PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

Pr**LEDAGA**™

Chlormethine Gel

gel, 160 micrograms chlormethine (as chlormethine hydrochloride) / gram gel, topical

Antineoplastic Agent

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PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

LEDAGA™ (chlormethine gel) is indicated for:

- The topical treatment of stage IA and IB mycosis fungoides-type cutaneous T-cell Lymphoma (MF-CTCL) in adult patients who have received prior skin-directed therapy.

1.1 Pediatrics

Pediatrics (≤ 18 years of age): Based on the data submitted and reviewed by Health Canada, the safety and efficacy of LEDAGA in pediatric patients has not been established; therefore, Health Canada has not authorized an indication for pediatric use. See 7 WARNINGS AND PRECAUTIONS, Special Populations.

1.2 Geriatrics

Geriatrics (≥*65* years of age): Of the 130 LEDAGA enrolled subjects, 22% were age 65 and over, while 6% were 75 and over. Among patients treated with either LEDAGA or the comparator in the clinical trial, there was a higher frequency of adverse events (AEs) in elderly patients and higher proportions of elderly patients discontinued due to an AE.

Evidence from clinical studies and experience suggests that overall there are no differences in effectiveness in elderly patients.

2. CONTRAINDICATIONS

LEDAGA is contraindicated in patients who are hypersensitive to this drug or to any ingredient in the formulation, including any non-medicinal ingredient, or component of the container. For a complete listing, see 6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING.

4 DOSAGE AND ADMINISTRATION

4.1 Dosing Considerations

- LEDAGA is for topical use only.
- Treatment with LEDAGA should be initiated under the supervision of a physician experienced in the treatment of MF-CTCL.

4.2 Recommended Dose and Dosage Adjustment

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.

Health Canada has not authorized an indication for pediatric use.

4.3 Administration

For topical application to the skin. LEDAGA is a cytotoxic drug (see 12 SPECIAL HANDLING INSTRUCTIONS). The following instructions should be followed by patients or caregivers when applying LEDAGA:

- Patients should apply LEDAGA to affected areas of the skin only. Patients must wash hands thoroughly with soap and water immediately after handling or applying LEDAGA. In case of LEDAGA exposure to non-affected areas of the skin, patients should wash the exposed area with soap and water thoroughly.
- 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 child-resistant, 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.

A patient card describing the correct way to apply LEDAGA will be included in the carton packaging at the time of dispensing. A copy of this card is found on the last page of the Product Monograph.

4.5 Missed Dose

If a dose of this medication is missed, it is not necessary to make up the missed dose. Skip the missed dose and continue with the next scheduled dose.

5 OVERDOSAGE

No cases of overdose after cutaneous use of LEDAGA were reported during the clinical development program or post-marketing period. In case of overdose the exposed area should be washed with soap and water.

For management of a suspected drug overdose, contact your regional poison control centre.

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Table 1 – Dosage Forms, Strengths, Composition and Packaging.

Route of Administration	Dosage Form / Strength/Composition	Non-medicinal Ingredients
Topical	160 micrograms chlormethine/g gel (equivalent to 0.02% chlormethine hydrochloride)	Butylhydroxytoluene Diethylene glycol monoethyl ether Disodium edetate Glycerol Hydroxypropylcellulose Isopropyl alcohol Lactic acid Menthol racemic Propylene glycol Sodium chloride

LEDAGA is a clear, colourless gel, supplied in an aluminum foil tube, sealed with an aluminum film with a white polypropylene resealable screw-on cap. Each tube contains 60 g of gel containing 160 micrograms of chlormethine (as chlormethine hydrochloride) per gram of gel (equivalent to 0.02% chlormethine hydrochloride).

The carton includes one LEDAGA tube and information for the patient in the form of a leaflet and a patient card.

A child-resistant transparent, sealable plastic bag is also supplied with the carton. The carton (with LEDAGA, the leaflet and the patient card) is dispensed inside the supplied plastic bag.

7 WARNINGS AND PRECAUTIONS

General

Mucosal and/or eye injury

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).

Hypersensitivity

Hypersensitivity reactions, including isolated cases of anaphylaxis, have been reported in the literature after the use of topical formulations of chlormethine.

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.

Carcinogenesis and Mutagenesis

Skin cancer

Skin-directed therapies of MF-CTCL have been associated with secondary skin cancers, although the specific contribution of chlormethine has not been established.

During the Study 201 and twelve months follow up period, the occurrence of skin cancer was observed with overall incidence of 4.3%. Non-melanoma skin cancer cases, for which a causal association was not established, were seen in LEDAGA (2% (3/128)) and comparator arms (6% (8/127)).

Some of these non-melanoma skin cancers occurred in patients who had received prior therapies known to cause non-melanoma skin cancer. Non-melanoma skin cancer may occur on any area of the skin, including untreated areas. Therefore, regular skin monitoring is strongly advised during and after discontinuation of the treatment with LEDAGA.

Sexual Health

Reproduction

Advise women to avoid becoming pregnant while using LEDAGA.

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 of reproductive potential and men 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.

If the patient becomes pregnant while taking this drug, the patient should be apprised of the

potential hazard to a fetus. See 16 NON-CLINICAL TOXICOLOGY.

Fertility

Based on animal data, chlormethine may impair fertility in males and females. See 16 NON-CLINICAL TOXICOLOGY.

Skin

Local skin reactions

Patients should be assessed during treatment for skin reactions such as dermatitis (e.g., redness, swelling, and inflammation), pruritus, blisters, ulceration, and skin infections. The face, genitalia, anus, and intertriginous skin are at increased risk of skin reactions to topical 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 4 DOSAGE AND ADMINISTRATION.

7.1 Special Populations

7.1.1 Pregnant Women

LEDAGA is not recommended during pregnancy.

There are case reports of children born with malformations in pregnant women systemically administered chlormethine.

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.

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. See 16 NON-CLINICAL TOXICOLOGY.

7.1.2 Breast-feeding

It is not known if 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.

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.

7.1.3 Pediatrics

Pediatrics (≤ 18 years of age): Safety and effectiveness in pediatric patients has not been established; therefore, Health Canada has not authorized an indication for pediatric use.

7.1.4 Geriatrics

Of the 130 LEDAGA enrolled subjects, 22% were age 65 and over, while 6% were 75 and over.

No overall differences in effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients. However, results from the clinical trial revealed that the incidence of adverse events is higher in patients older than 65 years.

8 ADVERSE REACTIONS

8.1 Adverse Reaction Overview

The most frequent adverse reactions to LEDAGA were skin related: dermatitis (e.g., skin irritation, erythema, rash, urticaria, skin-burning sensation, pain of the skin), pruritus, skin infections, skin ulceration and blistering, skin hyperpigmentation, and cutaneous hypersensitivity reactions.

In the clinical trial, moderately-severe to severe skin-related adverse events were managed with treatment reduction, suspension, or discontinuation. Discontinuations due to adverse events 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.

The following safety topics are discussed in greater detail in the Warnings and Precautions section of this product monograph:

- Mucous membrane or/and eye injury
- Local skin reactions
- Skin cancer
- Secondary exposure to LEDAGA

8.2 Clinical Trial Adverse Reactions

Because clinical trials are conducted under very specific conditions, the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

Table 2 – Summary of Treatment-Emergent Adverse Events ≥ 2% in Study 201, by Modified SOC and Preferred Term (re-coded)[a] (Safety analysis set)

Modified SOC Preferred Term, n (%)	Chlormethine Gel (N=128) n (%)	AP (N=127) n (%)	All Patients (N=255) n (%)
Skin and subcutaneous tissue disorders			
Dermatitis	70 (54.7)	73 (57.5)	143 (56.1)
Pruritus	26 (20.3)	21 (16.5)	47 (18.4)
Skin infections	15 (11.7)	14 (11.0)	29 (11.4)
Skin hyperpigmentation	7 (5.5)	9 (7.1)	16 (6.3)
Skin ulceration or blistering	8 (6.3)	5 (3.9)	13 (5.1)
Actinic keratosis	5 (3.9)	2 (1.6)	7 (2.7)
Respiratory, thoracic and mediastinal disorders			
Upper respiratory tract infection	11 (8.6)	10 (7.9)	21 (8.2)
Nasopharyngitis	1 (0.8)	6 (4.7)	7 (2.7)
Influenza	2 (1.6)	4 (3.1)	6 (2.4)
Cough	3 (2.3)	3 (2.4)	6 (2.4)
Pharyngolaryngeal pain	3 (2.3)	3 (2.4)	6 (2.4)
Bronchitis	2 (1.6)	3 (2.4)	5 (2.0)
Dyspnoea	4 (3.1)	0 (0.0)	4 (1.6)
Pneumonia	3 (2.3)	0 (0.0)	3 (1.2)
General disorders			
Fatigue	3 (2.3)	6 (4.7)	9 (3.5)
Influenza like illness	2 (1.6)	3 (2.4)	5 (2.0)
Pyrexia	3 (2.3)	2 (1.6)	5 (2.0)
Pain	1 (0.8)	3 (2.4)	4 (1.6)
Oedema	3 (2.3)	1 (0.8)	4 (1.6)
Xerosis	3 (2.3)	0 (0.0)	3 (1.2)
Infections and infestations			
Sinusitis	6 (4.7)	3 (2.4)	9 (3.5)
Urinary tract infection	4 (3.1)	2 (1.6)	6 (2.4)
Fungal infection	0 (0.0)	3 (2.4)	3 (1.2)
Gastrointestinal disorders			
Nausea	6 (4.7)	3 (2.4)	9 (3.5)
Diarrhoea	4 (3.1)	3 (2.4)	7 (2.7)
Abdominal pain	3 (2.3)	1 (0.8)	4 (1.6)
Musculoskeletal and connective tissue disorders			
Arthralgia	5 (3.9)	3 (2.4)	8 (3.1)
Back pain	5 (3.9)	2 (1.6)	7 (2.7)
Nervous system disorder			
Headache	4 (3.1)	5 (3.9)	9 (3.5)
Dizziness	2 (1.6)	3 (2.4)	5 (2.0)
Paraesthesia	1 (0.8)	3 (2.4)	4 (1.6)
Carpal tunnel syndrome	0 (0.0)	3 (2.4)	3 (1.2)
Injury, poisoning and procedural complications			
Excoriation	0 (0.0)	3 (2.4)	3 (1.2)
Neoplasms benign (incl cysts and polyps)			
Cyst	3 (2.3)	1 (0.8)	4 (1.6)
Neoplasms malignant			

Basal cell carcinoma	2 (1.6)	4 (3.1)	6 (2.4)
Blood and lymphatic system disorders			
Lymphadenopathy	1 (0.8)	4 (3.1)	5 (2.0)
Immune system disorders			
Hypersensitivity	3 (2.3)	2 (1.6)	5 (2.0)
Drug hypersensitivity	0 (0.0)	3 (2.4)	3 (1.2)

a: Post-hoc analysis with pooling and re-coding of preferred terms
AP = chlormethine HCl 0.02% compounded in Aquaphor® ointment; SOC = system organ class

9 DRUG INTERACTIONS

9.2 Drug Interactions Overview

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.

9.3 Drug-Drug Interactions

Interactions with other drugs have not been established.

9.4 Drug-Food Interactions

Interactions with food have not been established.

9.5 Drug-Herb Interactions

Interactions with herbal products have not been established.

9.6 Drug-Laboratory Test Interactions

Interactions with laboratory tests have not been established.

10 ACTION AND CLINICAL PHARMACOLOGY

10.1 Mechanism of Action

Chlormethine is a bifunctional alkylating agent that inhibits rapidly proliferating cells. Alkylation of DNA is the primary basis for the cytotoxic actions of chlormethine. Chlormethine binds to N7 positions in guanines via its reactive chloroethyl moieties, potentially binding also to N3 positions in adenines. The bifunctional nature of chlormethine along with its small molecular size allows it to form interstrand cross-links within DNA, by alkylation of guanine-N7 positions in opposite DNA strands. Monoadducts and intrastrand biadducts are also formed, but the formation of interstrand cross-links makes chlormethine a more effective tumor chemotherapeutic agent than monofunctional analogues. Unrepaired interstrand cross-links prevent transcription, replication, and segregation of DNA, and ultimately cause cell death.

10.2 Pharmacodynamics

Pharmacodynamic interactions following topical administration of chlormethine gel have not been investigated.

10.3 Pharmacokinetics

Systemic exposure was undetectable after topical administration of LEDAGA to patients in Study 201and 202. 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 (blood samples drawn at 1, 3 and 6 hours post-application), 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 its degradation product (half-mustard) 1 hour post-application on day 1 or after 2, 4, or 6 months of treatment.

11 STORAGE, STABILITY AND DISPOSAL

Prior to dispensing, store unopened tube in the freezer (-15°C to -25°C).

After dispensing, advise patients to store under refrigeration (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 original box inside the child-resistant, transparent, sealable, plastic bag.

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

LEDAGA is a cytotoxic drug, See 12 SPECIAL HANDLING INSTRUCTIONS.

Keep out of reach and sight of children.

12 SPECIAL HANDLING INSTRUCTIONS

The following instructions should be followed by patients or caregivers when applying LEDAGA.

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. 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.

LEDAGA is an alcohol-based product and is flammable. The recommended application instructions should be followed (see 6 DOSAGE AND ADMINISTRATION).

Store LEDAGA refrigerated at temperatures between 2°C to 8°C. Advise patients that adherence to the recommended storage condition will ensure LEDAGA will work as expected. Patients should consult a pharmacist prior to using LEDAGA that has been left at room temperature for longer than one hour per day. With clean hands, replace tube in the original box, then place in the refrigerator inside the child-resistant, transparent, sealable, plastic bag

out of the reach of children and avoiding contact with food.

Unused refrigerated LEDAGA should be discarded after 60 days. Patients and caregivers should be advised to ask their pharmacist about how to properly dispose of unused LEDAGA and waste materials, including the plastic bag and the nitrile gloves used for application. These materials should not be disposed of in the regular trash to minimize secondary exposure.

PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

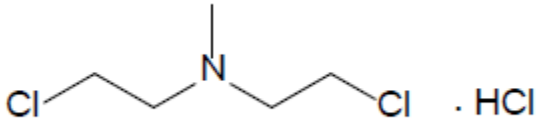
Drug Substance

Proper name: Chlormethine Hydrochloride

Chemical name: 2-chloro-N-(2-chloroethyl)-N-methylethanamine hydrochloride

Molecular formula and molecular mass: $C_5H_{11}Cl_2N$, HCl; 192.51 g/mol

Structural formula:



Physicochemical properties:

Physical form: White to off-white crystalline solid

Solubility: Soluble in water, methanol and isopropanol; partially soluble in acetone

pKa: 6.1

14 CLINICAL TRIALS

14.1 Trial Design and Study Demographics

Table 3 – Summary of patient demographics for clinical trials in topical chlormethine gel

Study #	Trial design	Dosage, route of administration and duration	Study subjects (n)	Median age	Sex
2005NMMF-201-US	Multi-center, randomized, third party (observer) blinded study	160 micrograms chlormethine/g gel (PG) ointment (AP) once daily topical treatment for max. 12 months	260 patients enrolled onto the trial 255 patients received at least one dose of study medication	58 (11-88) years	PG/AP 77 (59.2%) male 53 (40.8%) female

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.

14.2 Study Results

2005NMMF-201-US Study (Study 201)

The efficacy and safety of LEDAGA were assessed in a randomized, multicentre, observer-blinded, active-controlled, non-inferiority clinical trial of 260 adult patients with Stage IA (141), IB (115), and IIA (4) MF-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 randomized 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).

In this trial the use of topical corticosteroids to treat dermatitis resulting from study treatment was not allowed per protocol.

The primary efficacy endpoint was the Composite Assessment of Index Lesion Severity (CAILS) response rate. Assessment was undertaken by a blinded observer. 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 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 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. 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 4], and in the Intent-To-Treat (ITT) population, which included all 260 randomized patients.

Table 4 – CAILS and SWAT -confirmed response rates by 12 months in Study 201 (EE population)

	Response rates (%)		Ratio	95% CI
	LEDAGA N=90	Comparator N=95		
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.

16 NON-CLINICAL TOXICOLOGY

General:

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.

Carcinogenicity:

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.

Application of chlormethine on the skin of mice at a dose of 0.1 mg in 0.2 ml of 95% Ethanol once weekly for 33 weeks was not tumorigenic while an increase of the dose or of the application frequency resulted in the development of squamous cell carcinomas and papillomas.

In particular the application of 0.3 mg weekly resulted in skin tumours in 8 out of 24 mice [7 papilloma (P), 1 squamous cell carcinoma (SCC)], while the application of chlormethine at the dose of 0.1 mg 3 times per week in two different groups of animals resulted in skin tumours in 6(P) out 29 mice and 10 (1 P, 9 SCC) out 33 mice, respectively.

When mice were exposed to a topical solution of chlormethine 0.1mg in 0.1ml of 95% Ethanol two times a week, with or without UVB exposure three times a week, in comparison to 0.1ml of 95% Ethanol twice a week, with or without UVB exposure three times a week over 52 weeks, higher incidence and faster growing tumors (including squamous cell carcinomas) were observed in the mice treated with chlormethine, concomitantly with UVB.

Genotoxicity:

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

Reproductive and Development Toxicology:

The reproductive effects of chlormethine have not been studied; however, published literature indicates that fertility may be impaired by systemically administered chlormethine. Chlormethine was shown to significantly impair fertility in male rats and cause mitochondrial damage in mice oocytes. Chlormethine impaired fertility in the male rats at a dose of 0.25 to 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. Teratogenicity and embryo lethality were observed in mice and rats treated systemically with chlormethine HCl. Intraperitoneal administration of chlormethine in pregnant mice caused decrease in viable embryos, chromosomal aberrations and gross malformations in the fetuses. Similarly, a single subcutaneous injection of 1 mg/kg chlormethine in rats induced fetal mortality or resorption, general growth retardation and malformations in 90% of the fetuses.

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

PATIENT MEDICATION INFORMATION

PrLEDAGA™
Chlormethine Gel

Read this carefully before you start using **LEDAGA** and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **LEDAGA**.

You will be given a patient card in the LEDAGA carton. The card is entitled "Patient and Caregiver Instructions." It contains instructions on the correct way to apply the medicine. In addition to the leaflet, also read the patient card before starting LEDAGA. Follow the instructions on the card or leaflet when applying LEDAGA. A copy of the patient card is found on the last page of the Product Monograph.

What is LEDAGA used for?
LEDAGA is a medicine used on the skin (topical) to treat adults:

- with Stage 1A and 1B mycosis fungoides-type cutaneous T-cell lymphoma (MF-CTCL) who have received previous skin treatment.

LEDAGA is not approved for use in children and adolescents under 18 years of age.

How does LEDAGA work?
LEDAGA belongs to a group of anticancer medications called "alkylating agents". Alkylating agents work by stopping cancer cells from dividing and growing.

What are the ingredients in LEDAGA?
Medicinal ingredients: chlormethine hydrochloride
Non-medicinal ingredients: butylhydroxytoluene, diethylene glycol monoethyl ether, disodium edetate, glycerol, hydroxypropylcellulose, isopropyl alcohol, lactic acid, menthol racemic, propylene glycol, sodium chloride.

LEDAGA comes in the following dosage forms:
Gel, 160 microgram (mcg) chlormethine (as chlormethine hydrochloride) / g gel

Do not use LEDAGA if:

- you are allergic to chlormethine or any of the other ingredients of this medicine.

To help avoid side effects and ensure proper use, talk to your healthcare professional before you use LEDAGA. Talk about any health conditions or problems you may have, including if you:

- have ever had an allergic reaction to chlormethine, propylene glycol or butylhydroxytoluene

Other warnings you should know about:

Mucosal and/or eye injury:
Keep away from your eyes, nose, mouth and other mucous membranes.

- If LEDAGA gets in your eyes, it can cause pain, burning, swelling, redness, sensitivity to light, and blurred vision. It may cause blindness and permanent injury to your eyes. If LEDAGA gets in your eyes, rinse your eyes right away for at least 15 minutes with a large amount of water, normal saline or an eye wash solution. After rinsing your eyes, get medical help right away. See an eye doctor as soon as possible.
- If LEDAGA gets in your mucous membranes, such as your mouth or nose, it can cause pain, redness, and ulcers. If this happens, rinse the affected area right away for at least 15 minutes with a large amount of water. After rinsing the area, get medical help right away.

Skin reactions: LEDAGA can cause skin reactions, such as **dermatitis** (inflammation, redness and swelling), **itching, blisters, ulcers** and **skin infections**. Your risk of dermatitis is increased if LEDAGA is applied to your face, genital area, anus or skin folds. Your healthcare professional will check your skin for skin reactions during your treatment.

Allergic reactions, including anaphylaxis: Allergic reactions, including anaphylaxis, have been reported in patients treated with chlormethine. Tell your healthcare professional or get medical help right away if you develop an allergic reaction. See the **Serious side effects and what to do about them** table, below, for signs and symptoms to be aware of.

Skin cancers (abnormal growth of the cells in the skin): Skin cancers have occurred in patients treated with chlormethine, including LEDAGA. It is not known whether chlormethine causes this. Your healthcare professional will check your skin for skin cancers during and after treatment with LEDAGA. See the **Serious side effects and what to do about them** table, below, for signs and symptoms to be aware of.

Secondary exposure: Skin contact with LEDAGA should be avoided in individuals other than the patient, such as the caregiver. Risks of contact include dermatitis, injury to the eyes, mouth, or nose, and skin cancers. Caregivers should follow the recommended instructions when applying LEDAGA to prevent exposure, see **How to apply LEDAGA** below**.**

Pregnancy and Breastfeeding:

Female patients:

- If you are pregnant, able or planning to get pregnant or think you are pregnant, there are specific risks you should discuss with your healthcare professional.
- You should not use LEDAGA if you are pregnant. It can harm your unborn baby.
- Avoid becoming pregnant during treatment with LEDAGA. If you are able to become pregnant, use a barrier method of birth control, such as a male condom or spermicide.
- Tell your healthcare provider right away if you become pregnant during or think you may be pregnant during treatment with LEDAGA.
- Do not breastfeed during treatment with LEDAGA. It is not known if LEDAGA passes into your breast milk. LEDAGA can also harm your baby through contact with your treated skin. Talk to your healthcare professional about the best way to feed your baby during this time.

Male patients with female partners who are able to become pregnant:

- Avoid fathering a child while you are using LEDAGA.
- During your treatment with LEDAGA, use a barrier method of birth control, such as a male condom or spermicide.
- If, during your treatment with LEDAGA, your partner becomes pregnant, tell your healthcare professional right away.

Fertility: LEDAGA may affect your ability to have a child. If you have questions about this, talk to your healthcare professional.

Adults aged 65 and over: Patients aged 65 years and older may be at an increased risk of developing side effects during treatment.

LEDAGA contains propylene glycol and butylhydroxytoluene: Propylene glycol may cause skin irritation. Butylhydroxytoluene may cause local skin reactions like an itchy rash called contact dermatitis, or irritation to the eyes and mucous membranes (for example, the inside of your nose or mouth).

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

There are no known interactions with LEDAGA.

How to apply LEDAGA:

- LEDAGA is a cytotoxic drug. Handle with caution.
- LEDAGA is for topical use only. Use exactly as directed by your healthcare professional.
- Caregivers must wear disposable nitrile gloves when applying LEDAGA to patients for their protection. This is a special type of glove. Ask your healthcare professional if you have questions.
- Remove the cap from the tube just before use. Use the cap to pierce the seal. Do not use if seal is missing or damaged and contact your pharmacist.
- **Apply LEDAGA immediately or within 30 minutes after removal from the refrigerator.**
- Apply a thin layer to completely dry skin at least 4 hours before or 30 minutes after showering or washing**.**
- If non-affected areas of the skin come into contact with LEDAGA, wash the area with soap and water.
- Allow treated areas to dry for 5 to 10 minutes after application before covering with clothing**.**
- For patients applying the gel, wash your hands with soap and water immediately after applying**.**
- For caregivers applying the gel, carefully remove gloves (turning them inside out during the removal to avoid contact with LEDAGA) and then, wash hands thoroughly with soap and water. If your skin accidently comes into contact with LEDAGA, wash the affected area with soap and water right away for at least 15 minutes and remove and wash any contaminated clothing.
- With clean hands, close the tube. Place it back in the box it came in and the box in the child-resistant transparent, sealable, plastic bag. Zip it closed. **Return it to the refrigerator right away after each use. It is important that LEDAGA is stored in the**

refrigerator to ensure that it will work as expected.

- You should not use air or water-tight bandages on the areas of the skin treated with LEDAGA.
- Avoid contact with fire, flame and smoking until LEDAGA has dried on the skin. LEDAGA is flammable.
- Moisturisers or any other skin products (including medicines applied to the skin) may be applied to the treated area 2 hours before or 2 hours after applying LEDAGA.

Usual dose:
Apply a thin layer of LEDAGA once daily to affected areas of the skin.

Your doctor may interrupt your treatment if you develop a skin reaction. When your skin reaction improves, your doctor may restart your treatment at a reduced frequency. If you tolerate LEDAGA well, your doctor may continue to adjust your dose.

Overdose:

If you think you, or a person you are caring for, have used too much LEDAGA, contact your healthcare professional, hospital emergency department or regional poison control centre immediately, even if there are no symptoms.

Missed Dose:
If you miss a dose of LEDAGA, wait for your next scheduled application and then continue with your regular routine. Do not use a double dose to make up for a forgotten dose.

What are possible side effects from using LEDAGA?

These are not all the possible side effects you may have when using LEDAGA. If you experience any side effects not listed here, contact your healthcare professional.

LEDAGA can decrease the amount of hemoglobin, white blood cells and platelets in your blood.

Serious side effects and what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Stop using drug and get immediate medical help**
	Only if severe	**In all cases**	
VERY COMMON			
Dermatitis: burning, dryness, itching pain, rash, redness, swelling		✓	
Skin infections: painful red lump or bump, hot, red and swollen skin, sores, crusts or blisters		✓	
Pruritus (itchy skin)		✓	
COMMON			
Allergic reactions, including		✓	

anaphylaxis: skin reactions (such as dry skin, scaly skin, swelling, itchiness, hives or welts), feeling sick to your stomach and throwing up, runny nose, watery eyes, difficulty swallowing or breathing, wheezing, shortness of breath, fever			
Blistering: pain, a raised lump filled with clear fluid or sometimes blood, a reddened and tender patch of skin, skin irritation, swelling		✓	
Skin cancer (abnormal growth of cells in the skin): a sore that doesn't heal or comes back after healing, raised and scaly red patches, a growth with raised edges, a sore that is crusty or bleeds, a growth or area that is itchy, irritated or sore			✓
Skin hyperpigmentation (irregular colouring of skin): patches or spots of darkened skin		✓	
Skin ulcers: clear, bloody, or pus-filled discharge from the ulcer, discolouration of the skin, dry or flaky skin around the ulcer, itching, pain or tenderness near the affected area, scabbing, swelling of the skin near the ulcer			✓

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, talk to your healthcare professional.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:

- **Store** LEDAGA **in a refrigerator (+2°C to +8°C) at all times.** Keep the tube in its box inside the child-resistant, transparent, sealable, plastic bag to prevent accidental exposure and contact with food.
- Keep out of reach and sight of children.
- On the carton, write the date that LEDAGA was refrigerated in the space provided.
- **Do NOT use** an opened or unopened tube of LEDAGA **after 60 days** in the refrigerator.
- If left at room temperature for longer than one hour, talk to your healthcare professional before using it.
- Ask your pharmacist how to safely dispose of used nitrile gloves, the plastic bag and any unused LEDAGA. Do not throw these away in the household waste. These measures will help to prevent secondary exposure to LEDAGA. It will also help protect the environment.

If you want more information about LEDAGA:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html); the manufacturer's website http://www.recordatirarediseases.com/ca, or by calling 1-877-827-1306.

This leaflet was prepared by Recordati Rare Diseases Canada Inc.

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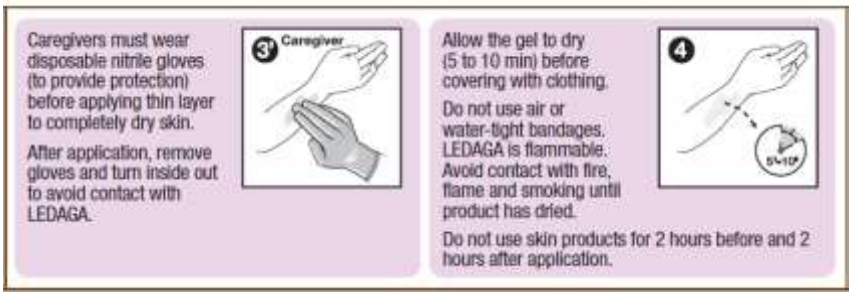
A copy of the patient card included in the LEDAGA carton is shown below.

Outside Front Panel

Outside Panel 1

Outside Panel 2



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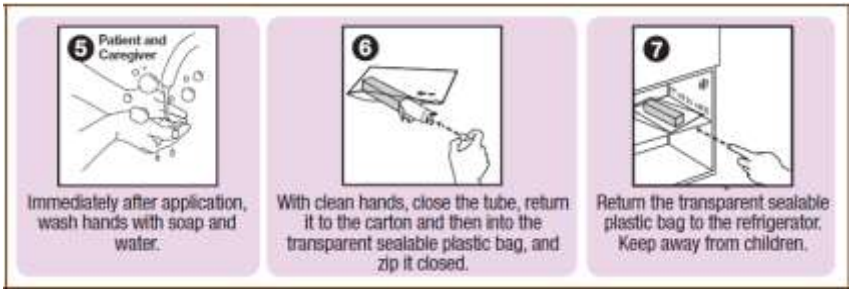
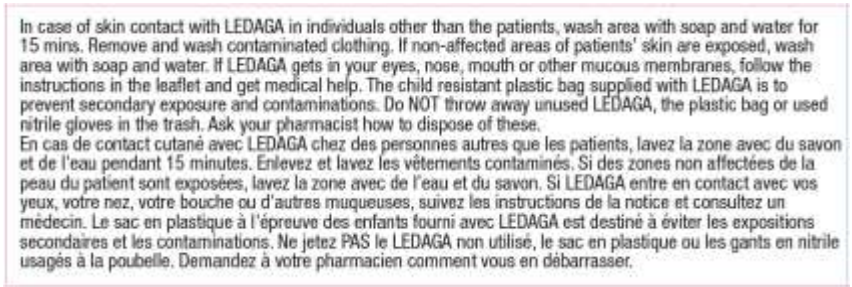


Inside Panel



In case of skin contact with LEDAGA in individuals other than the patients, wash area with soap and water for 15 mins. Remove and wash contaminated clothing. If non-affected areas of patients' skin are exposed, wash area with soap and water. If LEDAGA gets in your eyes, nose, mouth or other mucous membranes, follow the instructions in the leaflet and get medical help. The child resistant plastic bag supplied with LEDAGA is to prevent secondary exposure and contaminations. Do NOT throw away unused LEDAGA, the plastic bag or used nitrile gloves in the trash. Ask your pharmacist how to dispose of these.

En cas de contact cutané avec LEDAGA chez des personnes autres que les patients, lavez la zone avec du savon et de l'eau pendant 15 minutes. Enlevez et lavez les vêtements contaminés. Si des zones non affectées de la peau du patient sont exposées, lavez la zone avec de l'eau et du savon. Si LEDAGA entre en contact avec vos yeux, votre nez, votre bouche ou d'autres muqueuses, suivez les instructions de la notice et consultez un médecin. Le sac en plastique à l'épreuve des enfants fourni avec LEDAGA est destiné à éviter les expositions secondaires et les contaminations. Ne jetez PAS le LEDAGA non utilisé, le sac en plastique ou les gants en nitrile usagés à la poubelle. Demandez à votre pharmacien comment vous en débarrasser.