

EVIDENCE BRIEFING
January 2019

**Mechlorethamine gel for mycosis fungoides in
cutaneous T-cell lymphoma**

NIHRI ID	4160	NICE ID	7126
Developer/Company	Actelion Pharmaceuticals/Helsinn Healthcare SA	UKPS ID	644674

**Licensing and market
availability plans**

Currently in phase II clinical trials.

SUMMARY

Mechlorethamine gel has been developed for the treatment of mycosis fungoides (MF) which is the most common type of cutaneous T-cell lymphoma (CTCL). MF is a slow growing type of CTCL that initially manifests as red patches in body areas not exposed to sunlight. The main symptom is itching. There is currently no cure for MF and management is focussed at alleviating symptoms and avoiding spread to other parts of the body. People with MF type of cancer can live for many years with this condition. Relapse or progression can happen during ongoing treatment or after its cessation.

Mechlorethamine gel is applied topically to the affected skin area and works by stopping cancer cell reproduction. Mechlorethamine has been in use to treat MF-CTCL but has been available as water or oil base formulations. The availability of these formulations are limited due to toxicity and can be difficult to prepare due to instability (water base) or irritating properties (oil base). In clinical trials, mechlorethamine gel formulation has shown greater efficacy and faster response than an oil-based formulation whilst retaining the same safety profile which in turn will contribute to greater patient compliance and convenience.

PROPOSED INDICATION

Topical treatment of mycosis fungoides-type cutaneous T-cell lymphoma (MF-CTCL) in adult patients, for all stages MF-CTCL.^a

TECHNOLOGY

DESCRIPTION

Mechlorethamine (also known as mustine, nitrogen mustard, and HN2) is a synthetic agent related to sulphur mustard with antineoplastic and immunosuppressive properties. Mechlorethamine (a member of a family of chemotherapy agents including cyclophosphamide and chlorambucil) is an irritant and carcinogenic agent metabolized to a highly reactive ethylene immonium derivative that alkylates DNA and inhibits DNA replication. This agent also exhibits lympholytic properties.¹ Mechlorethamine exerts its cytotoxic effects by forming DNA adducts and DNA interstrand crosslinks, thereby inhibiting rapidly proliferating cells.^{1,2}

Mechlorethamine gel (Ledaga) formulation contains diethyleneglycol monoethyl ether, glycerine, propylene glycol and isopropanol base. The lack of water in this gel composition affects the higher stability of chlormethine, which under the influence of water decomposes to the reactive and toxic metabolites. This new form of anhydrous gel makes possible the self-administration by the patient in a home setting, thus without professional assistance of healthcare experts.

Mechlorethamine gel 160 micrograms/g gel is indicated for the treatment of MF-CTCL.³ Mechlorethamine gel is applied topically once a day.⁴ The most common side effects (which may affect more than 1 in 10 people) are dermatitis (skin inflammation with reddening, rash, pain and burning sensation), skin infection and itching.⁵ The efficacy and safety of the new form of chlormethine in gel has been confirmed by clinical studies that showed that chlormethine in the form in which it occurs in the product mechlorethamine gel has no systemic effect, which means no toxicity to viable organs, while maintaining the cytotoxic local action constituting therapeutic action.⁶

INNOVATION AND/OR ADVANTAGES

Topical mechlorethamine 0.01% or 0.02% in the treatment of MF-CTCL has been in use since the 1930s.⁶ It may be available as an aqueous solution (in normal saline) or in an ointment base (emulsifying ointment). In practice, pharmacy preparations have extremely limited availability due to the toxicity and difficulty in preparing.⁷ The aqueous solution of mechlorethamine is relatively unstable, and the ointment base, which is more irritant than the aqueous solution, can cause irritant or allergic dermatitis in sensitized individuals (35–58%), but its efficacy is similar. Furthermore, petrolatum-based ointments may often be difficult to apply to the skin, are aesthetically unappealing, and can compromise patient compliance.^{6,8} The gel formulation of mechlorethamine has showed greater efficacy and faster response than a petroleum-based formulation whilst retaining the same safety profile.⁶

^a Information provided by Helsinn Healthcare SA

DEVELOPMENT STATUS AND/OR REGULATORY DESIGNATIONS

- Mechlorethamine gel was licensed in the EU under the commercial name of Ledaga in March 2017.⁵
- Mechlorethamine gel was approved by the US Food & Drug Administration (for MF-CTCL patients in stages IA and IB who have received prior skin-directed therapy) in 2013 under the commercial name of Valchlor.⁹
- On 22 May 2012, orphan designation (EU/3/12/963) was granted by the European Commission to TMC Pharma Services Ltd, United Kingdom, for chlormethine for the treatment of cutaneous T-cell lymphoma. The sponsorship was transferred to Actelion Registration Limited, United Kingdom, in April 2014.⁴
- Mechlorethamine gel is commercialized in the U.S. and Israel and available in France since 2014 under Autorization temporaire d'utilisation (ATU) program.¹⁰

PATIENT GROUP

DISEASE BACKGROUND

Cutaneous T-cell lymphoma (CTCL) is a rare type of non-Hodgkin lymphoma that affects the skin. It develops due to the uncontrolled growth of T-lymphocytes within the skin.^{11,12}

There are different types of CTCL. The most common type is called mycosis fungoides (MF). MF-CTCL is usually a very slow-growing type of lymphoma that often only affects the skin. For most people, MF-CTCL will develop slowly or stay under control for many years. In a small number of people (about 10%), MF-CTCL may spread to other parts of the body such as lymph nodes and internal organs over time.^{11,13}

MF-CTCL can look like other common skin conditions like eczema or psoriasis, and might be present for years or even decades before it is diagnosed correctly.¹³ MF-CTCL can appear anywhere on the body, but tends to affect areas of the skin protected from sun by clothing. Patches, plaques and tumours are the clinical names for different skin manifestations and are generally defined as 'lesions'.¹³ A common symptom of MF-CTCL is itching, with 80% or more of people with the condition suffering from itching.¹³

There is no known cure for MF-CTCL. Some patients have long-term remission with treatment, and many more live with minimal or no symptoms for many years. Research indicates that most patients diagnosed with MF-CTCL live with early stage disease, and have a normal life span.¹³ However, almost all patients will eventually experience relapse or progression either during ongoing treatment or after its cessation.¹⁴

CLINICAL NEED AND BURDEN OF DISEASE

In England, 1,659 new cases of CTCL were diagnosed from 2009 to 2013, of which around 55% were MF-CTCL.¹⁵ In 2016 in England, there were a total of 199 newly diagnosed cases of MF-CTCL (ICD-10 code C84.0).¹⁶ The overall incidence of cutaneous T-cell lymphomas in 2013 was around 0.75 per 100,000 (England)^{15,17} MF-CTCL can occur at any age but it is most common in the 40 to 60 year-old age group.¹⁸

The prognosis of MF-CTCL depends on the stage of the disease. A patient's life expectancy is not adversely affected in stage IA disease, patients with stage IB/IIA disease have a 73–86% or 49–73% overall 5-year survival, respectively, while patients with stage IIB disease have a 40– 65% 5-year survival. The 5-year survival of patients with erythrodermic stage III disease is 45–57%, 15–40% for

those with stage IVA and 0–15% for IVB disease.⁸ In England in 2016 there were a total of 19 deaths with MF-CTCL recorded as the underlying cause of death.¹⁶

PATIENT TREATMENT PATHWAY

PATIENT PATHWAY

A multidisciplinary approach to CTCL is recommended to accurately diagnose, stage, and treat this group of patients.¹⁹

The following is a summary of recommendations by the joint British Association of Dermatologists and UK Cutaneous Lymphoma Group guidelines on the management and treatment of MF and Sézary syndrome (SS) (a type of CTCL that may be an advanced form of MF):^{20,21}

- The diagnosis of MF and SS is based on a combination of clinical and pathological criteria and requires close multidisciplinary team (MDT) collaboration between different specialities. All patients with early-stage MF refractory to skin-directed therapy (SDT) and late-stage MF/SS should be reviewed by supranetwork MDTs to agree a management plan and provide the opportunity for consideration in appropriate clinical trials.
- The aim of treatment is to control the patient's disease and symptoms with the minimum of intervention.
- Current standard of care requires SDTs, including phototherapy and local radiotherapy.
- Systemic therapies as methotrexate, photopheresis, bexarotene and interferon-alpha may be offered to those at more advanced stages.
- Autologous HSCT should not be considered for advanced stages of MF/SS.
- Reduced-intensity allogeneic HSCT should be considered for selected groups of patients with advanced MF/SS to consolidate treatment responses.
- The conditioning regimens and outcomes of RIC alloHSCT should be collected through data registries such as the EBMT registry.

CURRENT TREATMENT OPTIONS

MF-CTCL is rarely curable, and treatment aims mainly to reduce the abnormal appearance of the skin and to control any itching or other symptoms.^{22,23}

Treatment can be local or systemic. The most common local treatments are the use of steroid creams and moisturisers. If widespread areas are affected, or if the symptoms are not controlled, then other treatments such as phototherapy with either ultraviolet B or PUVA can be considered.¹⁸

If the disease causes the skin to become very thick in places then radiotherapy can be used as a form of treatment. Methotrexate tablets, used for more extensive lesions not responding to cream treatments and in rare occasions for severe cases, oral retinoids, immunotherapy, photopheresis or even chemotherapy may be used.^{8,18}

Pharmacy preparations have limited availability in the UK due to the toxicity and difficulty in preparing.⁷

It is not always clear which treatment option (or if a combination of more treatments) might work best as a first approach. Indeed, current guidelines (US, EU) offer many possibilities for all stages of MF-CTCL, including Ledaga, listed according to stage in no particular order of preference.^b

PLACE OF TECHNOLOGY

Mechlorethamine gel provides an additional treatment option for patients with all stages of MF-CTCL that offers greater patient convenience due to its ready-made formulation and availability.

CLINICAL TRIAL INFORMATION

Trial	NCT00168064 , 2005NMMF-201-US; children, adults and older adults (ages not specified); mechlorethamine-MCH proprietary gel (PG) vs a compounded ointment formulation in Aquaphor (AP); phase II
Sponsor	Yaupon Therapeutics
Status	Published
Source of Information	Publication ⁶ and Trial registry ²⁴
Location	USA
Design	Randomised, active-controlled
Participants	n=260; children to older adults with mycosis fungoides confirmed by a skin biopsy, Stage I or IIA patients must have been treated previously with prior topical therapies including PUVA, UVB, topical steroids, but not NM within the past 2 years, or topical carmustine (BCNU)
Schedule	Randomised to: <ul style="list-style-type: none"> PG - mechlorethamine-MCH (nitrogen mustard) 0.02% gel once daily for twelve months AP - mechlorethamine-MCH (nitrogen mustard) 0.02% compounded in Aquaphor once daily for twelve months
Follow-up	Active treatment for 12 months
Primary Outcomes	<ul style="list-style-type: none"> Ratio of Response Rates Based Composite Assessment of Index Lesion Severity (CAILS)
Secondary Outcomes	<ul style="list-style-type: none"> Severity-weighted Assessment Tool (SWAT) Percent of Participants Achieving at Least 50% Improvement of Severity Weighted Assessment Tool (SWAT)
Key Results	Response rates for mechlorethamine gel vs ointment were 58.5% vs 47.7% by CAILs and 46.9% vs 46.2% by the Modified Severity-Weighted Assessment Tool. By CAILs, the ratio of gel response rate to ointment response rate was 1.23 (95% CI, 0.97-1.55), which met the pre-specified criterion for non-inferiority. Time-to-response analyses demonstrated superiority of mechlorethamine gel to ointment (P< .01). No drug-related serious adverse events were seen. Approximately 20.3% of enrolled patients in the gel treatment arm and 17.3% of enrolled patients in the ointment treatment arm withdrew because of drug-related skin irritation. No systemic absorption of the study medication was detected.
Adverse effects (AEs)	No drug-related severe adverse events were reported during this trial.
Expected reporting date	-

^b Information provided by Helsinn Healthcare SA

ESTIMATED COST

The cost of mechlorethamine gel is not yet known.

ADDITIONAL INFORMATION

RELEVANT GUIDANCE

NICE GUIDANCE

- NICE Technology Appraisal Guidance in development. Mogamulizumab for previously treated cutaneous T-cell lymphoma ID1405 (GID-TA10305). Expected publication date to be confirmed.
- NICE Technology Appraisal Guidance in development. Brentuximab vedotin for treating CD30-positive cutaneous T-cell lymphoma ID1190 (GID-TA10201). Expected publication date: 22 May 2019.

NHS ENGLAND (POLICY/COMMISSIONING) GUIDANCE

- NHS England. 2013/14 NHS Standard Contract for Cancer: Chemotherapy (Adult). B15/S/a.
- NHS England. 2013/14 NHS Standard Contract for Cancer: Radiotherapy (All Ages). B01/S/a.
- NHS England. 2013/14 NHS Standard Contract for Cancer: Skin (Adult). A12/S/b.

OTHER GUIDANCE

- European Society of Medical Oncology (ESMO). Clinical Practice Guidelines. Primary cutaneous lymphomas: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. 2018¹⁴
- NHS Pan Birmingham Cancer Network. Guideline for the Management of Patients with Cutaneous T-Cell Lymphoma. 2011⁸

REFERENCES

- 1 National Center for Biotechnology Information. *Mechlorethamine*: CID=4033. Available from: <https://pubchem.ncbi.nlm.nih.gov/compound/4033> [Accessed 17 December 2018]
- 2 Drugbank.ca. *Mechlorethamine*. Available from: <https://www.drugbank.ca/drugs/DB00888> [Accessed 5 December 2018]
- 3 European Medicines Agency (EMA). *Summary of Product Characteristics*. 2017. Available from: https://www.ema.europa.eu/documents/product-information/ledaga-epar-product-information_en.pdf.
- 4 European Medicines Agency. *Public summary of opinion on orphan designation: Chlormethine for the treatment of cutaneous T-cell lymphoma*. 2015. Report No.: EU/3/12/963. Available from: https://www.ema.europa.eu/documents/orphan-designation/eu/3/12/963-public-summary-opinion-orphan-designation-chlormethine-treatment-cutaneous-t-cell-lymphoma_en.pdf.

- 5 European Medicines Agency. *European Public Assessment Report summary for the public: Ledaga (chlormethine)*. 2017. Report No.: EMA/880957/2016. Available from: https://www.ema.europa.eu/documents/overview/ledaga-epar-summary-public_en-0.pdf.
- 6 Lessin SR, Duvic M, Guitart J, et al. Topical chemotherapy in cutaneous t-cell lymphoma: Positive results of a randomized, controlled, multicenter trial testing the efficacy and safety of a novel mechlorethamine, 0.02%, gel in mycosis fungoides. *JAMA Dermatology*. 2013;149(1):25-32. Available from: 10.1001/2013.jamadermatol.541.
- 7 UK Medicines Information (UKMi). *Is there a topical preparation of chlormethine available for the treatment of mycosis fungoides?* : 2015. Available from: https://www.sps.nhs.uk/wp-content/uploads/2015/02/QA314_3_Chlormethine.doc.
- 8 NHS: Pan Birmingham Cancer Network. *Guideline for the Management of Patients with Cutaneous T-Cell Lymphoma* Last Update Date: 2011. Available from: <https://www.uhb.nhs.uk/Downloads/pdf/CancerPbCutaneousTcellLymphoma.pdf> [Accessed 10 December 2018].
- 9 Center for Drug Evaluation and Research (CDER). *CDER Rare Disease And Orphan Drug Designated Approvals*. 2013. Available from: <https://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/DrugandBiologicApprovalReports/NDAandBLAApprovalReports/UCM404471.pdf>.
- 10 Helsinn. *Helsinn Group announces agreement to acquire worldwide rights to Valchlor®/Ledaga® - an approved and marketed alkylating agent for the topical treatment of mycosis fungoides-type cutaneous T-cell lymphoma, a rare type of skin cancer*. Available from: <https://www.helsinn.com/news-and-events/helsinn-group-announces-agreement-to-acquire-worldwide-rights-to-valchlorledaga-an-approved-and-marketed-alkylating-agent-for-the-topical-treatment-of-mycosis-fungoidestype-cutaneous-tcell-lymphoma-a-rare-type-of-skin-cancer/> [Accessed 5 December 2018]
- 11 MacMillan Cancer Support. *Cutaneous T-cell lymphoma*. Available from: <https://www.macmillan.org.uk/information-and-support/lymphoma/lymphoma-non-hodgkin/understanding-cancer/types-of-non-hodgkin-lymphoma/cutaneous-t-cell-lymphoma-skin.html> [Accessed 5 December 2018]
- 12 Cancer Research UK. *Skin lymphoma*. Available from: <https://www.cancerresearchuk.org/about-cancer/non-hodgkin-lymphoma/types/skin> [Accessed 24/ January 2019]
- 13 Cutaneous Lymphoma Foundation. *Mycosis Fungoides*. Available from: <https://www.clfoundation.org/mycosis-fungoides> [Accessed 5 December 2018]
- 14 Willemze R, Hodak E, Zinzani PL, Specht L, Ladetto M. Primary cutaneous lymphomas: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol*. 2018 Oct 1;29(Supplement_4):iv30-iv40. Available from: 10.1093/annonc/mdy133.
- 15 Public Health England. *Registration of Cutaneous T-Cell Lymphoma (CTLC) in England*. 2016. Available from: <http://www.ncin.org.uk/view?rid=3275>.
- 16 Office for National Statistics (ONS). *Cancer Registration Statistics, England, 2016*. Available from: <https://www.ons.gov.uk/peoplepopulationandcommunity/healthandsocialcare/conditionsanddiseases/datasets/cancerregistrationstatisticscancerregistrationstatisticsengland> [Accessed 17 December 2018].
- 17 National Institute for Health and Care Excellence (NICE). *Single Technology Appraisal. Brentuximab vedotin for treating relapsed or refractory CD30-positive cutaneous T-cell lymphoma: Draft scope* Last Update Date: Available from: <https://www.nice.org.uk/guidance/gid-ta10201/documents/draft-scope-post-referral> [Accessed 5 December 2018].
- 18 British Association of Dermatologists (BAD). *Mycosis Fungoides*. 2015. Available from: <http://www.bad.org.uk/shared/get-file.ashx?id=170&itemtype=document>.
- 19 Devata S, Wilcox RA. Cutaneous T-Cell Lymphoma: A Review with a Focus on Targeted Agents. *Am J Clin Dermatol*. 2016 Jun;17(3):225-37. Available from: 10.1007/s40257-016-0177-5.

- 20 Gilson D, Whittaker SJ, Child FJ, Scarisbrick JJ, Illidge TM, Parry EJ, et al. British Association of Dermatologists and UK Cutaneous Lymphoma Group guidelines for the management of primary cutaneous lymphomas 2018. *British Journal of Dermatology*. 2018. Available from: doi.org/10.1111/bjd.17240.
- 21 Clinic C. *Mycosis Fungoides and the Sezary Syndrome*. Available from: <https://my.clevelandclinic.org/health/articles/8493-mycosis-fungoides-and-the-sezary-syndrome> [Accessed 15/01/2019]
- 22 NHS Musgrove Park Hospital. *Mycosis Fungoides Dermatology*. Available from: <https://www.tsft.nhs.uk/media/44762/Mycosis-Fungoides.pdf> [Accessed 5 December 2018]
- 23 Tidy C. *Mycosis Fungoides and Cutaneous T-cell Lymphomas*. Available from: <https://patient.info/doctor/mycosis-fungoides-and-cutaneous-t-cell-lymphomas#nav-7> [Accessed 10 December 2018]
- 24 Clinicaltrials.gov. *Safety and Efficacy of Nitrogen Mustard in Treatment of Mycosis Fungoides (Therapeutics Y)*. NCT00168064. 2012. Status: Completed. Available from: <https://clinicaltrials.gov/ct2/show/NCT00168064> [Accessed 10 December 2018].

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