ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Ledaga 160 micrograms/g gel

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

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

Excipients with known effect

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

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Gel.

Clear, colourless gel.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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

4.2 Posology and method of administration

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

Posology

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

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

Elderly

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

Paediatric population

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

Method of administration

Ledaga is for topical application to the skin.

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

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

4.3 Contraindications

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

4.4 Special warnings and precautions for use

Mucosal or eye exposure

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

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

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

Local skin reactions

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

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

Hypersensitivity

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

Skin cancer

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

Secondary exposure to Ledaga

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

Excipients

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.

4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential

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

Pregnancy

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

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

Ledaga is not recommended during pregnancy.

Breast-feeding

It is unknown whether chlormethine is excreted in human milk.

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

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

Fertility

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

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

Summary of the safety profile

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

Tabulated list of adverse reactions

Adverse reactions reported with Ledaga in an active-controlled trial in patients with MF-type CTCL are shown below. Frequencies were defined using the following convention: very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1,000 to < 1/100); rare (≥ 1/10,000 to < 1/1,000); very rare (< 1/10,000); not known (cannot be estimated from the available data). Within each frequency grouping, adverse reactions are presented in order of decreasing severity.

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

Elderly population

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

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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

Mechanism of action

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

Clinical efficacy and safety

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

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

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

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

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

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

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

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

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

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

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

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

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

Paediatric population

The European Medicines Agency has waived the obligation to submit the results of studies with Ledaga in all subsets of the paediatric population in cutaneous T-cell lymphoma (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

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

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

5.3 Preclinical safety data

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

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

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

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

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Diethylene glycol monoethyl ether
Propylene glycol
Isopropyl alcohol
Glycerol
Lactic acid
Hydroxypropylcellulose

Sodium chloride
Menthol racemic
Disodium edetate
Butylhydroxytoluene

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

Unopened tube
3 years in the freezer (–15 °C to –25 °C).

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

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

6.4 Special precautions for storage

Store and transport frozen (–15 °C to –25 °C).

For storage conditions after defrosting Ledaga, see section 6.3.

6.5 Nature and contents of container

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

6.6 Special precautions for disposal and other handling

Ledaga is a cytotoxic medicinal product.

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

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

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

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

7. MARKETING AUTHORISATION HOLDER

Actelion Registration Ltd
Chiswick Tower, 13th Floor
389 Chiswick High Road
London W4 4AL
United Kingdom

8. MARKETING AUTHORISATION NUMBER

EU/1/16/1171/001

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 3 March 2017

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu.

ANNEX II

A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer responsible for batch release

Actelion Manufacturing GmbH
Emil-Barell-Strasse 7
79639 Grenzach-Wyhlen
Germany

Actelion Pharmaceuticals Belgium NV
Bedrijvenlaan 1
2800 Mechelen
Belgium

The printed package leaflet of the medicinal product must state the name and address of the manufacturer responsible for the release of the concerned batch.

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to medical prescription.

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic Safety Update Reports**

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of European Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web portal.

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk Management Plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

- **Additional risk minimisation measures**

In order to minimise and prevent the Important Identified Risk of “Toxicity to mucous membranes / eye” and the Important Potential Risk of “Secondary exposure to someone other than the patient”, the

MAH shall ensure that, the following additional risk minimisation measures are fulfilled in each Member State (MS) where Ledaga is marketed:

- Ledaga should be supplied with a transparent, sealable, child-resistant plastic bag to prevent secondary exposure and contamination when Ledaga is stored in the refrigerator:
    - Instruction on how to accurately use, open and dispose a plastic bag should be printed on the plastic bag. The MAH must agree about the content and format of the text prior to the launch of Ledaga in each MS with the National Competent Authority (NCA).
    - The plastic bag should not be used for any other purposes and must be disposed after 60 days, together with unused refrigerated Ledaga and any waste material, including nitrile gloves in accordance with local requirements.

- A patient alert card, sized to be included in Ledaga outer packaging, together with the Patient Information Leaflet (PIL) is provided to all patients and caregivers who are expected to administer and use Ledaga.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON

1. NAME OF THE MEDICINAL PRODUCT

Ledaga 160 micrograms/g gel
chlormethine

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each gram of gel contains 160 micrograms of chlormethine.

3. LIST OF EXCIPIENTS

Diethylene glycol monoethyl ether, propylene glycol, isopropyl alcohol, glycerol, lactic acid, hydroxypropylcellulose, sodium chloride, menthol racemic, disodium edetate, butylhydroxytoluene.
See package leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Gel
60 g

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Topical use.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Cytotoxic: Handle with caution
Flammable: Avoid fire, flame, and smoking

8. EXPIRY DATE

EXP
Discard 60 days after defrosting: ../../....

9. SPECIAL STORAGE CONDITIONS

Store and transport frozen (–15 °C to –25 °C)
After defrosting, store in a refrigerator (+2 °C to +8 °C)
Keep Ledaga in its box and inside the child-resistant plastic bag

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

Dispose of the tube, plastic bag and nitrile gloves in accordance with local requirements.

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Actelion Registration Ltd
Chiswick Tower 13th Floor
389 Chiswick High Road
London W4 4AL
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/16/1171/001

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Ledaga

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC:
SN:
NN:

PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING

60 g TUBE

1. NAME OF THE MEDICINAL PRODUCT

Ledaga 160 micrograms/g gel
chlormethine

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each gram of gel contains 160 microgams of chlormethine.

3. LIST OF EXCIPIENTS

Diethylene glycol monoethyl ether, propylene glycol, isopropyl alcohol, glycerol, lactic acid, hydroxypropylcellulose, sodium chloride, menthol racemic, disodium edetate, butylhydroxytoluene.
See package leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Gel
60 g

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Topical use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Cytotoxic
Flammable

8. EXPIRY DATE

EXP
Discard 60 days after defrosting

9. SPECIAL STORAGE CONDITIONS

Store and transport frozen.
After defrosting, store in a refrigerator.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

Dispose of the tube, plastic bag and nitrile gloves in accordance with local requirements.

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Actelion Registration Ltd
Chiswick Tower 13th Floor
389 Chiswick High Road
London W4 4AL
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/16/1171/001

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC:
SN:
NN:

Patient alert card

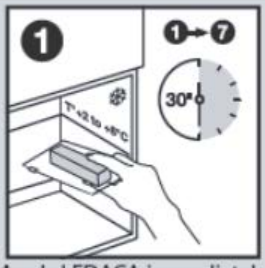
Panel 1

Patient and Caregiver instructions

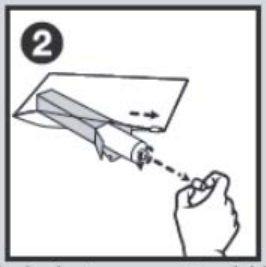
LEDAGA® 160 micrograms/g
gel
chlormethine

Panel 2

In case of direct skin contact with LEDAGA in individuals other than the patients, wash abundantly with water and contact your doctor.
The transparent sealable plastic bag supplied with LEDAGA to prevent secondary exposure and contaminations is child resistant.
Do not throw away any medicinal product or nitrile gloves used for application and ask your pharmacist.



Apply LEDAGA immediately or within 30 min after taking it out of the refrigerator.



Unzip the transparent sealable plastic bag, take LEDAGA out of the carton and open the tube.

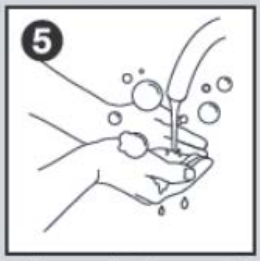
Panel 3

Apply a thin layer to completely dry skin.

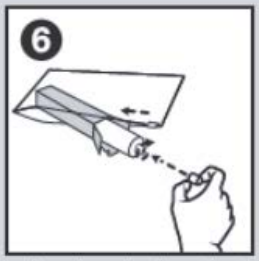
Caregivers must wear nitrile gloves before applying a thin layer to completely dry skin.

Allow the gel to dry (5-10 min).

Panel 4



After application, wash hands with soap and water.



With clean hands, close the tube, return it to the carton and then into the transparent sealable plastic bag, and zip it closed.

Return the transparent sealable plastic bag to the refrigerator.

B. PACKAGE LEAFLET

Package leaflet: Information for the patient

Ledaga 160 micrograms/g gel
chlormethine

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Ledaga is and what it is used for

Ledaga contains the active substance chlormethine. This is an anti-cancer medicine used on the skin to treat mycosis fungoides-type cutaneous T-cell lymphoma (MF-type CTCL).

MF-type CTCL is a condition in which certain cells of the body's immune system called T-lymphocytes become cancerous and affect the skin. Chlormethine is a type of anti-cancer medicine called an 'alkylating agent'. It attaches to the DNA of dividing cells, like cancer cells, which stops them from multiplying and growing.

Ledaga is for use in adults only.

2. What you need to know before you use Ledaga

Do not use Ledaga
- if you are allergic (hypersensitive) to chlormethine or any of the other ingredients of this medicine (listed in section 6).

Warnings and precautions
Talk to your doctor or pharmacist before using Ledaga.

- Contact with your eyes must be avoided. Do not apply the medicine near the eyes, to the inside of the nostrils, the inside of the ear or on the lips.
- If Ledaga gets in your eyes, it can cause pain, burning, swelling, redness, sensitivity to light, and blurred vision. It may also cause blindness and severe permanent injury to your eyes. If Ledaga gets in your eyes, rinse your eyes right away for at least 15 minutes with large amounts of water, a solution known as "0.9% sodium chloride solution" or an eye-wash solution, and seek medical assistance (including an eye doctor) as soon as possible.
- If this medicine gets in your mouth or nose, it can cause pain, redness, and ulcers that may be severe. Rinse the affected area right away for at least 15 minutes with large amounts of water, and seek medical assistance as soon as possible.

- This medicine can cause skin reactions, such as inflammation of your skin (redness and swelling), itching, blisters, ulcers and skin infections (see section 4). The risk for inflammation of the skin is increased if you apply Ledaga to your face, genital area, anus or skin folds.
- Tell your doctor if you have ever had an allergic reaction to chlormethine. Contact your doctor or seek immediate medical attention if you experience allergic reactions to Ledaga (see section 4).
- Skin cancers (abnormal growth of the cells in the skin) have been reported after application of chlormethine to the skin, although it is not known whether chlormethine causes this. Your doctor will check your skin for skin cancers during and after your treatment with Ledaga. Tell your doctor if you get any new damaged areas or ulcers on your skin.
- Direct skin contact with Ledaga should be avoided in individuals other than the patient, such as caregivers. Risks of direct skin contact include inflammation of the skin (dermatitis), injury to their eyes, mouth, or nose, and skin cancers. Caregivers who accidentally come into contact with Ledaga must wash the affected area right away for at least 15 minutes. Remove and wash any contaminated clothing. Get medical help right away if Ledaga gets into your eyes, mouth, or nose.

Children and adolescents
Do not give this medicine to children and adolescents under the age of 18 years because the safety and effectiveness have not been established for this age group.

Other medicines and Ledaga
Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines.

Pregnancy and breast-feeding
If you are pregnant or breast-feeding, think you may be pregnant or are planning to become pregnant, ask your doctor for advice before taking this medicine.

There is limited experience of chlormethine in pregnant women. Therefore, the use of this medicine is not recommended during pregnancy and in women of childbearing age not using contraception.

It is not known whether Ledaga passes into breast milk, and there may be a risk that the breast-feeding baby is exposed to Ledaga via contact with the mother’s skin. Therefore, it is not recommended to breast-feed while taking this medicine.You should talk to your doctor before breast-feeding to determine whether or not it is best to breast-feed or to use Ledaga.

Driving and using machines
This medicine is not expected to have any effect on your ability to drive or to use machines.

Ledaga contains propylene glycol and butylhydroxytoluene
Propylene glycol and butylhydroxytoluene may also cause skin irritation. In addition, butylhydroxytoluene may also cause irritation to the eyes and mucous membranes (i.e., mouth and nose).

3. How to use Ledaga

Always use this medicine exactly as your doctor or pharmacist has told you. Check with your doctor or pharmacist if you are not sure.

Ledaga is intended only for use on the skin.

The recommended dose is application as a thin film once a day to the affected areas. The dose is the same for elderly patients (aged 65 years and older) as for younger adult patients (aged 18 years and older).

Your doctor may stop your treatment if you develop severe inflammation of the skin (i.e., redness and swelling), blisters and ulcers. Your doctor may restart the treatment upon improvement of your symptoms.

Instructions for use:

- Use Ledaga exactly as your doctor or pharmacist tells you.
- Caregivers must wear disposable nitrile gloves when applying this medicine to patients (this is a special type of glove; ask your doctor or pharmacist if you have questions).
- Remove the cap from the tube just before use. Use the cap to pierce the seal.
- Apply Ledaga immediately or within 30 minutes of removing it from the refrigerator.
- Apply a thin layer of this medicine to completely dry skin at least 4 hours before or 30 minutes after showering or washing.
- Apply Ledaga to affected areas of the skin. In case of Ledaga exposure to non-affected areas of the skin, wash the exposed area with soap and water.
- Allow the area to dry for 5 to 10 minutes after applying your medicine and 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.
- Ledaga is supplied within a child-resistant transparent, sealable, plastic bag. If it is not, ask your pharmacist.
- With clean hands, place Ledaga back in the box it came in and the box in the plastic bag. Return it to the refrigerator after each use.
- Do not cover the treated area with air- or water-tight bandages after you have applied this medicine.
- Until Ledaga has dried on the skin, avoid contact with an open flame or a lit cigarette. Ledaga contains alcohol and is therefore considered flammable.
- Do not apply moisturisers or any other skin products (including medicines applied to the skin) for 2 hours before or 2 hours after the daily application of Ledaga.
- Keep away from children and contact with food by storing Ledaga in its box and inside the plastic bag.

If you use Ledaga more than you should
Do not apply Ledaga more than once per day. If you apply more than recommended, talk to your doctor.

If you forget to use Ledaga
Do not use a double dose to make up for a forgotten dose. Apply your next dose when it is due.

If you stop using Ledaga
Your doctor will determine how long you should use Ledaga for and when treatment may be stopped. Do not stop using your medicine until your doctor advises you to do so.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

STOP taking Ledaga and tell your doctor **immediately** if you experience allergic reactions (hypersensitivity).

These reactions may include some or all of the following symptoms:

- Swelling of the lips, face, throat or tongue

- Rash
- Difficulty breathing

Other side effects may include
Tell your doctor or pharmacist as soon as possible if you notice any of the following side effects listed below.

Very common side effects on the treatment area (may affect more than 1 in 10 people):
- Skin inflammation
- Infections of the skin
- Itching (pruritus)

Common side effects on the treatment area (may affect up to 1 in 10 people):
- Skin ulcers
- Blisters
- Darkening of the skin

Reporting of side effects
If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects, you can help provide more information on the safety of this medicine.

5. How to store Ledaga

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date, which is stated on the tube label and box after EXP. The expiry date refers to the last day of that month.

Store in a refrigerator (+2 °C to +8 °C) at all times, ensuring the tube is in the box inside the child-resistant, transparent, sealable, plastic bag.

Do not use an opened or unopened tube of Ledaga after 60 days of storage in the refrigerator.

Ask your pharmacist how to throw away used nitrile gloves, the plastic bag and the medicine you no longer use. Do not throw away any medicines via wastewater or household waste. These measures will help protect the environment.

6. Contents of the pack and other information

What Ledaga contains

- The active substance is chlormethine. Each gram of gel contains 160 micrograms of chlormethine.

- The other ingredients are: diethylene glycol monoethyl ether, propylene glycol, isopropyl alcohol, glycerol, lactic acid, hydroxypropylcellulose, sodium chloride, menthol racemic, disodium edetate, and butylhydroxytoluene.
  See end of section 2 for further information on propylene glycol and butylhydroxytoluene.

What Ledaga looks like and contents of the pack

Ledaga is a clear, colourless gel.
Each aluminium tube contains 60 grams of gel and has a white screw cap.

Marketing Authorisation Holder
Actelion Registration Ltd
Chiswick Tower 13th Floor
389 Chiswick High Road
London W4 4AL
United Kingdom
Tel: +44 208 987 3333

Manufacturer
Actelion Manufacturing GmbH
Emil-Barell-Strasse 7
79639 Grenzach-Wyhlen
Germany

Actelion Pharmaceuticals Belgium NV
Bedrijvenlaan 1
2800 Mechelen
Belgium

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

België/Belgique/Belgien
Actelion Pharmaceuticals Belgium N.V.
Tél/Tel: +32-(0)15 284 777

България
Аквахим АД
Тел.: +359 2 807 50 00

Česká republika
Actelion Pharmaceuticals CZ, s.r.o.
Tel: +420 221 968 006

Danmark
Actelion Danmark,
Filial af Actelion Pharmaceuticals Sverige AB, Sverige
Tlf: +45 3694 45 95

Deutschland
Actelion Pharmaceuticals Deutschland GmbH
Tel: +49 761 45 64 0

Eesti
Algol Pharma OÜ
Tel: +372 605 6014

Ελλάδα
Actelion Pharmaceuticals Ελλάς A.E.
Τηλ: +30 210 675 25 00

Lietuva
UAB ALGOL PHARMA
Tel: +370 37 40 86 81

Luxembourg/Luxemburg
Actelion Pharmaceuticals Belgium N.V.
Tél/Tel: +32-(0)15 284 777

Magyarország
Actelion Pharmaceuticals Hungaria Kft.
Tel: +36-1-413-3270

Malta
Actelion Pharmaceuticals UK Ltd
Tel: +44 208 987 3333

Nederland
Actelion Pharmaceuticals Nederland B.V.
Tel: +31 (0)348 435950

Norge
Actelion Pharmaceuticals Sverige AB,
Filial Norge
Tlf: +47 22480370

Österreich
Actelion Pharmaceuticals Austria GmbH
Tel: +43 1 505 4527

España
Actelion Pharmaceuticals España S.L.
Tel: +34 93 366 43 99

France
Actelion Pharmaceuticals France SAS
Tél: +33 1 58 62 32 32

Hrvatska
Medis Adria d.o.o.
Tel: + 385 (0) 1 2303 446

Ireland
Actelion Pharmaceuticals UK Ltd
Tel: +44 208 987 3333

Ísland
Actelion Pharmaceuticals Sverige AB
Sími: +46 (0)8 544 982 50

Italia
Actelion Pharmaceuticals Italia S.r.l.
Tel: +39 0542 64 87 40

Κύπρος
Actelion Pharmaceuticals Ελλάς A.E.
Τηλ: +30 210 675 25 00

Latvija
Algol Pharma SIA
Tel: +371 6761 9365

Polska
Actelion Pharma Polska Sp. z o.o.
Tel: +48 (22) 262 31 00

Portugal
Actelion Pharmaceuticals Portugal Lda.
Tel: +351 21 358 6120

România
Geneva Romfarm International SRL
Tel: + 40 (021) 231 3561

Slovenija
Medis d.o.o.
Tel: +386-(0)1 589 69 00

Slovenská republika
Actelion Pharmaceuticals SK, s.r.o.
Tel: +420 221 968 006

Suomi/Finland
Actelion Pharmaceuticals Sverige AB,
Filial Finland
Puh/Tel: +358 9 2510 7720

Sverige
Actelion Pharmaceuticals Sverige AB
Tel: +46 8 544 982 50

United Kingdom
Actelion Pharmaceuticals UK Ltd
Tel: +44 208 987 3333

This leaflet was last revised in

Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu.