions and 38% discontinued treatment due to adverse reactions, compared to 58% and 14% in patients below the age of 65, respectively. Similar differences in discontinuation rates between age subgroups were observed in the comparator group.

4.8 DESCRIPTION

LEDAGA is a topical product that contains chlormethine HCl, an alkylating drug. Chlormethine HCl is a white to off white solid that is very soluble in water and methanol, partially soluble in acetone, and generally not soluble in organic solvents.

Chlormethine HCl is designated chemically as 2-chloro-N-(2-chloroethyl)-N-methylethanamine hydrochloride. The molecular weight is 192.52 and the melting point is 108-111°C. The empirical formula is C5H11Cl2N•HCl, and the structural formula is: CH3N(CH2CH2Cl)2•HCl.

Each tube of LEDAGA contains 60g of a gel containing 0.016% w/w of chlormethine (equivalent to 0.02% chlormethine HCl) in a base of the following inactive ingredients: diethylene glycol monoethyl ether, propylene glycol, isopropyl alcohol, glycerin, lactic acid, hydroxypropyl cellulose, sodium chloride, menthol, edetate disodium dihydrate, butylated hydroxytoluene.

5. PHARMACOLOGICAL PROPERTIES

5.1 CLINICAL PHARMACOLOGY

5.1.1 Mechanism of Action

Chlormethine, also known as nitrogen mustard, is an alkylating agent which inhibits rapidly proliferating cells.

5.1.2 Pharmacokinetics

Systemic exposure was undetectable after topical administration of LEDAGA to patients. Blood samples were analyzed from 16 and 15 patients following treatment with LEDAGA (chlormethine gel 0.016%) and an identical formulation consisting of chlormethine 0.032% w/w, respectively. For patients who received chlormethine 0.016%, samples were collected to measure chlormethine concentrations prior to dosing, on day 1, and at the first month visit. Following the topical administration of chlormethine 0.016%, there were no detectable plasma chlormethine concentrations observed in any of the patients. Patients who received chlormethine 0.032% had no measurable concentrations of chlormethine or half-mustard after 2, 4, or 6 months of treatment.

5.2 NONCLINICAL TOXICOLOGY

5.2.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Chlormethine was carcinogenic in mice when injected intravenously with four doses of 2.4 mg/kg (0.1% solution) at 2-week intervals with observations for up to 2 years. An increased incidence of thymic lymphomas and pulmonary adenomas was observed. Painting chlormethine on the skin of mice at a dose of 4 mg/kg for periods of up to 33 weeks resulted in squamous cell tumors in 9 of 33 mice.

Chlormethine was genotoxic in multiple genetic toxicology studies, which included mutations in the bacterial reverse mutation assay (Ames test) and chromosome aberrations in mammalian cells. Dominant lethal mutations were produced in ICR/Ha Swiss mice.

The reproductive effects of LEDAGA have not been studied; however, published literature indicates that fertility may be impaired by systemically administered chlormethine. Chlormethine impaired fertility in the male rats at a daily dose of 0.25 -0.5 mg/kg when given intravenously every two weeks for up to 12 doses.
When chlormethine was administered intraperitoneally to male and female mice for 4 consecutive days at a dose of 0.5 mg/kg the pregnancy rate decreased (from 80% to 12.5%) when treated males were paired with treated females. Treatment with intravenous chlormethine has been associated with delayed catamenia, oligomenorrhea, and temporary or permanent amenorrhea.

5.2.2 Animal Toxicology and/or Pharmacology

Animal studies have shown chlormethine to be corrosive to skin and eyes, a powerful vesicant, irritating to the mucous membranes of the respiratory tract, and highly toxic by the oral route.

5.3 CLINICAL STUDIES

The efficacy of LEDAGA was assessed in a randomized, multicenter, observer-blind, active-controlled, non-inferiority clinical trial of 260 patients with Stage IA, IB, and IIA mycosis fungoides-type cutaneous T-cell lymphoma (MF-CTCL) who had received at least one prior skin-directed therapy. Qualifying prior therapies included topical corticosteroids, phototherapy, Targretin® gel, 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 randomized to receive LEDAGA 0.016% (equivalent to 0.02% chlormethine HCl) or Aquaphor®-based chlormethine HCl 0.02% ointment (Comparator) at 13 centers in the United States. Eighteen patients were excluded from the efficacy analysis due to protocol violations involving randomization at a single site.

Study drug was to be applied topically on a daily basis for 12 months. Concomitant use of topical corticosteroids was not permitted during the study. Dosing could be suspended or continued with reduced frequency for dermatitis. The mean daily usage of LEDAGA gel was 2.8 g (1 to 2 tubes per month). The maximum daily usage was 10.5 g (5 to 6 tubes per month).

Patients were evaluated for a response on a monthly basis for the first 6 months and then every 2 months for the last 6 months using the Composite Assessment of Index Lesion Severity (CAILS) score. The CAILS score is obtained by adding the severity score of each of the following categories for up to 5 index lesions: erythema, scaling, plaque elevation, and surface area. Severity was graded from 0 (none) to 8 (severe) for erythema and scaling; 0 to 3 for plaque elevation; and 0 to 9 for surface area. A response was defined as greater than or equal to 50% reduction in baseline CAILS score which was confirmed at the next visit at least 4 weeks later. A complete response was defined as a confirmed CAILS score of 0. Non-inferiority was considered to have been demonstrated if the lower bound of the 95% confidence interval (CI) around the ratio of response rates (LEDAGA/Comparator) was greater than or equal to 0.75.

Patients were also evaluated using the Severity Weighted Assessment Tool (SWAT). The SWAT score is derived by measuring each involved area as a percentage of total body surface area (%BSA) and multiplying it by a severity weighting factor (1=patch, 2=plaque, 3=tumor or ulcer). A response was defined as greater than or equal to 50% reduction in baseline SWAT score which was confirmed at the next visit at least 4 weeks later.

The baseline demographics and disease characteristics were balanced between treatment arms. The median age was 57 years in the LEDAGA arm and 58 years in the comparator arm. The majority of the patients were male (60% in LEDAGA arm, 59% in Comparator arm) and white (75% in both treatment arms). The median number of prior therapies was 2 in both treatment arms. The most common prior therapy was topical corticosteroids (used in 86% of patients in both treatment arms). The median body surface area (BSA) involvement at baseline was 8.5% (range 1%, 61%) in the LEDAGA arm and 9% (range 1%, 76%) in the comparator arm.

Sixty percent (60%) of the patients on the LEDAGA arm and 48% of patients on the comparator arm achieved a response based on the CAILS score. LEDAGA was non-inferior to the comparator based on a CAILS overall response rate ratio of 1.24 (95% CI 0.98, 1.58). Complete responses constituted a minority of the CAILS or SWAT overall responses (Table 2). The onset of CAILS overall response for both treatment arms showed a wide range from 1 to 11 months.

Table 2. Efficacy in Patients with Mycosis Fungoides-Type Cutaneous T-Cell Lymphoma (MF-CTCL)

Response Rates	**LEDAGA N=119**	**Comparator N=123**
CAILS Overall Response (CR+PR)	**60%**	**48%**
Complete Response (CR)	14%	11%
Partial Response (PR)	45%	37%
SWAT Overall Response (CR+PR)	**50%**	**46%**
Complete Response (CR)	7%	3%
Partial Response (PR)	43%	43%

6 PHARMACEUTICAL PARTICULARS

6.1 HOW SUPPLIED/STORAGE AND HANDLING

LEDAGA is supplied in 60g tubes of 0.016% w/w chlormethine as a clear gel.

Manufacturer and warehouse: store in the freezer (-25°C to -15°C).
At the pharmacy and at home: store in a refrigerator (2°C to 8°C), use within 60 days.

LEDAGA is a cytotoxic drug. Follow applicable special handling and disposal procedures.

6.3 REGISTRATION NUMBER

157 12 34556 00

6.4 MANUFACTURER

Helsin Birex Pharmaceuticals Ltd., Dublin, Ireland

6.5 MARKETING AUTHORIZATION HOLDER

Rafa Laboratories Ltd., P.O. Box 405, Jerusalem 9100301