Australian Government
Department of Health
Therapeutic Goods Administration

Australian Public Assessment Report for Chlormethine hydrochloride

Proprietary Product Name: Ledaga

Sponsor: Recordati Rare Disease Australia Pty Ltd

September 2021

TGA Health Safety Regulation

About the Therapeutic Goods Administration (TGA)

- The Therapeutic Goods Administration (TGA) is part of the Australian Government Department of Health and is responsible for regulating medicines and medical devices.
- The TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety and efficacy (performance) when necessary.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to consumers outweigh any risks associated with the use of medicines and medical devices.
- The TGA relies on the public, healthcare professionals and industry to report problems with medicines or medical devices. TGA investigates reports received by it to determine any necessary regulatory action.
- To report a problem with a medicine or medical device, please see the information on the TGA website <https://www.tga.gov.au>.

About AusPARs

- An Australian Public Assessment Report (AusPAR) provides information about the evaluation of a prescription medicine and the considerations that led the TGA to approve or not approve a prescription medicine submission.
- AusPARs are prepared and published by the TGA.
- An AusPAR is prepared for submissions that relate to new chemical entities, generic medicines, major variations and extensions of indications.
- An AusPAR is a static document; it provides information that relates to a submission at a particular point in time.
- A new AusPAR will be developed to reflect changes to indications and/or major variations to a prescription medicine subject to evaluation by the TGA.

Contents

List of abbreviations

Abbreviation	Meaning
ACM	Advisory Committee on Medicines
AE	Adverse event
ARTG	Australian Register of Therapeutic Goods
ASA	Australian specific annex
AusPAR	Australian Public Assessment Report
BSA	Body surface area
CAILS	Composite Assessment of Index Lesion Severity
CI	Confidence interval
CMI	Consumer Medicines Information
CR	Complete response
CTCL	Cutaneous T-cell lymphoma
DLP	Data lock point
DNA	Deoxyribonucleic acid
EE	Efficacy evaluable
EU	European Union
GVP	Good Pharmacovigilance Practices
HPLC	High performance liquid chromatography
ISCL	International Society for Cutaneous Lymphoma
ITT	Intent to treat
LLOQ	Lower limit of quantification
PI	Product Information
PSURs	Periodic safety update reports
PUVA	Psoralen plus ultraviolet A radiation
QoL	Quality of life
RMP	Risk management plan

Abbreviation	Meaning
SAE	Serious adverse event
SOC	System Organ Class
SWAT	Severity Weighted Assessment Tool
TGA	Therapeutic Goods Administration
TNMB	Tumour, Node, Metastasis, Blood classification
USA	United States of America
UVA	Ultraviolet A
UVB	Ultraviolet B

I. Introduction to product submission

Submission details

Type of submission:	New chemical entity
Product name:	Ledaga
Active ingredient:	Chlormethine hydrochloride
Decision:	Approved
Date of decision:	8 June 2021
Date of entry onto ARTG:	22 June 2021
ARTG number:	338551
, *Black Triangle Scheme:*[1]	Yes This product will remain in the scheme for 5 years, starting on the date the product is first supplied in Australia
Sponsor's name and address:	Recordati Rare Diseases Australia Pty Ltd Level 6, 69 Reservoir St Surry Hills, NSW 2010
Dose form:	Gel
Strength:	160 µg/g chlormethine
Container:	Tube
Pack size:	One
Approved therapeutic use:	*Ledaga is indicated for the topical treatment of mycosis fungoides-type cutaneous T-cell lymphoma (MF-type CTCL) in adult patients*
Route of administration:	Topical
Dosage:	*General use and application* Treatment with Ledaga should be initiated by an appropriately experienced physician. 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

[1] The **Black Triangle Scheme** provides a simple means for practitioners and patients to identify certain types of new prescription medicines, including those being used in new ways and to encourage the reporting of adverse events associated with their use. The Black Triangle does not denote that there are known safety problems, just that the TGA is encouraging adverse event reporting to help us build up the full picture of a medicine's safety profile.

dermatitis (for example, marked skin redness with oedema). Upon improvement, treatment with Ledaga can be restarted at a reduced frequency of once every three days. If reintroduction of treatment is tolerated for at least one week, the frequency of application can be increased to every other day for at least one week and then to once-daily application if tolerated.

Use in the elderly population

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

For further information regarding dosage, refer to the Product Information.

Pregnancy category: B3

Drugs which have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human fetus having been observed.

Studies in animals have shown evidence of an increased occurrence of fetal damage, the significance of which is considered uncertain in humans.

The use of any medicine during pregnancy requires careful consideration of both risks and benefits by the treating health professional. This must not be used as the sole basis of decision making in the use of medicines during pregnancy. The TGA does not provide advice on the use of medicines in pregnancy for specific cases. More information is available from obstetric drug information services in your State or Territory.

Product background

This AusPAR describes the application by Recordati Rare Diseases Australia Pty Ltd (the sponsor) to register Ledaga (chlormethine hydrochloride) 160 µg/g, gel for the following proposed indication:

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

Mycosis fungoides (MF) and Sézary syndrome (leukemic involvement) are neoplasias of malignant T lymphocytes that usually possess the helper/inducer cell surface phenotype. These kinds of neoplasms initially present as skin involvement and, as such, have been classified as cutaneous T-cell lymphomas. Cutaneous T-cell lymphomas should be distinguished from other T-cell lymphomas that involve the skin, such as anaplastic large cell lymphoma (CD30 positive), peripheral T-cell lymphoma (CD30 negative, with no epidermal involvement), adult T-cell leukaemia/lymphoma (usually with systemic involvement), or subcutaneous panniculitic T-cell lymphoma.

Typically, the natural history of mycosis fungoides is indolent. Symptoms of the disease may present for long periods, in a range of 2 to 10 years, because cutaneous eruptions wax and wane before they receive a biopsy confirmation. Mycosis fungoides and Sézary syndrome are treatable with available topical therapy, systemic therapy, or both. To date,

curative modalities have proven elusive, with the possible exception of patients with minimal disease confined to the skin.[2]

Cutaneous T-cell lymphoma (CTCL) refers to a heterogeneous group of primary, epidermotropic (cutaneous) and non-epidermotropic (subcutaneous and systemic) non-Hodgkin lymphomas involving malignant proliferation of mature T lymphocytes, primarily in the skin. Although T-cell lymphomas typically begin in the skin, aggressive forms involve extra-cutaneous sites such as bone marrow, blood, lymph nodes, and visceral organs.[3] The epidermotropic form of CTCL is the most common and is referred to as mycosis fungoides, accounting for 60% of new CTCL cases.

The Tumour, Node, Metastasis, Blood (TNMB) classification of the mycosis fungoides-type of CTCL;[4,5] for early stage disease (Stages IA, IB, IIA), is characterised by skin lesions (patches, papules, and/or plaques, but no cutaneous tumour or generalised erythema), with normal or clinically enlarged lymph nodes but not histologically involved, no visceral involvement and no high blood tumour burden. Late stage disease (Stages IIB, IIIA, IIIB, and IV) is characterised by skin lesions (one or more cutaneous tumour or generalised erythema), normal or clinically enlarged lymph nodes with possible histopathological involvement, possible visceral involvement, and/or high blood tumour burden.

Mycosis fungoides-type CTCL can mimic benign skin conditions such as chronic eczema, allergic contact dermatitis, or psoriasis, thus posing a diagnostic challenge to the clinicians involved in the diagnosis. It is not unusual for the diagnosis to remain elusive for years. Nevertheless, early stages accounts for the majority of the patients.[6]

Survival prognosis is related to the disease stage at diagnosis, the type and extent of skin lesions and the presence of extracutaneous disease. Median survival time ranges from 35.5 years for Stage IA to two years for Stage IV.[7]

The likelihood of progression is unpredictable, with a quarter of early stage patients progressing to advanced stage disease which presents a poor prognosis and median survival of just 3 years. Thus, effective treatment of early stage disease is an important factor in preventing disease progression and death from mycosis fungoides, as well as relief of symptoms.[8]

There remain no approved topical treatments for mycosis fungoides-type CTCL in Australia. In the absence of an approved topical treatment, prescribers use unapproved products (for example, carmustine) compounded extemporaneously in pharmacies in a non-standardised manner. Systemically administered products are approved and available but are mainly reserved for patients who are refractory to topical treatment or show signs

[2] Physician Data Query (PDQ) adult treatment editorial board: Mycosis fungoides (including Sézary syndrome) treatment (Physician Data Query), health professional version, Bethesda, USA: National Cancer Institute. Updated 20 September 2019. Available at: https://www.cancer.gov/types/lymphoma/hp/mycosis-fungoides-treatment-pdq

[3] Burg G, et al. (2005) WHO/EORTC classification of cutaneous lymphomas 2005: histological and molecular aspects. *J Cutan Pathol*; 32:647-74.

[4] Trautinger F, et al. (2006) EORTC consensus recommendations for the treatment of mycosis fungoides/Sezary syndrome. *Eur J Can*;42: 1014–30.

[5] Olsen 2011, Clinical End Points and Response Criteria in MycosisFungoides and Sezary Syndrome: A Consensus Statement of the International Society for Cutaneous Lymphomas, the United States Cutaneous Lymphoma Consortium, and the Cutaneous Lymphoma Task Force of the European Organisation for Research and Treatment of Cancer.

[6] Trautinger F, et al. (2017) European Organisation for Research and Treatment of Cancer consensus recommendations for the treatment of mycosis fungoides/Sézary syndrome - Update 2017. *Eur J Cancer*; 77:57-74.

[7] Agar, N. S, et al (2010). Survival outcomes and prognostic factors in mycosis fungoides/Sézary syndrome: validation of the revised International Society for Cutaneous Lymphomas/European Organisation for Research and Treatment of Cancer staging proposal. *J clinical oncology*, 28(31), 4730–4739.

[8] Kim YH, et al. (1996) Clinical Stage IA (limited patch and plaque) mycosis fungoides. A long-term outcome analysis. *Arch Dermatol*; 132:1309-13

of progressive disease. Accordingly, there is an unmet medical need for a topical treatment for mycosis fungoides-type CTCL, particularly a topical chlormethine containing product such as Ledaga.

Gliadel,[9] an implant indicated for glioma and BiCNU,[10] an intravenous product, remain the only carmustine products on the Australian Register of Therapeutic Goods (ARTG).

Clinical staging of mycosis fungoides-type CTCL is based on the classification by Bunn and Lamberg (1979).[11] For patients with Stage IA, IB skin disease only (without lymph node involvement) or IIA (enlarged but histologically uninvolved lymph nodes), treatment is with skin directed therapy. These include topical corticosteroids, topical chemotherapy with chlormethine (also known as nitrogen mustard and as mechlorethamine) or carmustine, ultraviolet B (UVB) therapy, psoralen plus ultraviolet A radiation (PUVA), retinoids and total skin electron beam therapy. Whilst in clinical series topical nitrogen mustard concentrations of 0.01% to 0.02% demonstrate significant clinical efficacy in early plaque/patch disease, the major toxicity of this approach is allergic contract dermatitis occurring in up to 35 to 70% of patients and often leading to cessation of therapy. Furthermore, due to the known alkylation of deoxyribonucleic acid (DNA) induced by nitrogen mustard, there has been concern of an increase in the risk of other forms of skin cancer, including squamous cell carcinoma and basal cell carcinoma.

Systemic therapies that have been used include: interferon-alpha, interferon-gamma, methotrexate, doxorubicin, fludarabine, 2-chlorodeoxyadenosine, pentostatin, prednisone, cyclophosphamide, lenalidomide, vorinostat, brentuximob vedotin and allogeneic or autologous bone marrow transplantation.

These types of treatments produce remission, but long term remission is uncommon. Treatment, therefore, is considered palliative for most patients, although major symptomatic improvement is regularly achieved. Survival in excess of 8 years, however, is common for patients with early stages of disease. All patients with mycosis fungoides-type CTCL and Sézary syndrome are candidates for clinical trials evaluating new approaches to treatment.[2]

Regulatory status

This product is considered a new chemical entity or biosimilar medicine for Australian regulatory purposes.

At the time the TGA considered this application, similar applications had been approved in the European Union (EU) on the 3 March 2017 and the United States of America (USA) on 23 August 2013. It has also been approved in Israel (28 September 2016). It was under consideration in Canada (submitted on 30 April 2020) and Switzerland (submitted on 10 May 2020).

Table 1: International regulatory status details the International regulatory status for similar indications as discussed in this AusPAR.

[9] Gliadel was registered in Australia on 16 May 2002, ARTG number: 77283.
[10] BiCNU was registered in Australia on 30 September 1991, ARTG number: 19243.
[11] Bunn, P. A., Jr, & Lamberg, S. I. (1979). Report of the Committee on Staging and Classification of Cutaneous T-Cell Lymphomas. *Cancer treatment reports*, 63(4), 725–728.

Table 1: International regulatory status

Region	Submission date	Status	Approved indications
European Union (via Centralised procedure)	28 May 2015	Approved on 3 March 2017	*Ledaga is indicated for the topical treatment of mycosis fungoides-type cutaneous T cell lymphoma (MF-type CTCL) in adult patients*
United States of America	27 July 2011	Approved on 23 August 2013	*Valchlor is indicated for the topical treatment of Stage IA and IB mycosis fungoides-type cutaneous T cell lymphoma in patients who have received prior skin-directed therapy.*[12]
Israel	3 August 2015	28 September 2016	*Topical treatment of Stage 1A and 1B mycosis fungoides-type cutaneous T cell lymphoma in patients who have received prior skin-directed therapy*
Canada	30 April 2020	Under consideration	Under consideration
Switzerland	10 May 2020	Under consideration	Under consideration

Product Information

The Product Information (PI) approved with the submission which is described in this AusPAR can be found as Attachment 1. For the most recent PI, please refer to the TGA website at <https://www.tga.gov.au/product-information-pi>.

[12] Valchlor is the tradename for sale of Ledaga (chlormethine hydrochloride) in the United States of America.

II. Registration timeline

The following table captures the key steps and dates for this application and which are detailed and discussed in this AusPAR.

Table 2: Timeline for Submission PM-2020-03014-1-6

Description	Date
Designation: Orphan[13] Extension	15 August 2019 4 December 2019
Submission dossier accepted and first round evaluation commenced	31 July 2020
First round evaluation completed	24 December 2020
Sponsor provides responses on questions raised in first round evaluation	2 March 2021
Second round evaluation completed	13 April 2021
Delegate's Overall benefit-risk assessment	15 April 2021
Sponsor's pre-Advisory Committee response	Not applicable
Advisory Committee meeting	Not applicable
Registration decision (Outcome)	8 June 2021
Completion of administrative activities and registration on the ARTG	22 June 2021
Number of working days from submission dossier acceptance to registration decision*	170

*Statutory timeframe for standard applications is 255 working days

III. Submission overview and risk/benefit assessment

The submission was summarised in the following Delegate's overview and recommendations.

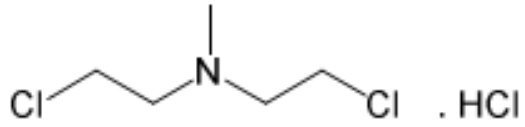
Quality

There were no objections to registration with respect to chemistry and quality control.

[13] *Orphan drugs* are often developed to treat small and very specific patient populations who suffer from rare diseases and conditions. In order to facilitate orphan drug access to the Australian marketplace and help offset orphan drug development costs the TGA waives application and evaluation fees for prescription medicine registration applications if a related orphan designation is in force. A medicine may be eligible for orphan drug designation if all orphan criteria set by the TGA are met. The orphan designation application precedes the registration application and the designation is specific to the sponsor, orphan indication for which designation was granted and dosage form of the medicine.

The drug substance, chlormethine hydrochloride is a nitrogen mustard analogue, similar to bendamustine and cyclophosphamide, and is a cytotoxic DNA alkylating agent (see Figure 1).

Figure 1: Chemical structure of chlormethine hydrochloride



Chlormethine hydrochloride exhibits good stability and the data submitted supports a retest period of five years when stored below 25˚C.

The drug product is a clear colourless gel, free of particles and packaged in a resealable multiuse tube, for topical administration. Each tube contains 60 g of gel and each tube is packaged within a carton. The tube and carton is supplied with a child resistant plastic bag for storage in a home refrigerator.

Nonclinical

There were no nonclinical objections to registration of Ledaga (chlormethine hydrochloride).

- Chlormethine is an alkylating agent, and the prototypical nitrogen mustard.
- Chlormethine contains two reactive side chains that covalent bind to DNA to form cross-links, inducing cell death. Cytotoxicity by chlormethine was demonstrated *in vitro* (against various human cancer cell lines, including a leukaemic T-cell lymphoblast cell line) and *in vivo* (in mice).
- Topical application of chlormethine was shown to result in no apparent or negligible systemic exposure in studies in mice and rats. Chlormethine and its half mustard metabolite were not detected in the plasma of patients treated with Ledaga.
- Demonstration of systemic toxicity following topical dermal application of chlormethine in mice required the use of very high doses and formulations containing particular solvents that enhance skin permeability. Nitrogen mustards are well known vesicants, and local skin reactions are expected in patients treated with Ledaga. Monitoring, suspension of treatment and avoidance of application to particularly susceptible sites are described in the draft Product Information (PI) document (not shown in this AusPAR).
- Chlormethine is genotoxic. This is the key basis for its desired cytotoxic action.
- Carcinogenicity by chlormethine has been demonstrated in rodents following systemic administration and also topical dermal application. Notably, though, topical dermal application in mice was only seen to result in skin tumours (squamous cell carcinomas and papillomas), with no systemic tumours observed.
- Reproductive and developmental toxicity studies, all involving systemic administration only. It showed impairment of fertility (in males and possibly also females), fetal malformations, embryofetal lethality and fetal growth retardation with chlormethine. Pregnancy Category B3, as the sponsor proposes, is considered to be appropriated.

Clinical

The clinical dossier consisted of:

- three efficacy and safety studies, Studies 2005 NMMF-201-US, 2007 NMMF-202-US (abbreviated as Study 201 and Study 202 respectively) and the PROVe trial;
- a *post-hoc* analysis of Study 201;
- seven periodic safety update reports (PSURs); and
- supporting literatures.

Pharmacology

The Ledaga product is referred to as chlormethine hydrochloride in propylene glycol gel formulation and nitrogen mustard gel formulation in the text below.

Pharmacokinetics

The product is intended for topical administration. In the pivotal study, Study 201 and its extension, Study 202 no systemic nitrogen mustard was detected using sensitive assays.

In Study 201, blood samples were collected at pre-dose at the Baseline Visit and 1, 3, and 6 hours after the first application of study treatment. Samples were also collected at the Month 1 visit of the study, just prior to application. Plasma samples from 23 patients, 16 of whom had been treated with the propylene glycol gel formulation proposed for registration, were analysed using a high-performance liquid chromatography (HPLC) method with a lower limit of quantification (LLOQ) of 41.5 ng/mL for chlormethine. There was no evidence of systemic exposure following treatment with propylene glycol gel or the comparator, aquaphor ointment, with no measurable plasma concentrations of chlormethine in any of the samples assayed, including those taken from patients who received whole body treatment.

Pharmacodynamics

No specific pharmacodynamic investigations were included in the submission. The mechanism of action of nitrogen mustard is well established and it has had a long history of use in the management of other malignancies.

Efficacy

Based on historical literature suggesting efficacy and safety with 0.02% and 0.04% chlormethine, these concentrations were used in Studies 201 and 202.

Study 201 was the pivotal study. It evaluated the safety and efficacy of NM 0.02% gel in patients with Stage I or IIA mycosis fungoides-type CTCL. It was conducted in 13 centres in the USA, commencing in May 2006 and completed in July 2010.

The primary objective was to evaluate the efficacy of topical application of 0.02% nitrogen mustard in a propylene glycol gel (as proposed) versus 0.02% nitrogen mustard in an aquaphor ointment, in subjects with Stage I or IIA mycosis fungoides.

Secondary objectives were to evaluate tolerability and safety of topical application of both formulations in these patients.

This was a pivotal Phase II/III multicentre, randomised, third party (observer) blinded study in previously treated patients with Stage I or IIA mycosis fungoides-type CTCL comparing the proposed 0.02% nitrogen mustard compounded in propylene glycol gel, to 0.02% nitrogen mustard compounded in aquaphor ointment.

Patients were treated on this trial for 12 months unless disease progression, treatment limiting toxicity, concomitant illness, or other change in health status necessitated discontinuation of study therapy. Patients were also free to withdraw consent for any reason at any time during the trial. Patients were followed off study for an additional

12 months to assess the potential for the development of cutaneous tumours, in particular squamous cell carcinomas. During this 12-month follow up period, patients who had not achieved a complete response on either the propylene glycol or aquaphor formulation of topical 0.02% nitrogen mustard could enrol in the open label 7-month trial of the propylene glycol formulation containing 0.04% nitrogen mustard. Patients not entering that study were observed or treated in accordance with standard medical practice.

This was a non-inferiority study. The proposed propylene glycol chlormethine formulation would be designated as 'non-inferior' to the aquaphor formulation if the lower limit of the 95% confidence interval (CI) around the ratio of response rates (based on ≥ 50% improvement in the Baseline Composite Assessment of Index Lesion Severity (CAILS) score;[14] which was confirmed at the next visit at least four weeks later) of the propylene glycol formulation to the aquaphor formulation was ≥ 0.75, that is there was 95% confidence that the true response rate with the propylene glycol formulation was no more than 25% less than that of the aquaphor formulation. It was estimated that a total of 250 patients would be required. To control for multiple testing among the secondary efficacy endpoints a Type I error rate of 0.010 was applied for each endpoint.

The selected chlormethine hydrochloride 0.02% compounded in aquaphor corresponded to current standard of care in the USA and was considered to have an established efficacy and safety profile, based on published data.[15,16] The CAILS requires scoring of up to five index lesions (lesions selected for assessment of efficacy) for scaling (0 to 8), erythema (0 to 8), plaque elevation (0 to3), and surface area (0 to18). The sum of the scores for each of these categories and each of the five index lesions represents the total CAILS score.[17] CAILS was chosen as the primary efficacy endpoint because it had been previously used successfully in a study to support authorisation of bexarotene (Targretin) capsules as second line treatment for mycosis fungoides-type CTCL in both the EU and USA.

The most widely used method for total body skin scoring is the Severity Weighted Assessment Tool (SWAT).[18] This instrument involves the direct assessment of the body surface area (BSA) of each mycosis fungoides-type CTCL lesion. The SWAT score is intended to capture the extent and severity of all mycosis fungoides-type CTCL lesions, rather than just selected index lesions, thereby providing a better indication of global cutaneous disease activity. The SWAT score is derived by weighting BSA involvement for patches, plaques, and tumours, and summing the scores for each category.

The SWAT score is the sum of:

- (1 x patch %BSA) + (2 x plaque %BSA) + (3 x tumour/ulcer %BSA)

[14] The Composite Assessment of Index Lesion Severity CAILS score is obtained by adding the severity score of each of the following categories for up to 5 index lesions: erythema, scaling, plaque elevation, and surface area. Severity is graded from 0 (none) to 8 (severe) for erythema and scaling; 0 to 3 for plaque elevation; and 0 to 9 for surface area.

[15] Kim YH. Management with topical nitrogen mustard in mycosis fungoides. *Dermatol Ther*. 2003;16(4):288-98.

[16] Kim YH, et al. Topical Nitrogen Mustard in the Management of Mycosis Fungoides: Update of the Stanford Experience. *Arch Dermatol*. 2003;139(2):165–173.

[17] Olsen EA, et al. Clinical end points and response criteria in mycosis fungoides and Sézary syndrome: a consensus statement of the International Society for Cutaneous Lymphomas, the United States Cutaneous Lymphoma Consortium, and the Cutaneous Lymphoma Task Force of the European Organisation for Research and Treatment of Cancer. *J Clin Oncol*. 2011 Jun 20;29(18):2598-607.

[18] Severity Weighted Assessment Tool is one of several tools a health care provider uses to monitor active cutaneous T-cell lymphoma (CTCL). The provider inspected each individual patch, plaque, and tumor. Multipliers, also known as weighting factors, gave specific 'weight' or 'value' to each CTCL lesion type. Patches, which are flat, earned a multiplier of one. Plaques, which are raised, earned a multiplier of two. Tumors, which are larger and solid, earned a multiplier of three. Mathematically, a multiplier of three (tumor) contributed to a higher SWAT score than a multiplier of one or two. In the last step of the SWAT, the total in each of the three categories of lesions was added to obtain a final score.

The SWAT score was considered the most important secondary endpoint in Study 201.

The main inclusion criteria were:

- A diagnosis of Stage I or IIA (cutaneous only) mycosis fungoides confirmed by skin biopsy. Patients not to have used steroids for at least four weeks before the biopsy.
- Concordance between local site pathologist and pathologist at the lead site (Fox Chase Cancer Centre) using internationally agreed upon histologic and diagnostic criteria developed by the International Society for Cutaneous Lymphoma (ISCL).[19]
- Patients must have been treated previously with at least one skin directed therapy for mycosis fungoides including taking a combination treatment of PUVA, irradiation with shortwave UVB, corticosteroids but not nitrogen mustard within the last two years nor topical BiCNU (carmustine).[10]

The main exclusion criteria were:

- A prior history of treatment with topical nitrogen mustard within the last two years or topical BiCNU (carmustine).[10]
- Use of topical or systemic therapies including corticosteroids for mycosis fungoides within four weeks of entry into the study.
- Patients with Stage IIB to IV disease.
- Patients with a history of a higher T (Tumour) score than T2 or a higher N (Node)score than N1.
- Patients who had radiation therapy within 1 year of study start.

Patients were asked to apply a thin layer of product topically daily at approximately the same time each day for the duration of the study period (up to 12 months). The frequency of application could be adjusted for toxicity. Patients with Stage IA disease were generally instructed to treat all affected lesions and whole body application (excluding areas around the eyes and mucous membranes) was prescribed if the patient had either Stage IB or IIA mycosis fungoides or severity of new lesions developing after treatment initiation met criteria for progressive disease (> 25% worsening). Patients were instructed to wear disposable gloves and/or wash their hands after applying the study treatment. Topical steroids (up to 1%) were permitted on non-mycosis fungoides lesions and to areas where topical nitrogen mustard could not be applied, for example, the eyelids.

Usage of chlormethine was estimated by calculating the number of returned used tubes and assuming that the entire contents of each 25 g tube were used. Daily usage was then calculated from this total based on an individual patient's total days on study drug. Calculated mean daily use of propylene glycol gel was 2.81 g overall (1.77 g/day for Stage IA patients and 4.28 g/day for Stage IB/IIA patients). Calculated median daily use of propylene glycol gel was 1.83 g overall (1.24 g/day for Stage IA patients and 4.23 g/day for Stage IB/IIA patients). The maximum calculated daily usage of propylene glycol gel for a single subject was 10.5 g.

The primary efficacy endpoint was the CAILS score.[14] The score is obtained by adding the severity score of each of the following symptoms for up to five index lesions: erythema, scaling, plaque elevation, and surface area. Severity was graded from 0 (none) to 8 (severe) for erythema and scaling; 0 to 3 for plaque elevation; and 0 to 9 for surface area. A response is defined as ≥ 50% reduction in the Baseline CAILS score;[14] that is confirmed at the next visit at least four weeks later.

[19] Pimpinelli N, et al. Defining early mycosis fungoides. *J Am Acad Dermatol*. 2005 Dec;53(6):1053-63.

Secondary efficacy endpoints included > 50% improvement in SWAT score;[18] which is derived by measuring each involved area as a percentage of total body surface area and multiplying it by a severity-weighting factor (1 = patch, 2 = plaque, 3 = tumour). An additional secondary efficacy endpoint was change in percent of total body surface area involved, as a component of the SWAT. A final secondary efficacy endpoint was time to first confirmed response, duration of response and the time to disease progression based on the CAILS score.[14]

The efficacy evaluable (EE) population was the primary population for assessment of non-inferiority of response for CAILS, SWAT and % BSA. That population met the following criteria:

- did not have major exclusion or inclusion criteria exceptions;
- no major or prolonged deviations related to study drug administration;
- at least 6 months continuous treatment;
- no concomitant medication or treatment for mycosis fungoides during the randomised treatment period; and
- had two or more post baseline CAILS assessments.

The CAILS, SWAT and %BSA analyses were repeated for the intent-to-treat population.

Patients enrolled at one study site (NYU) were not randomised to treatment in accordance with the protocol. Patients were assigned to treatment based on mycosis fungoides Stage: Patients with Stage IA disease were assigned to Drug 'A' (propylene glycol formulation) and patients with Stage IB disease were assigned to Drug 'B' (aquaphor formulation). Rather than exclude data from these patients, efficacy data were analysed for three 'Intent to Treat' (ITT) data sets: all enrolled (n = 260); all excluding NYU (n = 242) and all as they should have been randomised, that is ITT with NYU as planned). 185 patients were included in the EE population. Demographic and other baseline characteristics (ITT population) are tabulated in Table 3.

Table 3: Study 201 Demographic characteristics

Characteristic	PG (N=130) n (%)	AP (N=130) n (%)
Gender		
Male	77 (59.2)	77 (59.2)
Female	53 (40.8)	53 (40.8)
Race		
Caucasian	97 (74.6)	96 (73.8)
Afro-American	16 (12.3)	19 (14.6)
Other	17 (13.1)	15 (11.5)
Age		
<18 years	0 (0.0)	1 (0.8)
18-64 years	93 (71.5)	86 (66.2)
65-74 years	29 (22.3)	33 (25.4)
≥75 years	8 (6.2)	10 (7.7)
Time From Initial Diagnosis		
<6 months	47 (36.2)	45 (34.6)
6 months-1 year	18 (13.8)	22 (16.9)
1 year- 2 years	14 (10.8)	13 (10.0)
≥ 2 years	51 (39.2)	50 (38.5)
Prior MF Therapies*		
Corticosteroids	112 (86.1)	113 (86.9)
Phototherapy	50 (38.5)	53 (40.8)
Targretin®	23 (17.7)	23 (17.7)
Topical NM (>2yrs from study)	16 (12.3)	13 (10.0)
Interferons	3 (2.3)	5 (3.8)
Methotrexate	3 (2.3)	3 (2.3)
Radiation	3 (2.3)	2 (1.5)
Other*	14 (10.8)	34 (26.2)
MF Stage		
Stratum 1 - Stage IA	76 (58.5)	65 (50.0)
Stratum 2	54 (41.5)	65 (50.0)
Stage IB	52 (40.0)	63 (48.5)
Stage IIA	2 (1.5)	2 (1.5)
Baseline CAILS Score		
Mean (±SD)	37.3 (17.54)	37.4 (17.56)
Median (range)	34 (2,79)	34 (6,87)
Baseline SWAT Score		
Mean (± SD)	14.4 (15.87)	19.2 (20.58)
Median(range)	9.0 (1,104)	11.0 (1,104)

AP = aquaphor; CAILS = Composite Assessment of Index Lesion Severity; PG = propylene glycol; SWAT = Severity Weighted Assessment Tool.

A total of 62% of the patients treated with the propylene glycol formulation and 66% of the patients treated with the aquaphor formulation completed the 12-month study. The most frequent reasons for discontinuation were: treatment limiting toxicity (16.2% propylene glycol and 12.3% aquaphor); other adverse events (AE) (3.8% propylene glycol and 4.6% aquaphor). Lack of efficacy accounted for 3.1% of withdrawals in both the propylene glycol and aquaphor treatment groups.

Non-inferiority of propylene glycol to aquaphor formulation was met in each of the ITT analyses and for the EE analysis (patients who completed at least 6 months treatment). CAILS and SWAT response rates were in each analysis population higher for the propylene glycol treated population compared with the aquaphor population.

Table 4: Study 201 Treatment response (intent to treat and efficacy evaluable population)

	PG Response Rates	AP Response Rates	Ratio Response	95% Confidence Interval
Primary Endpoint, %				
CAILS				
ITT INCLUDING NYU (as Treated)	58.5	47.7	1.226	0.974 – 1.552
ITT EXCLUDING NYU	59.7	48.0	1.244	0.983 – 1.582
NYU As Planned	57.8	48.5	1.192	0.948 – 1.506
EE	76.7	58.9	1.301	1.065 – 1.609
Secondary Endpoints, %				
SWAT				
ITT INCLUDING NYU	46.9	46.2	1.017	0.783 – 1.321
ITT EXCLUDING NYU	49.6	46.3	1.070	0.822 – 1.394
EE	63.3	55.8	1.135	0.893 – 1.448

AP = aquapor; CAILS = Composite Assessment of Index Lesion Severity; EE = efficacy evaluable; ITT = intent to treat; PG = propylene glycol; SWAT = Severity Weighted Assessment Tool.

Similar results were also apparent for other secondary efficacy endpoints. Of CAILS responders, 65 out of 76 (85.6%) in the propylene glycol arm and 51 out of 62 (82.2%) in the aquaphor arm maintained their response through to the end of the trial. Complete response, defined as a CAILS score;[14] of 0 confirmed at the next visit > 28 days was achieved by 14% of patients given propylene glycol gel and 11% given aquaphor in the ITT population analyses with both inclusion and exclusion of NYU patients.

Study 202 was an open label follow on study for patients who completed 12 months of treatment in Study 201 without a complete response. All patients received an investigational product containing 0.04% nitrogen mustard for up to seven months. A total of 100 patients were enrolled with 98 receiving study medication. 26 patients (26.5%) achieved a confirmed response defined as ≥ 50% improvement in CAILS score;[14] from the Baseline of Study 202 based on all index lesions followed and 14 (14.3%) additional patients had their first response (≥ 50% improvement in CAILS score) at their final visit for an overall response rate of 40.8%.

Study 501 (PROVetrial, a PROspective, observational, study assessing outcomes, adverse events (AEs), treatment patterns and quality of life (QoL) in patients with mycosis fungoides treated with the chlormethine gel and other therapies), conducted between March 2015 and October 2018, was designed to examine the real-world use of chlormethine gel in routine clinical practice in the US..

Patients did not receive experimental intervention or treatment as a consequence of this participation and standard medical care was provided in a real-world setting. The study was prematurely discontinued due to sponsor's decision, after change in ownership of worldwide rights to the product.[20]

A total of 300 patients from 46 treatment centres were enrolled with 298 receiving treatment with the chlormethine gel formulation prior to enrolment. Patients had newly initiated Valchlor or were continuing treatment with Valchlor, as well as multiple other mycosis fungoides-CTCL therapies. Patients were to be followed by their physician according to routine clinical practice. With the exception of protocol required patient-completed questionnaires, there were no specific or mandated clinical assessments and patients were not to receive experimental intervention or treatment as a consequence of their participation in this study. The study protocol did not mandate any specific schedule of visits. Patients were to undergo clinical assessments and receive standard medical care as determined by the patient's physician in a real world setting. The primary efficacy

[20] Sponsor clarification: Continuation in the study was not contingent on continuation of Valchlor (Tradename of the propylene glycol formulation in the USA).

endpoint was the proportion of Stage IA to IB patients who were responders to treatment at the 12 month timepoint using a ≥ 50% reduction from Baseline in BSA as the definition of a responder in the group of patients who used mechlorethamine gel plus corticosteroids and possibly another treatment. Responder rates were approximately 40 to 50% in all groups for Stages IA and IB, all staging and all patients with or without staging.

Safety

Study 201 is the only randomised, controlled study available using topical chlormethine. Controlled studies identified in the literature search were not randomised. Many of the studies were uncontrolled or retrospective.

The full safety analysis set comprised 255 patients who received at least one application of study treatment during the study (Safety analysis set), with 128 receiving propylene glycol. A total of 165 patients (81 on propylene glycol and 84 on aquaphor) received study treatment for > 48 weeks. Median exposure was 51.7 weeks in the propylene glycol arm and 52 weeks in the aquaphor arm.

Most patients tolerated daily application of topical chlormethine however more reductions in frequency or temporary suspension of dosing occurred in the propylene glycol arm, with 29 (23%) versus 15 (12%) in the aquaphor arm having at least one reduction in frequency dosing. Furthermore, 44 patients (34%) in the propylene glycol arm versus 25 patients (20%) in the aquaphor arm had study medication temporarily suspended at least once during the trial. Study withdrawal due to AEs occurred for 21.9% of patients given propylene glycol and 18.1% given aquaphor.

One patient in the propylene glycol arm died from metastatic colorectal cancer after less than two months on treatment. Twenty-five patients (14 with propylene glycol and 11 with aquaphor) experienced an serious adverse event (SAE). These were broadly comparable in both treatment groups and none of the SAEs were considered to be related to the study drug.

143 (56.1%) of patients in the study reported at least one AE with Skin and Subcutaneous Tissue Disorders the most frequently reported System Organ Class (SOC) with 78 (60.6%) given propylene glycol and 59 (46.5%) given aquaphor reporting an AE in this SOC. Most of the difference was due to the higher incidences of skin irritation (24.2% propylene glycol versus 11.8% aquaphor) and pruritus (15.6% propylene glycol versus 9.4% aquaphor). Grade 3 and 4 local dermal irritation was also more frequent in the patients given propylene glycol with 28.1% for propylene glycol vs. 17.3% for aquaphor.

The most frequent adverse events in patients given propylene glycol were: skin irritation 25%, pruritus 19.5%, erythema 17.2% and contact dermatitis 14.8%. Skin hyperpigmentation pigmentation was reported for 7 (5.5%) of patients.

Secondary skin cancers which were non-melanoma were diagnosed in eight patients (2 in propylene glycol and 6 with aquaphor). Two further patients (1 propylene glycol, 1 aquaphor) developed squamous cell carcinoma during the 12-month follow up period. The majority of these skin cancers occurred in untreated areas.

Nine patients using propylene glycol gel applied or were prescribed topical corticosteroids for use not directly involving index mycosis fungoides lesions in Study 201. This study did not allow for assessment of safety or efficacy of concomitant use of topical corticosteroid and Ledaga applied to mycosis fungoides lesions.

An addendum to Study 201provided longer term safety data with respect to skin cancer. A total of 11 (11 out of 255, 4.3%) patients developed a non-melanoma skin cancer during treatment or within one year of ending treatment in Study 201. Eight of these patients developed non-melanoma skin cancer during treatment; three additional patients developed non-melanoma skin cancer during the one year follow up period. Three of these

patients were treated only with propylene glycol gel 0.02%, seven were treated only with aquaphor 0.02%, and one patient was treated with aquaphor 0.02% followed by seven months treatment with a propylene glycol gel 0.04% in Study 202.

Five of these patients (two treated with propylene glycol gel 0.02% and three treated with aquaphor 0.02%) had a squamous cell carcinoma. None of these non-melanoma skin cancers were attributed specifically to the 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.

Haematology and serum chemistry parameters were assessed at Baseline and Months 4, 8 and 12 (or termination visit). There was no consistent pattern seen with any of the values measured during treatment exposure.

In Study 202, the seven months extension study to Study 201, a total of 98 patients who had not experienced a complete response received a 0.4% chlormethine formulation. Patients were treated for an average of 28.8 weeks (range 2 to 46 weeks). Most patients received > 24 weeks of treatment. There were no deaths on study. Four patients withdrew due to AEs, all in the Skin and Subcutaneous Tissues SOC. The relative frequencies of skin irritation, erythema and pruritus in Study 201 and 202. There was a small increase in skin irritation with the higher concentration of chlormethine.

Post-market study and literature reports of other formulations of topical chlormethine did not identify other safety concerns.

Clinical evaluator's recommendation

There were no clinical objections to registration.

Risk management plan

Recordati Rare Diseases Pty Ltd has submitted EU-risk management plan (RMP) version 2.0 (8 March 2017; data lock point (DLP): 22 February 2016) and Australian specific annex (ASA)version 2.0 (19 April 2021) in support of this application.

The summary of safety concerns and their associated risk monitoring and mitigation strategies are summarised in Table 5.[21]

[21] *Routine risk minimisation* activities may be limited to ensuring that suitable warnings are included in the product information or by careful use of labelling and packaging.
Routine pharmacovigilance practices involve the following activities:

- All suspected adverse reactions that are reported to the personnel of the company are collected and collated in an accessible manner;
- Reporting to regulatory authorities;
- Continuous monitoring of the safety profiles of approved products including signal detection and updating of labelling;
- Submission of PSURs;
- Meeting other local regulatory agency requirements.

Table 5: Summary of safety concerns and their associated risk monitoring and mitigation strategies

Summary of safety concerns		Pharmacovigilance		Risk Minimisation	
		Routine	Additional	Routine	Additional
Important identified risks	Hypersensitivity	ü	–	ü	–
	Local skin reactions	ü	–	ü	–
	Toxicity to mucous membranes/ eye	ü	–	ü*	–
Important potential risks	Skin cancers	ü	–	ü	–
	Secondary exposure to someone other than the patient	ü	–	ü*	–
	Use during pregnancy and lactation	ü	–	ü	–
Missing information	Use in paediatric patients	ü	–	ü	–
	Concomitant use with topical corticosteroids	ü	–	ü	–

*Patient Alert Card

The proposed summary of safety concerns is considered acceptable from an RMP perspective.

The sponsor has proposed routine pharmacovigilance activities only for all safety concerns. This is considered acceptable.

The sponsor has proposed routine risk minimisation activities for all safety concerns. A transparent sealable plastic bag is to be supplied separately to Ledaga at the time of dispensing. A patient alert card is to be included in the packaging with the package insert as a routine risk minimisation activity for an important identified risk (that is, toxicity to mucous membranes/eye) and an important potential risk (that is, secondary exposure to someone other than the patient). This is acceptable.

Wording for conditions of registration

Any changes to which the sponsor has agreed should be included in a revised RMP and ASA. However, irrespective of whether or not they are included in the currently available version of the RMP document, the agreed changes become part of the risk management system.

The suggested wording is:

The Ledaga EU-risk management plan (version 2.0, dated 8 March 2017, data lock point 22 February 2016), with Australian specific annex (version 2.0, dated 19 April 2021), included with submission 2020-03014-1-6, and any subsequent revisions, as agreed with the TGA will be implemented in Australia.

An obligatory component of risk management plans is routine pharmacovigilance. Routine pharmacovigilance includes the submission of periodic safety update reports (PSURs).

Reports are to be provided in line with the current published list of EU reference dates and frequency of submission of PSURs until the period covered by such reports is not less than three years from the date of this approval letter.

The reports are to at least meet the requirements for PSURs as described in the European Medicines Agency's Guideline on Good Pharmacovigilance Practices (GVP) Module VII- periodic safety update report (Rev 1), Part VII.B Structures and processes. Note that submission of a PSUR does not constitute an application to vary the registration.

As Ledaga is a new chemical entity it should be included in the Black Triangle Scheme as a condition of registration. The following wording is recommended for the condition of registration:

Ledaga (chlormethine) is to be included in the Black Triangle Scheme. The Product Information (PI) and consumer medicines information (CMI) for Ledaga must include the black triangle symbol and mandatory accompanying text for five years, which starts from the date that the sponsor notifies the TGA of supply of the product.

Risk-benefit analysis

Delegate's considerations

There is no registered topical treatment for mycosis fungoides. The comparator for the pivotal efficacy study was selected based on its long history of use in mycosis fungoides in the USA. The comparator, 0.02% nitrogen mustard compounded in an Aquaphor ointment base at a central pharmacy, is not commercially available however it had been used to treat early stage mycosis fungoides since the 1980s. Both the comparator and the non-inferiority margin of the propylene glycol formulation with the use of the aquaphor formulation as the comparator were agreed with the Food and Drug Administration (USA). Given the absence of any registered topical treatment the comparator is acceptable.

The primary efficacy endpoint, CAILS response, had previously been used in a study of bexarotene, an oral treatment for mycosis fungoides. Bexarotene is not registered in Australia. CAILS response is based on the response of a maximum of five lesions and as so has the potential to miss substantial changes in non-index lesions. It was therefore important to also include the SWAT assessment which allows for a global assessment of response in the description of efficacy from the pivotal study. The non-inferiority margin of -25% with 95% confidence was applied to both the CAILS and SWAT analyses and is an acceptable margin.

The study report for Study 201, the pivotal study, indicated that the evaluable population was the primary population for assessment of efficacy. While this may be useful for the demonstration of non-inferiority, given the high frequency of patients not meeting the eligibility criteria for inclusion in the efficacy-evaluable population it is important that emphasis be given to the ITT population because this population is more likely to closely reflect efficacy in the wider mycosis fungoides population. The NYU patient group should be excluded from the ITT analysis given they received mis-allocated treatment.

The sponsor proposed highlighting the evaluable for efficacy CAILS and SWAT results in the clinical trial description in the PI, subdividing each of these to present complete and partial response rates. Given that the CAILS assessment is based on criteria from a maximum of five index lesions a patient would be considered a CAILS complete response (CR) with complete resolution of all five index lesions, but may still have remaining disease (non-index lesions), or have developed new lesions. Of the 31 patients who

achieved a CAILS CR, only 11 (35%) had a global CR (SWAT response) as well. The remaining 18 patients had partial response on SWAT criteria, and two patients had stable disease on SWAT criteria. The Delegate considers it is inappropriate to include CR in the clinical trial description because it is potentially misleading in that it does not indicate an overall complete response to treatment. The Delegate considers that the ITT (excluding NYU patients who were mis-allocated to treatment) should be the primary population displayed in the clinical trials section because that population most closely reflects the expected efficacy in the wider patient population.

The sponsor proposes including all grades of mycosis fungoides in the indication though the pivotal study was restricted to patients with Stage I or IIA (cutaneous only) mycosis fungoides. The Delegate notes that the indication in the USA is restricted to patients with the Stage I and IIA mycosis fungoides while the indication in the EU includes all stages of mycosis fungoides. Patients enrolled in Study 201 had only early stage disease however skin manifestations occur in all stages of mycosis fungoides and topical treatment can be given in combination with systemic treatments, therefore it is appropriate that the indication not be restricted to patients with early stage disease.

Given that no systemic absorption of chlormethine was detected it could be anticipated that treatment related AEs would be concentrated in the Skin and Subcutaneous Tissue Disorders SOC as was demonstrated. Study 201 showed that the propylene glycol formulation proposed for registration showed somewhat more skin irritation and pruritus and a higher proportion of patients requiring treatment disruptions or study withdrawal due to AEs but the differences were relatively minor. Individuals would also be concerned with hyperpigmentation which occurred in 5.5% of patients.

There is potential for skin malignancies with long term use however the data presented was not sufficient to accurately determine the extent of this risk. Patients using Ledaga should be advised to notify their physician of any new skin lesions and to undergo periodic assessment for signs and symptoms of skin cancer, including in areas not directly treated with chlormethine.

Proposed action

There is no objection to approval of Ledaga topical gel containing 160 µg/g chlormethine for the topical treatment of mycosis fungoides type CTCL in adult patients subject to successful negotiation of the conditions of registration.

Advisory Committee considerations[22]

The Delegate did not refer this application to the Advisory Committee on Medicines (ACM) for advice.

[22] The ACM provides independent medical and scientific advice to the Minister for Health and the Therapeutic Goods Administration (TGA) on issues relating to the safety, quality and efficacy of medicines supplied in Australia including issues relating to pre-market and post-market functions for medicines.
The Committee is established under Regulation 35 of the Therapeutic Goods Regulations 1990. Members are appointed by the Minister. The ACM was established in January 2017 replacing Advisory Committee on Prescription Medicines (ACPM) which was formed in January 2010. ACM encompass pre and post-market advice for medicines, following the consolidation of the previous functions of the Advisory Committee on Prescription Medicines (ACPM), the Advisory Committee on the Safety of Medicines (ACSOM) and the Advisory Committee on Non-Prescription Medicines (ACNM). Membership comprises of professionals with specific scientific, medical or clinical expertise, as well as appropriate consumer health issues relating to medicines.

Outcome

Based on a review of quality, safety and efficacy, the TGA approved the registration of Ledaga (chlormethine hydrochloride) 160 µg/g, gel, tube, indicated for:

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

Specific conditions of registration applying to these goods

- Ledaga (chlormethine) is to be included in the Black Triangle Scheme. The PI and CMI for Ledaga must include the black triangle symbol and mandatory accompanying text for five years, which starts from the date that the sponsor notifies the TGA of supply of the product.
- The Ledaga EU-RMP (version 2.0, dated 8 March 2017, DLP: 22 February 2016), with ASA (version 2.0, dated 19 April 2021), included with submission 2020-03014-1-6, and any subsequent revisions, as agreed with the TGA will be implemented in Australia.

  An obligatory component of risk management plans is routine pharmacovigilance. Routine pharmacovigilance includes the submission of periodic safety update reports (PSURs).

  Reports are to be provided in line with the current published list of EU reference dates and frequency of submission of PSURs until the period covered by such reports is not less than three years from the date of this approval letter. The reports are to at least meet the requirements for PSURs as described in the European Medicines Agency's Guideline on Good Pharmacovigilance Practices (GVP) Module VII-periodic safety update report (Rev 1), Part VII.B Structures and processes. Note that submission of a PSUR does not constitute an application to vary the registration.

Attachment 1. Product Information

The PI for Ledaga approved with the submission which is described in this AusPAR is at Attachment 1. For the most recent PI, please refer to the TGA website at <https://www.tga.gov.au/product-information-pi>.

Therapeutic Goods Administration

PO Box 100 Woden ACT 2606 Australia
Email: info@tga.gov.au Phone: 1800 020 653 Fax: 02 6232 8605
https://www.tga.gov.au