Summary Report of Benefit-Risk Assessment

LEDAGA TOPICAL GEL 160 µg/g

NEW DRUG APPLICATION

Active Ingredient(s)	Chlormethine hydrochloride
Product Registrant	Juniper Biologics Pte Ltd
Product Registration Number	SIN16986P
Application Route	Abridged evaluation
Date of Approval	15 April 2024

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A INTRODUCTION

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

The active substance, chlormethine, is a cytotoxic, bi-functional alkylating agent that reacts with DNA to form cross-links, inducing the death of rapidly proliferating cells.

Ledaga is available as a topical gel containing 160 µg/g of chlormethine as a hydrochloride salt in an aluminium tube. Other ingredients in the tube are butylhydroxytoluene, diethylene glycol monoethyl ether, disodium edetate, glycerol, hydroxypropylcellulose, isopropyl alcohol, lactic acid, menthol, propylene glycol and sodium chloride.

B ASSESSMENT OF PRODUCT QUALITY

The drug substance, chlormethine hydrochloride, is manufactured at SAFC, Inc., Wisconsin, United States. The drug product, Ledaga Topical Gel 160 µg/g, is manufactured at University of Iowa Pharmaceuticals, Iowa, United States.

Drug substance:

Adequate controls have been presented for the starting materials, intermediates and reagents. The in-process control tests and acceptance criteria applied during the manufacturing of the drug substance are considered appropriate.

The characterisation of the drug substance and its impurities are appropriately performed. Potential and actual impurities are adequately controlled in accordance with ICH Q3A and Q3C guidelines.

The drug substance specifications are established in accordance with ICH Q6A and the impurity limits are considered appropriately qualified. The analytical methods used are adequately described and non-compendial methods have been validated in accordance with ICH guidelines. Information on the reference standards used for identity, assay and impurities testing is presented.

The packaging is [redacted]. The stability data presented was adequate to support the storage of the drug substance at 25°C with a re-test period of 5 years.

Drug product:

The gel is manufactured by a standard manufacturing process comprising of mixing the drug substance and excipients and filling into the final container.

The manufacturing site is compliant with Good Manufacturing Practice (GMP). Proper development and validation studies were conducted. It has been demonstrated that the manufacturing process is reproducible and consistent. Adequate in-process controls are in place.

The specifications are established in accordance with ICH Q6A and impurity limits are considered adequately qualified. The analytical methods used are adequately described and non-compendial methods have been validated in accordance with ICH guidelines. Information on the reference standards used for identity, assay and impurities testing is presented.

The container closure system is an aluminium tube containing 60 g of gel. The stability data submitted was adequate to support the approved shelf-life of 48 months when stored at or below -15°C to -25°C. The gel may be stored at 2-8°C for up to 60 days after opening and this in-use period is supported with appropriate data.

C ASSESSMENT OF CLINICAL EFFICACY

The clinical efficacy of Ledaga was supported by one pivotal study (Study 201), its extension study (Study 202) and a US post-marketing study (Study PROVe).

Study 201 was a Phase 2/3, multicentre, randomised, observer-blinded study that evaluated Ledaga (chlormethine hydrochloride 0.02% in propylene glycol gel [PG]) compared to chlormethine hydrochloride 0.02% compounded in Aquaphor ointment (AP) in previously treated patients with Stage IA, IB or IIA MF-type CTCL. Patients were randomised to receive either the PG or AP formulation of chlormethine hydrochloride 0.02% once daily for up to 12 months.

The active comparator used in the study, chlormethine hydrochloride 0.02% in Aquaphor, is not registered locally. Nevertheless, considering that there is currently no registered topical treatment for MF locally, and the AP formulation of chlormethine has a long history of use in the USA where it is considered a current standard of care, the choice of this comparator in the study is considered acceptable.

The primary efficacy endpoint was response rate defined as complete or partial response using the Composite Assessment of Index Lesion Severity (CAILS) score. The CAILS requires scoring of up to 5 index lesions (lesions selected for assessment of efficacy) for each of the following symptoms: 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 18 for surface area. The sum of the scores for each of these categories and each of the 5 index lesions represents the total CAILS score. A response was defined as ≥50% reduction in the baseline CAILS score that was confirmed at the next visit at least 4 weeks later.

Response rate based on the Severity Weighted Assessment Tool (SWAT) was a key secondary endpoint. 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=tumour). Response was defined as ≥50% improvement in the baseline SWAT score that is confirmed by two or more consecutive observations over at least 4 weeks. Both the CAILS and the SWAT scores are internationally accepted endpoints for the evaluation of response in MF, and are considered appropriate primary and key secondary endpoints for the study.

An additional secondary endpoint was the change in total percentage of BSA (%BSA), a component of the SWAT, as a measure of extent of cutaneous disease. Response was defined as ≥50% improvement from baseline in %BSA that is confirmed at the next visit at least 4 weeks later.

The study was designed as a non-inferiority study comparing the PG formulation of chlormethine hydrochloride 0.02% to the AP formulation of chlormethine hydrochloride 0.02%. The two treatment arms were compared with respect to the response rate defined as ≥50% improvement in baseline CAILS score during the 12-month study. Non-inferiority was assessed based on the 95% confidence interval (CI) around the ratio of the response rate of patients treated with the PG formulation to that of the AP formulation. The PG formulation was determined to be non-inferior to the AP formulation if the lower limit of the 95% CI was ≥0.75. The statistical methods and non-inferiority margin were considered acceptable.

A total of 260 patients were enrolled in the study and included in the intent-to-treat (ITT) population: 130 patients treated with the PG formulation and 130 patients treated with the AP formulation. Due to a randomisation error at one study site (site #7), a modified ITT population (ITT excluding site #7) comprising 242 patients who were randomised per protocol (excluding all 18 patients enrolled at site #7) was also analysed as a sensitivity analysis. A total of 185 patients with no major protocol violations and who were on study for at least 6 months were included in the efficacy evaluable (EE) population: 90 patients treated with the PG formulation and 95 patients treated with the AP formulation.

The demographic and baseline characteristics were generally well-balanced between the treatment arms. In the ITT population, the majority of patients were male (59.2%) and Caucasian (74.2%). All except one subject were adults aged 18 years and above; 30.8% were aged ≥65 years. The majority of patients had Stage IA (54.2%) or IB (44.2%) disease, and only 2 patients (1.5%) in each arm had Stage IIA disease. The most commonly used prior therapy was corticosteroids (86.5%), followed by phototherapy (39.6%) and bexarotene (17.7%).

Non-inferiority of the PG formulation compared to the AP formulation in terms of the primary endpoint, CAILS response rate, was met in each of the analysis populations. In the EE population, the CAILS response rate was 76.7% in the PG formulation arm and 58.9% in the AP formulation arm. The ratio of the CAILS response rate was 1.301 (95% CI: 1.065, 1.609), which met the protocol-defined criterion for non-inferiority (i.e., lower limit of the 95% CI ≥0.75). Similar results were demonstrated in the ITT population (58.5% vs 47.7%; rate ratio 1.226; 95% CI: 0.974, 1.552) and the ITT excluding site #7 (59.7% vs 48.0%; rate ratio 1.244; 95% CI: 0.983, 1.582).

Efficacy was further demonstrated based on the secondary efficacy endpoints. The SWAT results showed an overall response rate of 63.3% for the PG formulation vs 55.8% for the AP formulation in the EE population (rate ratio 1.135; 95% CI: 0.893, 1.448), 46.9% for the PG formulation vs 46.2% for the AP formulation in the ITT population (rate ratio 1.017; 95% CI: 0.783, 1.321), and 49.6% for the PG formulation vs 46.3% for the AP formulation in the ITT excluding site #7 (rate ratio 1.070; 95% CI: 0.822, 1.394). Non-inferiority was shown in all three analysis populations.

The %BSA response rates were 60.0% for the PG formulation vs 52.6% for the AP formulation in the EE population (rate ratio 1.140; 95% CI: 0.883, 1.478), 44.6% vs 43.1% in the ITT population (rate ratio 1.036; 95% CI: 0.786, 1.366), and 47.1% vs 43.1% in the ITT excluding site #7 (rate ratio 1.092; 95% CI: 0.826, 1.446). Non-inferiority was demonstrated in all three analysis populations.

Summary of efficacy endpoint results (Study 201)

Analysis set	Response rates, n (%)		Ratio (PG/AP) (95% CI)[b]
	PG formulation	AP formulation	
Primary endpoint – CAILS response[a]			
EE population	N=90	N=95	
Overall (CR+PR)	69 (76.7%)	56 (58.9%)	1.301
CR	17 (18.9%)	14 (14.7%)	(1.065, 1.609)
PR	52 (57.8%)	42 (44.2%)	
ITT population	N=130	N=130	
Overall (CR+PR)	76 (58.5%)	62 (47.7%)	1.226
CR	18 (13.8%)	15 (11.5%)	(0.974, 1.552)
PR	58 (44.6%)	47 (36.2%)	
ITT (excluding site #7)	N=119	N=123	
Overall (CR+PR)	71 (59.7%)	59 (48.0%)	1.244
CR	17 (14.3%)	14 (11.4%)	(0.983, 1.582)
PR	54 (45.4%)	45 (36.6%)	
Secondary endpoint – SWAT response[a]			
EE population	N=90	N=95	
Overall (CR+PR)	57 (63.3%)	53 (55.8%)	1.135
CR	8 (8.9%)	4 (4.2%)	(0.893, 1.448)
PR	49 (54.4%)	49 (51.6%)	
ITT population	N=130	N=130	
Overall (CR+PR)	61 (46.9%)	60 (46.2%)	1.017
CR	9 (6.9%)	4 (3.1%)	(0.783, 1.321)
PR	52 (40.0%)	56 (43.1%)	
ITT (excluding site #7)	N=119	N=123	
Overall (CR+PR)	59 (49.6%)	57 (46.3%)	1.070
CR	8 (6.7%)	4 (3.3%)	(0.822, 1.394)
PR	51 (42.9%)	53 (43.1%)	
Secondary endpoint – %BSA response[a]			
EE population			1.140
Responders	54/90 (60.0%)	50/95 (52.6%)	(0.883, 1.478)
ITT population			1.036
Responders	58/130 (44.6%)	56/130 (43.1%)	(0.786, 1.366)
ITT (excluding site #7)			1.092
Responders	56/119 (47.1%)	53/123 (43.1%)	(0.826, 1.446)

[a] Response was defined as ≥50% reduction in the baseline CAILS, SWAT and %BSA score, confirmed over two consecutive visits at least 4 weeks apart. For CAILS and SWAT response, complete response (CR) was defined as a score of zero and partial response (PR) was defined as ≥50% reduction from baseline but non-zero.
[b] PG was determined to be non-inferior to AP if the lower limit of the 95% CI of the response rate ratio (PG/AP) was ≥0.75.

Study 202 was a Phase 2, open-label, uncontrolled, 7-month extension study of patients who completed 12 months of treatment in Study 201 without a complete response. All 98 patients received a higher strength of chlormethine hydrochloride gel 0.04%. Relative to the baseline of Study 202, the CAILS response rate was 23.5%, with 10.2% of patients achieving a complete response and 13.3% a partial response. The study was limited by its single-arm uncontrolled design as well as the use of a higher strength formulation, hence the results could not be meaningfully interpreted in the context of the 0.02% formulation sought in the application.

Study PROVe was a prospective, observational, 2-year study conducted in the United States in 298 adult patients diagnosed with MF-type CTCL and treated with chlormethine hydrochloride gel 0.02%. In addition to chlormethine gel, patients also received standard medical care (including topical corticosteroids, phototherapy, oral bexarotene, etc.) as determined by the patient's physician in a real-world setting. Response rates (defined as ≥50% reduction from baseline in BSA at the 12-month timepoint) were approximately 40% to 50% regardless of treatment combinations in patients with Stage IA and IB disease, as well as in patients with all stages of disease. This study was considered supportive only, as it studied

chlormethine in combination with other therapies and there was no comparator arm to allow an evaluation of the efficacy of chlormethine gel.

Overall, the efficacy of Ledaga had been adequately demonstrated based on acceptable CAILS, SWAT and %BSA response rates that were shown to be non-inferior to that of the AP formulation of chlormethine hydrochloride 0.02% in the pivotal study (Study 201).

The requested indication was broader than the inclusion criteria of the pivotal study, which recruited patients with stage I or IIA disease who were previously treated with at least one skin-directed therapy. The clinical practice guidelines generally recommend the use of topical chlormethine as first-line treatment in early-stage MF, while later stages require treatment with systemic therapies. In later stages, systemic therapy can be used in combination with skin-directed therapy, as skin manifestations occur in all stages of MF. Hence, the requested indication that does not specify disease stage or line of therapy was considered reasonable.

D ASSESSMENT OF CLINICAL SAFETY

The safety data of chlormethine hydrochloride gel 0.02% was derived mainly from the pivotal study (Study 201), which comprised 255 patients who received at least one application of study treatment during the study (safety analysis set): 128 patients in the PG arm and 127 patients in the AP arm. The median duration of treatment was 51.7 weeks in the PG arm and 52.0 weeks in the AP arm. A total of 165 (65%) patients received study treatment for more than 48 weeks.

Supportive safety data were also provided from Study 202 comprising 98 patients who were treated with a higher strength (0.04%) of chlormethine hydrochloride gel, and from a post-marketing study conducted in the US (Study PROVe). Study 202 was a Phase 2, open-label, 7-month extension study of Study 201 in which patients who had completed up to 12 months of treatment with chlormethine hydrochloride 0.02% PG gel or AP ointment without achieving a complete response were treated with the higher strength, chlormethine hydrochloride 0.04% PG gel. In Study 202, the median duration of treatment was 30.0 weeks, and a total of 89 (90.8%) patients received more than 24 weeks of treatment. Considering the known and well-established safety profile of chlormethine, the safety database from the clinical studies was considered adequate in terms of number of exposed patients as well as duration of treatment.

Summary of adverse events (AEs)

AE	Study 201		Study 202
	PG 0.02% (N=128)	**AP 0.02% (N=127)**	**PG 0.04% (N=98)**
Any AE	108 (84.4%)	115 (90.6%)	71 (72.4%)
Treatment-related AE	79 (61.7%)	64 (50.4%)	32 (32.7%)
Serious AE (SAE)	14 (10.9%)	11 (8.7%)	6 (6.1%)
AE leading to treatment discontinuation	28 (21.9%)	23 (18.1%)	5 (5.1%)
Death	1 (0.8%)	0 (0.0%)	0 (0.0%)

The most commonly reported AEs in the clinical studies were skin-related AEs, which are known adverse reactions of chlormethine. In the pivotal study (Study 201), the most common AEs and their incidences (PG vs AP formulation) were dermatitis (54.7% vs 57.5%), pruritus (20.3% vs 16.5%) and skin infections (11.7% vs 11.0%). Other skin-related AEs reported in the study were skin hyperpigmentation (5.5% vs 7.1%) and skin ulceration or blistering (6.3% vs 3.9%).

SAEs were reported in 10.9% of patients in the PG arm and 8.7% in the AP arm. Other than pneumonia (2 subjects in PG arm), cardiac failure congestive (2 subjects in AP arm) and myocardial infarction (2 subjects in AP arm), the rest of the SAEs were reported in 1 subject each. None of the SAEs were considered related to study treatment. AEs leading to treatment discontinuation were reported in 21.9% of patients in the PG arm and 18.1% in the AP arm. The most frequently reported AEs leading to treatment discontinuation were skin-related AEs, including dermatitis contact (4.7% vs 7.9%), skin irritation (7.8% vs 3.9%), erythema (3.1% vs 1.6%), pruritus (2.3% vs 1.6%), blister (1.6% vs 0%) and impetigo (1.6% vs 0%).

One death was reported in Study 201 in the PG arm. The patient was diagnosed with widely disseminated metastatic cancer less than 2 months after initiation of study treatment and died on Day 84 of the study. The event was assessed as not related to study treatment.

In Study 201, 10 patients (3 in the PG arm and 7 in the AP arm) developed non-melanoma skin cancers during the study or during the 12-month follow-up period. The majority of skin cancers occurred in untreated areas. In Study 202, one patient who was treated with the AP formulation during Study 201 developed a basal cell carcinoma. None of these events were assessed as related to study treatment, as they occurred in untreated areas, in patients with a history of skin cancers, or in patients who had been previously treated with therapies recognised to increase the risk of skin cancer. Development of secondary skin cancers is a known risk of skin directed therapies in the treatment of MF. Given the known mechanism of action of chlormethine as a DNA alkylating agent, there is a potential for the drug to increase the risk of skin cancers, particularly squamous cell and basal cell carcinomas. The proposed package insert has included adequate warnings on skin cancers, including recommendations for monitoring for the development of skin cancers.

In Study 201, cutaneous hypersensitivity reactions were reported in 3 patients (2.3%) in the PG arm and 2 patients (1.6%) in the AP arm. All cases were considered related or possibly related to study drug and led to treatment discontinuation. Drug hypersensitivity was reported in 3 patients (2.4%) in the AP arm. In Study 202, no cases of hypersensitivity or drug hypersensitivity were reported. Hypersensitivity is a known AE of chlormethine and has been reported in the literature. The proposed package insert has included adequate warnings on hypersensitivity reactions.

Data from the US post-marketing study (Study PROVe) did not identify any unexpected safety concern with the use of chlormethine hydrochloride gel 0.02% in combination with other skin directed therapies including topical corticosteroids, phototherapy, oral bexarotene and other treatments. The most common AEs reported in the study were skin-related AEs that were as expected, including dermatitis (12.8%), pruritus (9.7%), skin irritation (7.4%), erythema (5.0%), skin burning sensation (3.7%), and rash (3.4%).

Overall, the safety of Ledaga has been adequately characterised in the target patient population in the clinical studies. The AEs observed in the clinical studies are generally consistent with what is known for topical chlormethine reported in the literature.

E ASSESSMENT OF BENEFIT-RISK PROFILE

MF-type CTCL is a rare and serious condition that presents initially with cutaneous symptoms that could progress to extracutaneous involvement (lymph nodes, blood and other organs) in the advanced stage. Median survival time ranges from 35.5 years for Stage IA to 2 years for

Stage IV disease. The likelihood of progression is unpredictable, with a quarter of early-stage patients progressing to advanced stage disease, which presents a poor prognosis. Effective treatment of the disease at the early stage is important for relief of symptoms as well as to prevent disease progression and death from MF. There is currently no approved treatment for MF-type CTCL in Singapore, hence there is an unmet medical need for the condition.

The pivotal study (Study 201) has demonstrated non-inferiority of Ledaga (chlormethine hydrochloride 0.02% in propylene glycol gel [PG]) compared to chlormethine hydrochloride 0.02% compounded in Aquaphor ointment (AP), in terms of the primary endpoint CAILS response rate in the EE population (76.7% for PG vs 58.9% for AP; rate ratio 1.301; 95% CI: 1.065, 1.609). This was supported by consistent results in the ITT population (58.5% vs 47.7%; rate ratio 1.226; 95% CI: 0.974, 1.552) and the ITT excluding site #7 (59.7% vs 48.0%; rate ratio 1.244; 95% CI: 0.983, 1.582).

Non-inferiority was also demonstrated in terms of the secondary endpoint, SWAT response rate, with an overall response rate of 63.3% for PG vs 55.8% for AP in the EE population (rate ratio 1.135; 95% CI: 0.893, 1.448). The SWAT results were also consistent in the ITT population (46.9% vs 46.2%; rate ratio 1.017; 95% CI: 0.783, 1.321) and the ITT excluding site #7 (49.6% vs 46.3%; rate ratio 1.070; 95% CI: 0.822, 1.394).

The safety profile of Ledaga is characterised primarily by skin-related AEs, including dermatitis (54.7% with PG vs 57.5% with AP), pruritus (20.3% vs 16.5%) skin infections (11.7% vs 11.0%), skin hyperpigmentation (5.5% vs 7.1%) and skin ulceration or blistering (6.3% vs 3.9%). In addition, cutaneous hypersensitivity reactions (2.3% vs 1.6%) and drug hypersensitivity (0% vs 2.4%) were reported. These skin and hypersensitivity AEs are known and expected adverse reactions consistent with that reported in the literature with topical chlormethine.

Given the known mechanism of action of chlormethine as a DNA alkylating agent, there is a potential for the drug to increase the risk of skin cancers, particularly squamous cell and basal cell carcinomas. In the clinical studies, 11 patients developed non-melanoma skin cancers following the use of topical chlormethine, although assessment of causality was hampered by confounding factors such as medical history or prior therapies. The package insert has included adequate warnings on the risk of skin cancers, including recommendations for monitoring for the development of skin cancers.

Overall, considering the efficacy demonstrated in terms of CAILS and SWAT responses, and the acceptable safety profile that is consistent with that known and documented in the literature for topical chlormethine, the benefit-risk profile of Ledaga for the topical treatment of MF-type CTCL in adult patients is deemed favourable.

F CONCLUSION

Based on the review of quality, safety and efficacy data, the benefits have been demonstrated to outweigh the risks of Ledaga for the topical treatment of mycosis fungoides-type cutaneous T-cell lymphoma (MF-type CTCL) in adult patients, and approval of the product registration was granted on 15 April 2024.

APPROVED PACKAGE INSERT AT REGISTRATION

LEDAGA®

Topical Gel 160 µg/g

1. QUALITIATIVE AND QUANTITATIVE COMPOSITION

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

For the full list of excipients, see section 5.1.

2. PHARMACEUTICAL FORM

Gel.
Clear, colourless gel.

3. CLINICAL PARTICULARS

3.1 THERAPEUTIC INDICATIONS

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

3.2 DOSE 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.

3.3 CONTRAINDICATIONS

Hypersensitivity to chlormethine or to any of the excipients listed in section 5.1.

3.4 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. Therefore, administration of Ledaga® in these areas should be avoided.
For dose modification information in case of skin reactions, see section 3.2.

Hypersensitivity

Hypersensitivity reactions, including isolated cases of anaphylaxis, have been reported in the literature after the use of topical formulations of chlormethine (see sections 3.3 and 3.8).

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. 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. 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. Direct skin contact with Ledaga® should also be avoided in non-affected areas in patients. 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 3.2).

Excipients

The medicinal product contains propylene glycol and butylhydroxytoluene, which may cause skin irritation (e.g., contact dermatitis). In addition, butylhydroxytoluene has been reported to cause irritation to the eyes and mucous membranes.

Use in the Elderly

The safety profile observed in elderly patients was consistent with that in the overall patient population. No dose adjustments are required (see section 3.2).

Paediatric Use

The safety of Ledaga® in children aged 0 to 18 years has not been established. No data are available.

Effects on Laboratory Tests

Clinical laboratory safety data were monitored throughout the two clinical studies and no trend toward abnormal values were noted following topical administration.

3.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

No interaction studies have been performed.

3.6 FERTILITY, PREGNANCY AND LACTATION

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

Effects on Fertility

Female patients of reproductive potential should be advised 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 with female partners of reproductive potential should be advised 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.
Adverse effects on fertility have been observed with chlormethine after systemic administration in animals. Fertility was impaired in male rats with intravenous administration at doses ≥0.25 mg/kg every 2 weeks, and in mice (treated males paired with treated females) with intraperitoneal administration at 0.5 mg/kg/day for 4 days. The relevance to humans receiving topical chlormethine is unknown.

Use in Pregnancy

Ledaga® is not recommended during pregnancy. 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 medicine is used during pregnancy or if the patient becomes pregnant while taking this medicine, the patient should be apprised of the potential hazard to a fetus.
Chlormethine has been shown to cause fetal malformations, embryofetal lethality and fetal growth retardation in mice and rats after a single injection at 1–2.5 mg/kg. Animal embryofetal development studies involving topical administration of chlormethine have not been performed

Use in Lactation

Breastfeeding during treatment with Ledaga® is not recommended 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. 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.

3.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

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

3.8 ADVERSE EFFECTS (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 events in controlled trial

Table 1
Number and Incidence of Adverse Events Occurring in ≥5% of Patients on Either Arm by SMQ and MedDRA Preferred Term

SMQ[b] MedDRA Preferred Term, n (%)	PG[d] (N 128) n (%)	AP[c] (N 127) n (%)	All Subjects (N 255) n (%)
Any Adverse Event	108 (84.4)	115 (90.6)	223 (87.5)
Skin and subcutaneous tissue disorders	92 (71.9)	85 (66.9)	177 (69.4)
Skin irr tation	32 (25.0)	18 (14.2)	50 (19.6)
Pruritus	25 (19.5)	20 (15.7)	45 (17.6)
Erythema	22 (17.2)	18 (14.2)	40 (15.7)
Dermatitis contact	19 (14.8)	19 (15.0)	38 (14.9)
Skin hyperpigmentation	7 (5.5)	9 (7.1)	16 (6.3)
Respiratory, thoracic and mediastinal disorders	26 (20.3)	26 (20.5)	52 (20.4)
Upper respiratory tract infection	11 (8.6)	10 (7.9)	21 (8.2)
Infections and infestations	23 (18.0)	25 (19.7)	48 (18.8)
Fo licu itis	7 (5.5)	5 (3.9)	12 (4.7)

a: P value from Fisher's exact test
b: SMQ (Standardized MedDRA Query) equates to System Organ Class with sponsor de ined except ons.
c: Chlormethine HCl 0.02% compounded in Aquaphor® ointment
d: Chlormethine HCl 0.02%

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.

Post marketing

An observational post-marketing study was undertaken in the United States. Non-serious AEs assessed as related to Chlormethine Gel were experienced by 83 of 298 patients (27.9%) in the Chlormethine Gel plus any other treatment group. No serious adverse events were assessed to be related to chlormethine gel.

Of the skin and subcutaneous tissue disorder AEs related to

Chlormethine Gel, dermatitis was assessed to be related in 37 patients (12.4%), pruritus in 22 patients (7.4%) and skin irritation in 21 patients (7.0%). These rates are lower than in the registration study and which may be due to:
- widespread concomitant use of topical corticosteroids
- periods of less frequent dosing
- most patients (254/298=85.2%) were already using chlormethine gel for >30 days at enrolment. Dermatitis reactions are known to occur more frequently early in treatment.

Based on the evaluation of the cumulative safety data from all global post-marketing sources, no new risks or signals have been identified with the chlormethine gel formulation.

Reporting of suspected adverse reactions

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. Healthcare professionals are asked to report any suspected adverse reactions.

3.9 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.

4. PHARMACOLOGICAL PROPERTIES

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

Mechanism of Action
Chlormethine is a bifunctional alkylating agent that reacts with DNA to form cross-links, inducing the death of rapidly proliferating cells.

Clinical Trials
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. 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. 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 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=tumour or ulcer). The response criteria were the same as for CAILS.

Efficacy was evaluated in the Intent-To-Treat (ITT) population, which included all 260 randomised patients [Table 2], and in the Efficacy Evaluable (EE) population, which included 185 patients who were treated for at least 6 months with no major protocol deviations.

Table 2
CAILS and SWAT-confirmed response rates by 12 months in Study 201 (intention-to-treat population)

	Response rates (%)		Ratio	95% CI
	Ledaga® N 130	Comparator N 130		
CAILS Overall Response (CR+PR)	**58.5%**	**47.7%**	**1.226**	**0.974 1.552**
Complete Response (CR)	13.8%	11.5%		
Partial Response (PR)	44.6%	36.2%		
SWAT Overall Response (CR+PR)	**46.9%**	**46.2%**	**1.017**	**0.783 1.321**
Complete Response (CR)	6.9%	3.1%		
Partial Response (PR)	40.0%	43.1%		

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 were 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.

4.2 PHARMACOKINETIC PROPERTIES
Patients who received Ledaga® in Study 201 had no measurable concentrations of chlormethine in blood samples 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.

4.3 PRECLINICAL SAFETY DATA
Genotoxicity
Chlormethine was shown to be genotoxic in multiple assays, including for mutagenicity in bacteria (Ames test), chromosomal aberrations in vitro (in cultured human lymphocytes) and for clastogenicity in vivo (mouse bone marrow micronucleus test). Covalent binding to DNA is the key mechanism for the desired cytotoxic action of chlormethine.

Carcinogenicity
Chlormethine has been shown to be carcinogenic in rodents after subcutaneous and intravenous injection, and with topical dermal administration. Dermal application of chlormethine to mice at a dose of 12 to 15 mg/kg/week for 20 weeks resulted in skin tumours (squamous cell carcinomas and skin papillomas). There were no reports of systemic tumours after topical administration of chlormethine.

5. PHARMACEUTICAL PARTICULARS

5.1 LIST OF EXCIPIENTS
Diethylene glycol monoethyl ether
Propylene glycol
Isopropyl alcohol
Glycerol
Lactic acid
Hyprolose
Sodium chloride
Menthol
Disodium edetate
Butylhydroxytoluene

5.2 INCOMPATIBILITIES
Not applicable.

5.3 SHELF LIFE
Unopened tube
4 years in the freezer (–15 C to –25 C).

After defrosting
Store at 2 C to 8 C for up to 60 days (Refrigerate. Do not freeze).

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.

5.4 SPECIAL PRECAUTIONS FOR STORAGE
Store at -15 C to -25 C (deep freeze).

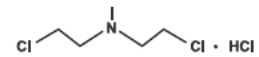
For storage conditions after defrosting Ledaga®, see section 5.3.

5.5 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 60g of gel.

5.6 SPECIAL PRECAUTIONS
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 3.2). Unused refrigerated Ledaga® should be discarded after 60 days, together with the plastic bag.

5.7 PHYSICOCHEMICAL PROPERTIES
Chemical Structure



Molecular Formula: $C_8H_{11}Cl_2N{\cdot}HCl$
Molecular Weight: 192.51

CAS Number
55-86-7

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