

## 5.05 CHLORMETHINE HYDROCHLORIDE

**0.016% (160 microgram/g) gel,**

**Ledaga<sup>®</sup>,**

**Juniper Biologics Pty Ltd.**

### 1 Purpose of submission

- 1.1 The Category 1 submission requested a Section 85, Authority Required listing for chlormethine hydrochloride gel (hereafter chlormethine gel) for the treatment of mycosis fungoides-type cutaneous T-cell lymphoma (MF-CTCL) in adult patients who have less than 25% of their body surface area (BSA) involved, have failed, are intolerant of or have a contraindication to treatment with topical corticosteroids.
- 1.2 The basis for the submission was a cost-utility analysis (CUA) against phototherapy. The key components of the submission are summarised in Table 1.

**Table 1: Key components of the clinical issue addressed by the submission**

Component	Description
Population	Mycosis fungoides-type cutaneous T-cell lymphoma (MF-type CTCL) in adult patients who have less than 25% of their body surface area involved and have failed, are intolerant of or have a contraindication to treatment with topical corticosteroids.
Intervention	Chlormethine (as hydrochloride) 160 microgram/g topical gel tube, 60 g
Comparator	Skin directed therapies such as phototherapy (5% psoralen plus ultraviolet A radiation [PUVA], 95% ultraviolet B [UVB])
Outcomes	<p>Derived primary outcome: Restricted mean duration of response (complete response)</p> <p>Other reported outcomes are those from study 201 and include:</p> <p><u>Primary:</u></p> <p>The primary efficacy endpoint was a <math>\geq 50\%</math> improvement (i.e., CR or PR) in a patient's CAILS score versus the baseline measurement</p> <p><u>Secondary:</u></p> <ul style="list-style-type: none"> <li>• CAILS response rate</li> <li>• mSWAT response rate</li> <li>• The time to a confirmed CAILS response</li> <li>• Duration of response</li> <li>• Adverse effects of treatment</li> </ul> <p>Health-related quality of life (PROVe Study)</p>
Clinical claim	Chlormethine provides non-inferior levels of efficacy in terms of restricted mean duration of complete response and improved effectiveness in terms of health related quality of life and has similar safety compared to phototherapy

Source: Table 1-1 p15 of the submission

CAILS=Composite Assessment of Index Lesion Severity; CR=complete response; MF-CTCL= mycosis fungoides-type cutaneous T-cell lymphoma; mSWAT= Modified Severity-Weighted Assessment Tool; PR=partial response; PUVA=psoralen ultraviolet A; UVA=ultraviolet A; UVB=ultraviolet B; QALY=quality adjusted life years.

## 2 Background

### Registration status

- 2.1 Chlormethine gel is registered for use in Australia, having been listed on the ARTG on 22 June 2021 for the topical treatment of MF-type CTCL in adult patients. The TGA approved indication is broader than the requested PBS restriction in that it is not restricted to those with who have failed, are intolerant of or have a contraindication to topical corticosteroids.
- 2.2 Chlormethine gel has not been previously considered by the PBAC for any indication.

## 3 Requested listing

- 3.1 Suggestions and additions proposed by the Secretariat are added in italics and suggested deletions are crossed out with strikethrough.

MEDICINAL PRODUCT medicinal product pack	Dispensed Price for Max. Qty	PBS item code	Max. qty packs	Max. qty units	No. of Rpts	Available brands
chlormethine 0.016% (160 microgram/g) gel, 60 g	\$ published price \$ effective price	NEW	1	1	5	Ledaga Juniper Biologics
<b>Restriction Summary [new] / Treatment of Concept: [new]</b>						
<b>Concept ID</b> (for internal Dept. use)	<b>Category / Program:</b> General Schedule (Code GE)					
	<b>Prescriber type:</b> <input checked="" type="checkbox"/> Medical Practitioners					
	<b>Restriction type:</b> <input checked="" type="checkbox"/> Authority Required – immediate/real time assessment by Services Australia (telephone/online PBS Authorities system)					
	<b>Condition:</b> Mycosis fungoides cutaneous T-cell Lymphoma					
	<b>Indication:</b> Mycosis fungoides cutaneous T-cell Lymphoma					
	<b>Treatment Phase:</b> <del>Stages IA, IIA, IB</del> <i>Initial treatment</i>					
	<b>Clinical criteria:</b>					
	<i>The condition must be any of: (i) Stage IA, (ii) IIA, (iii) IB mycosis fungoides cutaneous T-cell Lymphoma</i>					
	<b>AND</b>					
	<b>Clinical criteria:</b>					
	<i>The condition must have been confirmed through a diagnostic lesion biopsy from an Approved Pathology Authority</i>					
	<b>AND</b>					
	<b>Clinical criteria:</b>					
	Patients must have either of which: (i) failed treatment with topical corticosteroids, (ii) have intolerance/contraindication to <i>topical corticosteroids</i> <del>steroids</del> .					
	AND					
	<del>Patients with no more than 10% of their body surface area affected</del> <i>The condition must cover either of which: (i) no more than 10% of the patient's body surface, (ii) no more than 25% of the patient's body surface.</i>					
	<b>Treatment criteria:</b>					
	<i>Patient must be treated by a dermatologist of haematologist</i>					
	<b>Population criteria:</b>					

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	<del>Patients <math>\geq</math> 18 years Patient must be at least 18 years of age</del>
	<del><b>Prescribing Instructions:</b> Treatment can only be initiated by a dermatologist or haematologist.</del>
	<b>Prescribing Instructions:</b>
	<del>The medical practitioner should request 1 pack for patients with no more than 10% of the patients body surface and 2 packs for patients with no more than 25% of the patients to provide 4 weeks of treatment.</del>
	<b>Prescribing Instructions:</b>
	<del>Confirmation of eligibility for treatment with diagnostic reports must be documented in the patient's medical records.</del>
	<b>Administrative Advice:</b> Applications for authorisation under this restriction may be made in real time using the Online PBS Authorities system (see <a href="http://www.servicesaustralia.gov.au/HPOS">www.servicesaustralia.gov.au/HPOS</a> ) or by telephone by contacting Services Australia on 1800 888 333.
	<b>Category / Program:</b> General Schedule (Code GE)
	<b>Prescriber type:</b> <input checked="" type="checkbox"/> Medical Practitioners
	<b>Restriction type:</b> <input checked="" type="checkbox"/> Authority Required (STREAMLINED)
	<b>Condition:</b> Mycosis fungoides cutaneous T-cell Lymphoma
	<b>Indication:</b> Mycosis fungoides cutaneous T-cell Lymphoma
	<b>Treatment Phase:</b> Stages IA, IIA, IB <i>Continuing treatment</i>
	<b>Clinical criteria:</b>
	Patient must have previously received PBS-subsidised treatment with this drug for this condition
	AND
	<b>Clinical criteria:</b>
	Patient must not have developed disease progression while receiving PBS-subsidised treatment with this drug for this condition
	AND
	<del>Patients with no more than 10% of their body surface area affected</del>
	<b>Population criteria:</b>
	<del>Patients <math>\geq</math> 18 years Patient must be at least 18 years of age</del>
	<b>Prescribing Instructions:</b>
	<del>The medical practitioner should request 1 pack for patients with no more than 10% of the patients body surface and 2 packs for patients with no more than 25% of the patients to provide 4 weeks of treatment.</del>
	<b>Administrative Advice:</b> Applications for authorisation under this restriction may be made in real time using the Online PBS Authorities system (see <a href="http://www.servicesaustralia.gov.au/HPOS">www.servicesaustralia.gov.au/HPOS</a> ) or by telephone by contacting Services Australia on 1800 888 333.

MEDICINAL PRODUCT medicinal product pack	Dispensed Price for Max. Qty	Max. qty packs	Max. qty units	No. of Rpts	Available brands
chlormethine 0.016% (160 microgram/g) gel, 60 g	\$ <del> </del> published price \$ <del> </del> effective price	2	2	5	Ledaga Juniper Biologics
<b>Initial treatment criteria</b>					
<b>Category / Program:</b> General Schedule (Code GE)					
<b>Prescriber type:</b> <input checked="" type="checkbox"/> Medical Practitioners					
<b>Restriction type:</b> <input checked="" type="checkbox"/> Authority Required (telephone/online PBS Authorities system)					
<b>Condition:</b> Mycosis Fungoides Cutaneous T-cell Lymphoma					
<b>Indication:</b> Mycosis Fungoides Cutaneous T-cell Lymphoma					
<b>Treatment Phase:</b> Stages IA, IIA, IB					
<b>Clinical criteria:</b>					

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<del>Patients must have failed treatment with topical corticosteroids or are intolerant to these or have a contraindication to steroids</del>
<del>AND</del>
<del>Patients with no more than 25% of their body surface area affected</del>
<del>Population criteria: Patients ≥ 18 years</del>
<del>Prescribing Instructions: Treatment can only be initiated by a dermatologist or haematologist.</del>
<del>Continuing treatment criteria</del>
<del>Category / Program: General Schedule (Code GE)</del>
<del>Prescriber type: <input checked="" type="checkbox"/> Medical Practitioners</del>
<del>Restriction type: <input checked="" type="checkbox"/> Authority Required (STREAMLINED)</del>
<del>Condition: Mycosis Fungoides-Cutaneous T-cell Lymphoma</del>
<del>Indication: Mycosis Fungoides-Cutaneous T-cell Lymphoma</del>
<del>Treatment Phase: Stages IA, IIA, IB</del>
<del>Clinical criteria:</del>
<del>Patient must have previously received PBS-subsidised treatment with this drug for this condition</del>
<del>AND</del>
<del>Patient must not have developed disease progression while receiving PBS-subsidised treatment with this drug for this condition</del>
<del>AND</del>
<del>Patients with no more than 25% of their body surface area affected</del>
<del>Population criteria: Patients ≥ 18 years</del>

- 3.2 The pre-PBAC response offered a [REDACTED] % price reduction reducing the proposed ex-manufacturer price (EMP) from \$ [REDACTED] per tube to \$ [REDACTED] per tube.
- 3.3 Each chlormethine gel tube contains 60 g of gel. The submission specified separate restrictions for patients with disease that affected no more than 10% or no more than 25% BSA, to facilitate the greater quantity required to treat larger BSA involvement. This may be more efficiently managed through an amendment of the maximum quantity (and associated DPMQ) for the listing rather than proposing separate listings based on BSA. The pre-PBAC response stated that the sponsor was amenable to the restriction wording proposed by the Secretariat (see paragraph 3.1).
- 3.4 The maximum quantities of chlormethine gel are based on BSA involvement and are intended to provide enough repeats for a 6-month treatment course. Based on the average daily use of chlormethine gel reported in the key trial (Study 201), Stage IA patients required 1.77 g/day and Stage IB/IIA required 4.28 g/day. As such, most patients with Stage IB/IIA disease would require over 2 tubes per month, which exceeds the proposed maximum quantity for patients with 10% to 25% BSA involvement.
- 3.5 The proposed criteria restrict use to patients with ≤25% BSA affected. Study 201 included 15% of patients with BSA affected >25% (with the maximum being 77% affected in one patient). The results were not reported by BSA affected. It is unclear if restricting access to patients ≤25% BSA affected would deny access to PBS subsidised therapy to patients who might otherwise benefit. A recent Australian clinical practice statement noted that, “[chlormethine gel] is generally only useful for patients with

small BSA involvement because of the potential for systemic absorption.”<sup>1</sup> The ESC noted the Pre-Sub-Committee Response (PSCR) provided a revised economic model that excluded patients with a BSA >25%. The ESC advised that use in patients with >10% and <25% affected BSA was likely the most appropriate subgroup to benefit from treatment. However, the ESC considered the overarching concerns raised regarding the reliability of the economic model also applied to the revised version provided with the PSCR (see paragraph 6.33).

- 3.6 The ESC noted that there is no restriction on use with other therapies (e.g. steroids or phototherapy) included in the proposed listing. The ESC noted that during Study 201 the use of other therapies to treat MF-CTCL were prohibited.

*For more detail on PBAC’s view, see section 7 PBAC outcome.*

## 4 Population and disease

- 4.1 Primary cutaneous lymphomas are a heterogeneous group of T-cell and B-cell lymphomas. CTCLs account for approximately 80% of all cutaneous lymphomas. MF-CTCL is the most common form of CTCL; it primarily develops in the skin (as patches/plaques), with limited (if any) lymph node involvement and no visceral involvement. These patches and plaques can be painful and itchy and may progress to node-positive and visceral disease over time. There are three clinically significant variants of MF-CTCL: folliculotropic, pagetoid reticulosis and granulomatous slack skin. These variants have distinct clinicopathological features and prognoses, and the submission considered them separate to MF-CTCL. This is reasonable, however the proposed PBS restriction does not differentiate between these MF-CTCL variants.
- 4.2 MF-CTCL has been designated an orphan disease (rare disease; affects less than five in 10,000 persons) in Australia. The submission stated the estimated incidence in the population was between 0.12 and 0.69 per 100,000 adult population. The incidence of MF-CTCL is higher in males than females and increases with age, peaking in patients aged 50-70 years.
- 4.3 Monitoring of MF-CTCL involves the assessment of skin symptoms. The submission referred to two measures for assessment of MF-CTCL severity:
- The Composite Assessment of Index Lesion Severity (CAILS) index which is based on assessment of 5 index lesions, which are monitored for four clinical features of response (erythema, scaling, plaque elevation and surface area).
  - The modified Severity Weighted Assessment Tool (mSWAT) which is the most commonly used assessment tool; it scores the patient’s entire body for patches,

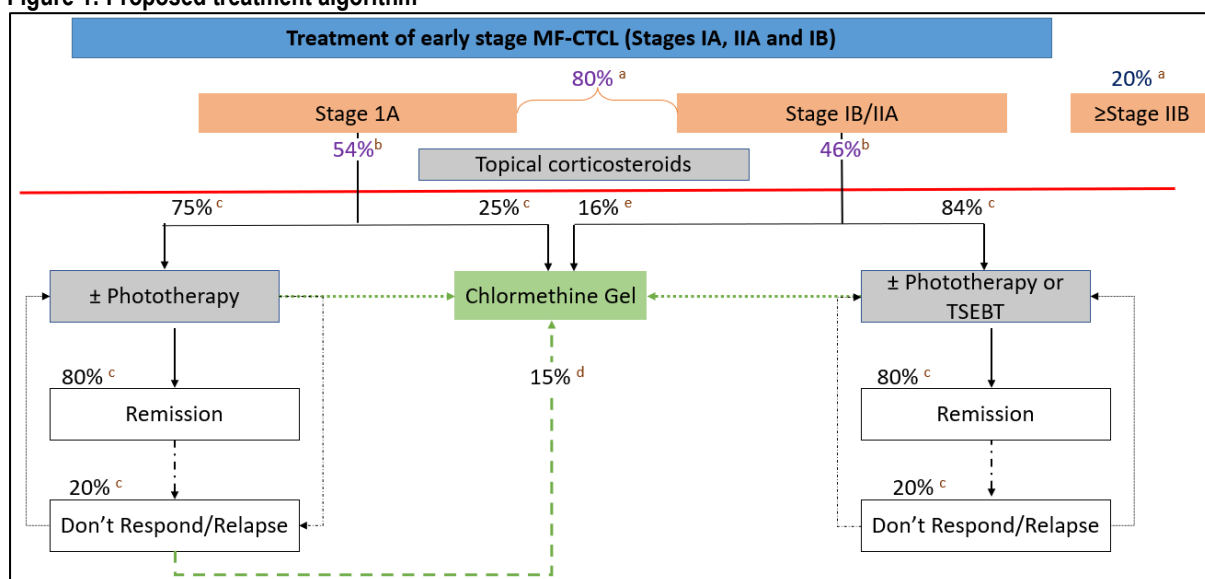
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<sup>1</sup> Bhabha, F.K., et al (2021), Mycosis fungoides and Sézary syndrome: Australian clinical practice statement. *Australas J Dermatol*, 62, p. e12.

plaques and tumours, assigning a numerical value to each of these three aspects (1 for patch, 2 for plaques and 3 for tumours).

- 4.4 The CAILS index is most useful in determining effectiveness of treatments which target some but not all lesions, or where it is desirable to monitor the effect of treatment to only one type of lesion.<sup>2</sup> As such, it is possible for a patient to be classified as a ‘complete responder’ in the CAILS score, but still have clinically apparent lesions (i.e. other than the 5 index lesions). Patients classified as a complete responder using the mSWAT must have no clinically apparent lesions of any type (patch/plaque/tumour). The PBAC have previously reviewed evidence utilising the mSWAT (brentuximab vedotin Public Summary Documents (PSD), July and November 2018 PBAC meetings).
- 4.5 BSA coverage of lesions is also used as an outcome in MF-CTCL trials and for disease monitoring, in addition to its importance in MF-CTCL diagnosis and staging and as a component of the mSWAT scoring system. The submission requested listing for MF-CTCL in adult patients who have less than 10% or 25% of their BSA involved.
- 4.6 Chlormethine gel is proposed as an alternative to phototherapy for use in patients with early-stage MF-CTCL who have failed, are intolerant of or contraindicated to topical corticosteroids. The clinical management algorithm for current practice and for the intended use of chlormethine gel as proposed by the submission is presented in Figure 1.

Figure 1: Proposed treatment algorithm



Source: Figure 1-4 p 49 of the submission.

MF=CTCL= mycosis fungoides-type cutaneous T-cell Lymphoma; TSEBT=total skin electron beam therapy.

<sup>2</sup> 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.

- 4.7 The proposed treatment algorithm does not provide a comprehensive overview of treatments in Australia; a recent Australian Clinical Practice Statement<sup>3</sup> recommended the following skin-directed therapies for Stage IA/IB/IIA disease:
- Corticosteroids.
  - Chemotherapy (for patients with small BSA involvement; requires compounding): nitrogen mustard 0.1% to 0.2% in an aqueous or ointment base, or carmustine, noting carmustine is now difficult to source.
  - Other therapy options: imiquimod 5% cream; 5-fluorouracil cream; tacrolimus 0.1% ointment; retinoids such as tretinoin 0.1% cream and acitretin.
  - Radiotherapy types: Phototherapy (psoralen ultraviolet A (PUVA) or narrowband ultraviolet B (NB UVB)); Localised radiotherapy; total skin electron beam therapy.
- 4.8 Systemic treatments (potentially in combination with skin-directed therapy) may be considered in patients who are refractory to skin-directed therapy alone.
- 4.9 It is noted that a gel preparation is preferable to cream for hair-bearing areas, as it is stable, non-greasy and quick-drying. The folliculotropic variant of MF-CTCL is an aggressive form which affects hair follicles, but is not part of the target population, and treated as advanced Stage IIIB-IV disease.<sup>4</sup>
- 4.10 The submission identified the following patient groups that would be eligible for treatment with chlormethine gel under the proposed PBS listing:
- 15% (20% of 75%) of Stage IA patients initiating phototherapy and not responding or relapsing.
  - 25% of patients with Stage IA that cannot access phototherapy or are claustrophobic.
  - 16% of Stage IIA/IB patients that cannot access phototherapy or are claustrophobic.
  - Chlormethine gel would not be prescribed to Stage IIA/IB patients who had >25% affected BSA.
- 4.11 Assuming these patient groups are mutually exclusive, patients eligible for chlormethine gel may represent 56% of early-stage patients. The proposed PBS listing did not include specific criteria on the eligibility of patients with respect to claustrophobia, non-response to phototherapy, or capacity to access phototherapy.

*For more detail on PBAC's view, see section 7 PBAC outcome.*

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<sup>3</sup> Bhabha, F.K., et al (2021), Mycosis fungoides and Sézary syndrome: Australian clinical practice statement. *Australas J Dermatol*, 62, p. e12

<sup>4</sup> Hodak, E, Amitay-Laish, I (2021), Variants of mycosis fungoides: Folliculotropic mycosis fungoides, UpToDate, Wolters Kluwer N.V.

## 5 Comparator

- 5.1 The submission nominated phototherapy as the main comparator, stating that chlormethine gel was expected to displace both PUVA and NB UVB. The submission stated that 95% of phototherapy treatment in MF-CTCL patients in Australia is provided with NB UVB and 5% with PUVA. Thus, while the Australian clinical guidelines considered PUVA to be the mainstay of SDTs for early-stage MF-CTCL in Australia, the lack of available facilities for treatment delivery means it is not readily utilised. A comparison between PUVA and NB UVB was not presented by the submission on the assumption that these therapies are non-inferior to each other with respect to efficacy and safety. The cost-effectiveness of phototherapy for MF-CTCL in Australia has not been previously assessed by the MSAC/PBAC.
- 5.2 The ESC considered that there would only be a small group of patients for whom phototherapy would not be an appropriate comparator (e.g., patients with small areas of skin affected, patients who live in regional/rural/remote areas). The ESC also noted that some patients may use chlormethine at the same time as phototherapy or after phototherapy. Also, because MF-CTCL tended to be a chronic disease, some patients might cycle back to steroids or cycle through more than one course of phototherapy or chlormethine. Overall, the ESC considered phototherapy was the most appropriate comparator.

*For more detail on PBAC's view, see section 7 PBAC outcome.*

## 6 Consideration of the evidence

### **Sponsor hearing**

- 6.1 The sponsor requested a hearing for this item. The dermatologist explained that although MF-type CTCL is rare in terms of incidence (new cases), the number of prevalent cases requiring treatment is much higher because the condition is chronic. The preferred treatment strategy depends on factors such as patient age, place of residence, and sites of disease. Multiple therapeutic options are needed because most patients relapse and require ongoing treatment. Both clearance and duration of response are important to patients and even a partial response could have a significant effect on the patient's quality-of-life. The dermatologist presented two case studies, which the PBAC considered provided useful clinical context.

### **Consumer comments**

- 6.2 The PBAC noted and welcomed the input from an individual (1), health care professionals (4) and an organisation (1) via the Consumer Comments facility on the PBS website. The comments from an individual who would like to access the medicine to treat their own health condition highlighted the lack of effective at home options when topical corticosteroids prove ineffective or when phototherapy is difficult to access. The comments from health care professionals outlined the need for an

increased choice of effective, easy to use topical preparations. Health care professionals also noted the access difficulties often associated with phototherapy. The comments from Lymphoma Australia emphasised that the condition can significantly reduce patients' quality-of-life and also emphasised that because the disease is chronic a range of treatment options are needed.

### Clinical trials

- 6.3 The clinical evidence presented in the submission was drawn from five studies:
- Chlormethine: one randomised, controlled trial (Study 201); and PROVe, a prospective observational study.
  - Phototherapy: three randomised, controlled trials (El-Mofty 2012; Whittaker 2012, and Vieyra-Garcia 2019).
- 6.4 All studies enrolled patients with early-stage MF-CTCL. The pivotal study for chlormethine (Study 201) has not been reviewed previously by the PBAC.
- 6.5 Details of the trials presented in the submission are provided in Table 2. These studies did not include a common reference that would have permitted an anchored indirect treatment comparison (ITC) of chlormethine gel against phototherapy. As such, the submission presented a naive ITC of evidence extracted from single arms of the included studies.

**Table 2: Trials and associated reports presented in the submission**

Trial ID	Protocol title/ Publication title	Publication citation
Study 201	<p>A phase II pivotal trial to evaluate the safety and efficacy of nitrogen mustard (nm) 0.02% ointment formulations in patients with stage i or iia mycosis fungoides (MF) (2005NMMF-201-US)</p> <p>Lessin, S. R., M. Duvic, J. Guitart, A. G. Pandya, B. E. Strober, E. A. Olsen, C. M. Hull, E. H. Knobler, A. H. Rook, E. J. Kim, M. F. Naylor, D. M. Adelson, A. B. Kimball, G. S. Wood, U. Sundram, H. Wu and Y. H. Kim (2013). 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. Yaupon Therapeutics. (2006).NCT00168064. Safety and Efficacy of Nitrogen Mustard in Treatment of Mycosis Fungoides.</p> <p>Assaf C, Querfeld C, et al. A Post-Hoc Analysis of Clinical Trial Data Shows That Prior Phototherapy Does Not Affect Response to Chlormethine Gel in Patients With Mycosis Fungoides.</p> <p>Geskin, L., E. Kim, J. Angello and Y. Kim. Evaluating the Treatment Patterns of Chlormethine/Mechlorethamine Gel in Patients With Stage I-IIA Mycosis Fungoides: By-time Reanalysis of a Randomized Controlled Phase 2 Study.</p>	<p>July 2010</p> <p>JAMA dermatology 2013; 149(1): 25-32</p> <p>Retrieved Sept 2022  <a href="https://clinicaltrials.gov/ct2/show/NCT00168064">https://clinicaltrials.gov/ct2/show/NCT00168064</a>.</p> <p>EORTC 2022. Madrid Spain.</p> <p>Clinical Lymphoma, Myeloma and Leukemia 2021; 21(2): 119-124.</p>

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Trial ID	Protocol title/ Publication title	Publication citation
	<p>Querfeld, C., J. J. Scarisbrick, C. Assaf, E. Guenova, M. Bagot, P. L. Ortiz-Romero, P. Quaglino, E. Bonizzoni and E. Hodak. "Post hoc Analysis of a Randomized, Controlled, Phase 2 Study to Assess Response Rates with Chlormethine/Mechlorethamine Gel in Patients with Stage IA-IIA Mycosis Fungoides."</p> <p>Querfeld, C., J. J. Scarisbrick, C. Assaf, Y. H. Kim, J. Guitart, P. Quaglino and E. Hodak. Chlormethine Gel Versus Chlormethine Ointment for Treatment of Patients with Mycosis Fungoides: A Post-Hoc Analysis of Clinical Trial Data.</p> <p>TGA. (2021). "Ledaga - AUSPAR."</p> <p>EMA. (2016). LEDAGA - Assessment Report (Procedure No. EMEA/H/C/002826/0000).</p>	<p>Dermatology (Basel, Switzerland) 2022; 238(2): 347-357.</p> <p>Am J Clin Dermatol 2022; 23(4): 561-570.</p> <p>Retrieved Sept 2022, from <a href="https://www.tga.gov.au/sites/default/files/auspar-chlormethine-hydrochloride-210902.pdf">https://www.tga.gov.au/sites/default/files/auspar-chlormethine-hydrochloride-210902.pdf</a>.</p> <p>Retrieved Sept 2022, from <a href="https://www.ema.europa.eu/en/documents/assessment-report/ledaga-epar-public-assessment-report_en.pdf">https://www.ema.europa.eu/en/documents/assessment-report/ledaga-epar-public-assessment-report_en.pdf</a>.</p>
PROVe	<p>Helsinn Therapeutics (U.S.) Inc. (2014). NCT02296164: Clinical Study Assessing Outcomes, Adverse Events, Treatment Patterns, and Quality of Life in Patients Diagnosed With Mycosis Fungoides Cutaneous T-cell Lymphoma (PROVe).</p> <p>Kim, E. J., J. Guitart, C. Querfeld, M. Girardi, A. Musiek, O. E. Akilov, J. T. Angello, W. L. Bailey and L. J. Geskin. The PROVe Study: US Real-World Experience with Chlormethine/Mechlorethamine Gel in Combination with Other Therapies for Patients with Mycosis Fungoides Cutaneous T-Cell Lymphoma.</p> <p>Kim, E., E. Gilmore, B. Poligone and C. Querfeld. Chlormethine Gel for Mycosis Fungoides T-cell Lymphoma: Recent Real-World Data.</p>	<p>Retrieved Sept 2022, from <a href="https://clinicaltrials.gov/show/NCT02296164">https://clinicaltrials.gov/show/NCT02296164</a>.</p> <p>Am J Clin Dermatol 2021; 22(3): 407-411.</p> <p>EMJ 2020; 5(2): 37-41.</p>
Phototherapy trials		
El-Mofty 2012	<p>El Mofty, M., S. Ramadan, M. M. Fawzy, R. A. Hegazy and S. Sayed. Broad band UVA: a possible reliable alternative to PUVA in the treatment of early-stage mycosis fungoides.</p> <p>Medical University of Graz. (2012). "NCT01686594: PUVA Maintenance Therapy in Mycosis Fungoides."</p>	<p>Photodermatol Photoimmunol Photomed 2012; 28(5): 274-277.</p> <p>Retrieved Sept 2022, from <a href="https://ClinicalTrials.gov/show/NCT01686594">https://ClinicalTrials.gov/show/NCT01686594</a>.</p>
Viyera-Garcia 2019	<p>Viyera-Garcia, P., R. Fink-Puches, S. Porkert, R. Lang, S. Pochlauer, G. Ratzinger, A. Tanew, S. Selhofer, S. Paul-Gunther, A. Hofer, A. Gruber-Wackernagel, F. Legat, V. Patra, F. Quehenberger, L. Cerroni, R. Clark and P. Wolf . Evaluation of Low-Dose, Low-Frequency Oral Psoralen-UV-A Treatment With or Without Maintenance on Early-Stage Mycosis Fungoides: A Randomized Clinical Trial.</p> <p>Anonymous. "Wording Errors in Abstract, Numeric Errors in Results, and Labeling Errors in Figure 2."</p> <p>Viyera-Garcia, P., R. Fink-Puches, R. Clark and et al. PUVA and maintenance treatment in mycosis fungoides: Systemic aberrant cytokine expression is a predictor of outcome.</p>	<p>JAMA dermatology 2019; 155(5): 538-547.</p> <p>JAMA Dermatol 2019; 155(5): 638. Correction to Viyera-Garcia 2019</p> <p>Journal of Investigative Dermatology 2018; 138(5 Suppl 1): S98.</p>

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Trial ID	Protocol title/ Publication title	Publication citation
	Vieyra-Garcia, P., R. Fink-Puches, S. Porkert and et al. Effectiveness of low-dose, low-frequency PUVA treatment and maintenance in early-stage (IA-IIA) mycosis fungoides.	Experimental Dermatology 2018; 27(Suppl 2): 46.
	Graier, T., R. Fink-Puches, S. Porkert, R. Lang, S. Pöchlauer, G. Ratzinger, A. Tanew, S. Selhofer, P. G. Sator, A. Hofer, A. Gruber-Wackernagel, F. J. Legat, P. A. Vieyra-Garcia, F. Quehenberger and P. Wolf. Quality of Life, Anxiety, and Depression in Patients With Early-Stage Mycosis Fungoides and the Effect of Oral Psoralen Plus UV-A (PUVA) Photochemotherapy on it.	Front Med (Lausanne) 2020; 7: 330.
	Graier, T., R. Fink-Puches, S. Porkert, R. Lang, S. Pöchlauer, G. Ratzinger, A. Tanew, S. Selhofer, P. G. Sator, A. Hofer, A. Gruber-Wackernagel, F. J. Legat, P. A. Vieyra-Garcia, F. Quehenberger and P. Wolf. Quality of Life, Anxiety, and Depression in Patients With Early-Stage Mycosis Fungoides and the Effect of Oral Psoralen Plus UV-A (PUVA) Photochemotherapy on it.	Front Med (Lausanne) 2020; 7: 330.
Whittaker 2012	European Organisation for Research and Treatment of Cancer – EORTC. (2007). NCT00056056: A Randomized, Open-Label Phase III Trial to Evaluate the Efficacy and Safety of Bexarotene (Targretin) Capsules Combined With PUVA, Compared to PUVA Treatment Alone in Patients With Mycosis Fungoides.	Retrieved Sept 2022, from <a href="https://www.clinicaltrials.gov/ct2/show/NCT00056056">https://www.clinicaltrials.gov/ct2/show/NCT00056056</a> .
	Whittaker, S., P. Ortiz, R. Dummer, A. Ranki, B. Hasan, B. Meulemans, S. Gellrich, R. Knobler, R. Stadler and M. Karrasch. "Efficacy and safety of bexarotene combined with psoralen-ultraviolet A (PUVA) compared with PUVA treatment alone in Stage IB-IIA mycosis fungoides: final results from the EORTC Cutaneous Lymphoma Task Force phase III randomized clinical trial (NCT00056056)	The British journal of dermatology 2012; 167(3): 678-687.

Source: Table 2-5 pp60-62 of the submission.

BB=broad band; EORT= European Organisation for Research and Treatment; EMA=European Medicines Agency; ITC=indirect treatment comparison; MF-CTCL= mycosis fungoides-type cutaneous T-cell Lymphoma; PUVA=psoralen ultraviolet A; UVA= ultraviolet A

6.6 The key features of the included studies are summarised in Table 3.

**Table 3: Key features of the included evidence**

Trial	N	Design/ duration	Risk of bias	Patient population	Outcome(s)	Use in modelled evaluation
<b>Chlormethine</b>						
Study 201	260	R, SB 12 mths	Low-Moderate	Stage IA-IIA MF-CTCL	CR, PR, DoR, SD, PD, TFR, Safety	Used <sup>b</sup>
PROVe	298	P, OS 24 mths	High	Stage IA-IV MF-CTCL	ORR <sup>a</sup> , QoL, Safety	Not used
<b>Phototherapy</b>						
El-Mofty 2012	30	R, DB 36 mths	Low	Stage IA-IB MF-CTCL	CR, Safety	Used <sup>b</sup>
Whittaker 2012	93	R, SB 76 mths	Low-Moderate	Stage IB-IIA MF-CTCL	CR, PR, SD, PD, TTR, DoR, Safety	Used <sup>b</sup>
Vieyra-Garcia 2019	27	R, DB 60 months	Low-Moderate	Stage IA-IB MF-CTCL	CR, PR, TTR, Safety	Used <sup>b</sup>

Source: Compiled during the evaluation based on Table 2-22 p100; Table 2-23 p102, Table 2-25 p104-105, Table 2-25 p106-108 of the submission; Table 5 p684 Whittaker 2012.

CR=complete response; DoR=duration of response; HRQoL=health-related quality of life; MF-CTCL= mycosis fungoides-type cutaneous T-cell lymphoma; mths= months; NR=not reported; OS=observational study; ORR=overall response rate; P=prospective; PD=progressive disease; PR=partial response; QoL= quality of life SB=single blinded; R=randomised; SD=stable disease; TFR=time to first response; TTR=time to relapse

a. Kim et al 2021 reported the evaluable clinical response, defined as  $\geq 50\%$  reduction from baseline in the body surface area percentage (%BSA) at 12 months and overall response rate (ORR-2) as the proportion of patients with a  $\geq 50\%$  reduction from baseline in %BSA for two consecutive visits; b. Applied the CR and PR.

6.7 The overall risk of bias in Study 201 (chlormethine), El-Mofty 2012, Vieyra-Garcia 2019 and Whittaker 2012 (phototherapy) was low to moderate. PROVe had a high likelihood of selection bias (no allocation concealment), performance bias (no blinding of participants or personnel) and detection bias (no blinding of outcomes assessment), the magnitude and direction of which cannot be determined. However, evidence from PROVe did not inform the naïve ITC presented by the submission. While Vieyra-Garcia 2019 was a prospective randomised trial, the randomisation was conducted among patients who achieved a complete response (CR) after a 9-month induction phase. As such, the submission reported the proportion of patients with a CR prior to randomisation, thereby essentially reporting the results as if from a single arm study. In the absence of a comparator group in either PROVe or Vieyra-Garcia 2019, it is difficult to conclude that the observed clinical outcomes in those studies are attributable to the nominated treatment. All studies (except El-Mofty 2012; 6%) reported a high proportion (30%-36%) of patients discontinuing from the respective trials.

6.8 The submission reported protocol violations in Study 201. In Study 201 there was an error in randomisation at one of the sites (New York University) where study treatment was assigned to 16 patients based on their MF stage and not as per randomisation. The analyses in Study 201 were performed for the ITT population, including the NYU patients as assigned and treated (N =260) and the ITT population that included all patients randomised and assessed by a blinded observer, excluding NYU patients (N =242). The results of analyses adjusting for the randomisation error

at the NYU site showed that inclusion of the results for patients from that site did not impact on the overall response rate.

- 6.9 The submission stated that clinically relevant outcomes were based on the CAILS and SWAT/mSWAT clinical end points. The primary efficacy endpoint in Study 201 was a  $\geq 50\%$  improvement (i.e., a partial response (PR) or CR) in a patient's CAILS score versus baseline measurement. PROVe did not mandate collection of specific response scores, and mSWAT scores were not documented universally during the study. The outcomes presented for the comparator studies were based on treatment response (CR, PR and duration of response). However, only Vieyra-Garcia 2019 reported response based on the mSWAT score. Neither El-Mofty 2012 nor Whittaker 2012 explicitly reported the use of either the CAILS or mSWAT scores for assessment of response.
- 6.10 The definition of PR varied across the trials. While the definition of PR was a  $>50\%$  reduction in skin symptoms (by some measure of skin symptoms) in Study 201, Vieyra-Garcia 2019 and Whittaker 2012, this outcome was not reported in El-Mofty 2012.
- 6.11 The submission conducted a meta-analysis across the studies of a derived outcome - restricted mean duration of complete response (rmDOCR). The rmDOCR is a bespoke outcome measure presented for the purposes of this submission. It has not been assessed previously by the PBAC in the context of other treatments for MF-CTCL or therapies used in the treatment of other skin conditions. The analysis was restricted to a maximum follow-up duration of 10 months for the duration of response outcome in Study 201 which did not account for the initial 8 weeks of time until first response reported in Study 201. The evaluation considered this was inappropriate. In addition, the follow-up in the comparator studies was well beyond this period (20, 36 and 76 months in Vieyra-Gracia 2019, El-Mofty 2012 and Whittaker 2012 respectively). Data verification and assessment of the impact of applying longer follow-up duration for the estimated rmDOCR outcome was not possible because the workbook with calculations and data applied in estimating the rmDOCR was not supplied by the submission. The ESC noted the PSCR provided additional detail on the derivation of rmDOCR in a revised statistical report, which also included individual patient data (IPD) applied in the estimation of rmDOCR. The results of the meta-analysis were verified using the IPD data provided with the PSCR. The ESC considered that, while the empirical application of rmDOCR appeared statistically sound, there were transitivity concerns regarding the use of this outcome in the naïve ITC (see paragraph 6.18).
- 6.12 There were issues identified in the evaluation with regards to comparability of the studies included in the naïve ITC, namely:
- There were limited data available for the phototherapy studies, which inhibited comparison of baseline demographic and disease characteristics. The available data indicated differences across the studies in gender and prior treatment. The sample size of the chlormethine studies were much larger than those of the phototherapy studies (see Table 4).

- The location and time at which the studies were conducted. The recruitment period for the phototherapy studies was on average later than that of Study 201. Patients recruited in later time periods are more likely to benefit from advances in treatment options and supportive care, which may have biased the analysis in favour of PUVA.
- Differences in the duration of follow-up (being 12 months for Study 201 and up to 76 months for the phototherapy studies) that impact the assessment of rmDOCR.

The PSCR (2) stated that while a naïve ITC introduces issues of transitivity related to potential differences in patient demographics and baseline disease characteristics and study design, this limitation primarily arises from the lack of well conducted, full reported phototherapy studies in this rare disease. The PSCR argued that differences in prior therapy may potentially bias against chlormethine gel since 38.5% of patients in Study 201 had experienced prior phototherapy (see Table 4). The ESC noted that the prior treatment with phototherapy seen in Study 201 was not consistent with the proposed treatment algorithm but acknowledged that such use is not prohibited by the restriction submitted.

- 6.13 The submission did not nominate a non-inferiority margin for rmDOCR. The non-inferiority finding in the naïve ITC was interpreted based on the absence of statistically significant differences in rmDOCR. Non-inferiority was also inferred based on the comparison of the point estimates of rmDOCR from each study. The rmDOCR outcome was not applied in the economic evaluation.

**Table 4: Baseline demographics and disease characteristics which may influence the transitivity of included studies**

Study	Study 201		El-Mofty 2012	Whittaker 2012	Vieyra-Garcia 2012
	Chlormethine gel	Chlormethine ointment	All	PUVA	PUVA
<b>N</b>	130	130	30	45	27
<b>Age</b>					
<65 years	NR	87 (66.9)	NR	33 (73)	NR
≥65 years	NR	43 (33.1)	NR	12 (27)	NR
Mean (range)	NR	NR	NR	NR	61.7 (48-75)
Mean (SD)	NR	NR	35.73 (16.34)	NR	NR
Duration (months)	12		24	36	76
Gender, males (n,%)	77 (59.2)	77 (59.2)	NA	NA	19 (70.0)
<b>Prior treatment</b>					
Topical steroids	112 (86.1)	113 (86.9)	NR	NR	NR
Phototherapy	50 (38.5)	53 (40.8)	NR	15 (33.3)	14 (52)
Bexarotene (topical and oral)	23 (17.7)	23 (17.7)	NR	NR	NR
Topical chlormethine	16 (12.3)	13 (10.0)	NR	NR	NR
IFNs	3 (2.3)	5 (3.8)	NR	NR	NR
Methotrexate	3 (2.3)	3 (2.3)	NR	NR	NR
Radiation (local and total skin)	3 (2.3)	2 (1.5)	NR	NR	NR
TSEB	NR	NR	NR	3 (6.7)	NR
Photopheresis, interferons, topical chemotherapy	NR	NR	NR	4 (8.9)	NR
Topical therapy, radiotherapy, UVB, retinoids, b-carotene	NR	NR	NR	24 (53.3)	NR
<b>Definition of response</b>					
CR	no evidence of disease; 100% improvement from Baseline CAILS score for five index lesion (score of 0), confirmed at the next visit ≥28 days later		complete clinical and histopathological clearance	complete resolution of all clinically apparent cutaneous disease for at least 28 days	mSWAT score reduced to zero
PR	partial but incomplete clearance of disease (evidence of disease remains); ≥50% improvement from baseline CAILS score for five index lesions, confirmed at the next visit ≥28 days later		Not measured	>50% reduction of cutaneous disease burden based on tumour burden index score compared with baseline score and sustained for at least 4 weeks	mSWAT score reduction of more than 50%

Source: Table 2-12 p88, Table 2-26 p 109 of the submission

BSA=body surface area; CAILS= Composite Assessment of Index Lesion Severity CR=complete response; IFN=interferon; MF-CTCL= mycosis fungoides-type cutaneous t-cell Lymphoma; ITT=intention to treat; mSWAT= Mycosis Fungoides-type Cutaneous T-cell Lymphoma; mSWAT= Modified Severity-Weighted Assessment Tool; n= number of participants with event; N=total participants in group NA=not available; nm=nanometre; NR= not reported; NYU=New York University; PUVA=psoralen ultraviolet A; PR=partial response; TSEB= total skin electron beam UVA=ultraviolet A; UVB=ultraviolet B; SD=standard deviation.

## Comparative effectiveness

6.14 A summary of the primary efficacy outcome (response rate) reported in Study 201 and the phototherapy studies is provided in Table 5. The proportion of patients with CR varied across the studies. The results of Study 201 for the ITT including NYU population, showed that the confirmed response rate (CR+PR) was higher for chlormethine gel versus chlormethine ointment, with response rates of 58.5% and 47.7%, respectively. The ratio of these response rates was 1.23 (95% CI: 0.97, 1.55;  $p=0.068$ ), which met the pre-defined non-inferiority criterion.

**Table 5: Results of objective response rate across the single-arm studies**

Regimen	N	CR n (%)	PR n (%)
<b>Randomised studies</b>			
<b>Chlormethine gel - Study 201</b>			
<b>CAILS (primary outcome)</b>			
Chlormethine gel	130	18 (13.8)	58 (44.6)
Chlormethine ointment	130	15 (11.5)	47 (36.2)
<b>mSWAT (secondary outcome)</b>			
Chlormethine gel	130	9 (6.9)	52 (40.0)
Chlormethine ointment	130	4 (3.1)	56 (43.1)
<b>Single arm studies</b>			
<b>Phototherapy (PUVA)</b>			
El-Mofty 2012	15	11 (73.3) <sup>a</sup>	NR
Whittaker 2012	45	10 (22.2) <sup>b</sup>	22 (48.9) <sup>b</sup>
Vieyra-Garcia 2019	27	19 (70.4) <sup>c</sup>	8 (29.6) <sup>c</sup>

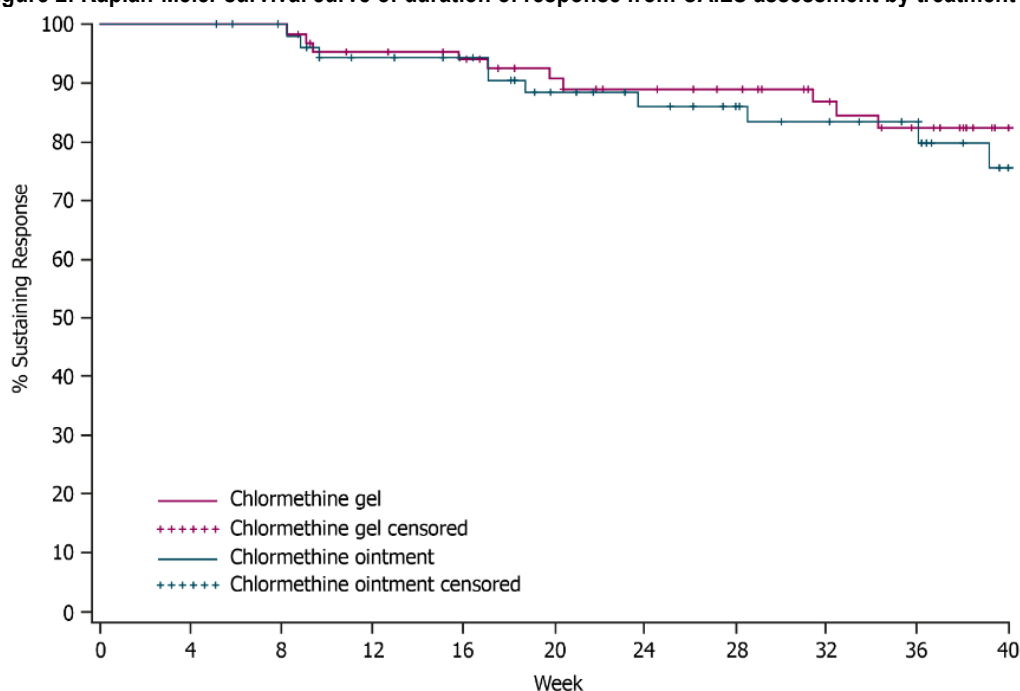
Source: Table 2-30 p115; Table 2-39 p132 of the submission, p275 El-Mofty et al 2012, Table 5 p694 Whittaker 2012

CR=complete response; n=number of participants with event; N=total participants in group; PR=partial response; PUVA= psoralen ultraviolet A.

a. Based on complete clinical and histopathological clearance; b. Based on complete resolution of all clinically apparent cutaneous disease for at least four weeks; c. Based on mSWAT score

6.15 The results of Study 201 showed 65/76 (85.6%) patients in the chlormethine gel arm and 51/62 (82.2%) patients in the chlormethine ointment arm maintained their CAILs response through to the end of the trial. Figure 2 provides the Kaplan-Meier survival curve for duration of response from CAILs assessment. The submission stated that 11 patients in total “lost” their response during the trial, and of these patients 4 in the chlormethine gel arm and 7 in the chlormethine ointment arm re-achieved a response (i.e., had a second response) prior to the end of the trial. This approach to treatment is incongruent with the proposed PBS continuation criteria, which state “Patient must not have developed disease progression while receiving PBS-subsidised treatment with this drug for this condition.”

Figure 2: Kaplan-Meier survival curve of duration of response from CAILS assessment by treatment group, ITT

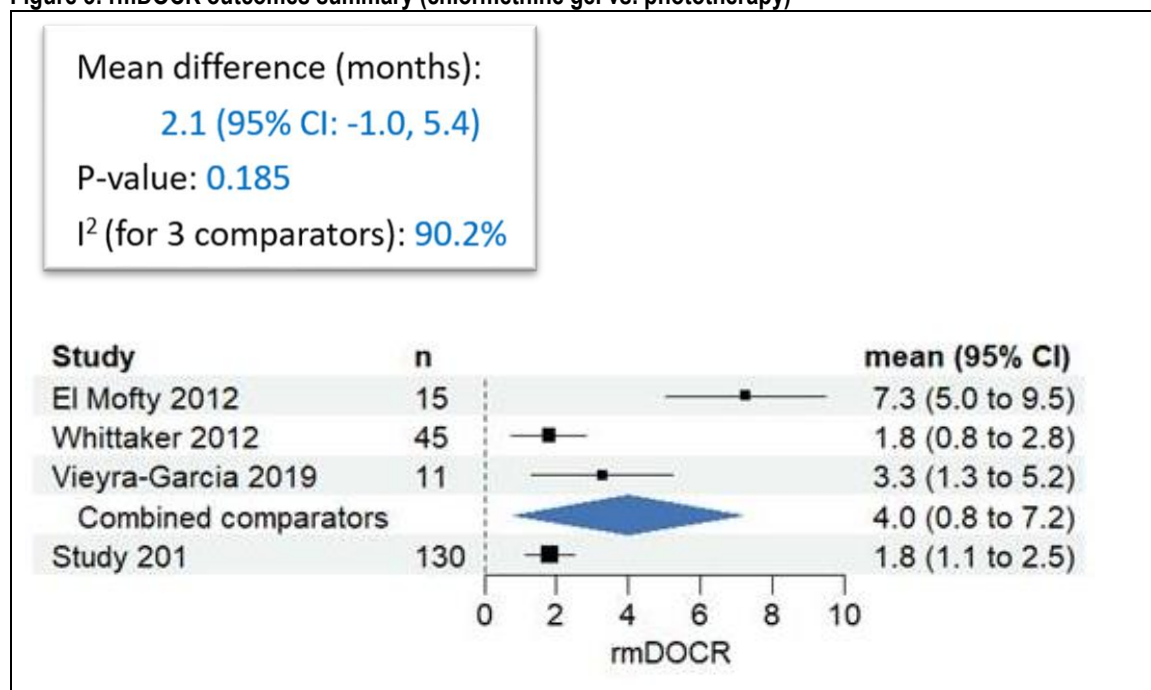


Source: Figure 2-5 p119 of the submission

CAILS= Composite Assessment of Index Lesion Severity; ITT=intention to treat; NYU=New York University

- 6.16 The mean duration of CR in the phototherapy studies was obtained by the submission using the Kaplan-Meier curves presented in Vieyra-Garcia 2019 and Whittaker 2012. Response times were not directly provided in El-Mofty 2012 and were inferred by the mean duration of response (26.6 months) and its range (9-36 months), with the assumption that 1 patient relapsed prior to 10 months. Data verification was not possible for the estimated duration of response in the phototherapy trials because the workbook containing those estimates was not supplied by the submission.
- 6.17 Based on the results of the naïve ITC the submission stated there was no statistically significant difference between phototherapy and chlormethine gel in rmDOCR (mean difference in months = 2.1; 95% CI: -1.0, 5.4; p=0.185) (Figure 3). The reported difference favoured phototherapy but is difficult to interpret given the nature of the comparison, the variability in the definition of response included in the assessment of rmDOCR and the high degree of heterogeneity identified in the studies for which estimates of effect are being compared (with an  $I^2 > 90\%$ ). Further, the lack of a statistically significant difference does not necessarily imply treatments are equivalent, unless the study was powered to detect a difference.

Figure 3: rmDOCR outcomes summary (chlormethine gel vs. phototherapy)



Source: Figure 2-12 p139 of the submission

I<sup>2</sup>=heterogeneity statistic; CI=confidence interval; n = number of participants with event; rmDOCR=restricted mean duration of complete response.

6.18 The submission presented a naïve ITC of rmDOCR. The following decisions biased the naïve ITC in favour of chlormethine gel:

- The efficacy data were truncated to 10 months, which was the maximum follow-up of Study 201. The comparator trials had follow-up periods ranging 20 to 76 months, and two of them had a mean duration of complete response of 18 and 27 months; these were censored at 10 months in the ITC.
- The classification of CR used the CAILS scores from Study 201, while the comparator trials used ‘complete clinical and histopathological clearance’, ‘complete resolution of all clinically apparent cutaneous disease for at least four weeks’ or ‘mSWAT score reduced to zero’; the comparator scores required all clinically apparent lesions to completely resolve, whereas the CAILS score only requires the 5 index lesions to resolve (see Table 4). This means patients may be classified as a ‘complete responder’ by the CAILS score, but not mSWAT; this is evident in Table 5, which shows that 18 (13.8%) patients in the chlormethine gel arm of Study 201 achieved a CAILS CR, but only 9 (6.9%) achieved an mSWAT CR. The potential for bias with respect to the comparison of rmDOCR would have been reduced if the analysis had applied the mSWAT definition of CR in the ITC, and included patients who met the Study 201 protocol-definition of a complete responder, which was similar to the definitions used in the comparator trials. The PSCR (p2) argued that as only one of the comparator studies used mSWAT, it was considered more reasonable to use the primary Study 201 outcome based on

CAILS response for the ITC. The PSCR stated the CAILS is a sensitive instrument and could also be considered more relevant to measure response in the early stages of MF-CTCL in patients with a BSA  $\leq$  25%. The ESC was concerned about the comparability of the endpoints used to inform the ITC of rmDOCR. The ESC considered that mSWAT, or as a surrogate the ‘complete resolution of all clinically apparent cutaneous disease for at least four weeks’, would be a more reliable estimate of response that better reflects disease control and the requirement for potential future therapy.

- The ITC classified 28 (21.5%) chlormethine gel patients as ‘complete responders’ – 10 more than reported in Study 201 (Table 6). The submission did not discuss this discrepancy, but it was noted these 10 patients had a single ‘CR’ classification at one visit, and did not meet the Study 201 protocol definition of complete responder (that the complete response was maintained for at least two consecutive visits, or at least 28 days). The PSCR (p3) noted that only one of the comparator studies (Whittaker 2012) required a confirmed response after 28 days. As such, the PSCR argued inclusion of Study 201 patients who reported any response (i.e. removing the requirement for the patient to have a confirmed response 28 days later) would allow a more consistent comparison with the phototherapy studies. The ESC considered the 10 patients classified as having a CR during the post hoc analysis of Study 201 should be excluded from the analysis.

**Table 6: rmDOCR in the studies**

Study	N	Non-responders	Mean	SE	95% CI	Notes
<b>Chlormethine</b>						
Study 201	130	102	1.82	0.35	(1.14, 2.50)	Actual follow-up times utilised for each patient from trial listings. Individual patient data utilised for all patients reporting a CR up to Month 12.
<b>Phototherapy</b>						
El Mofty 2012 <sup>a</sup>	15	4	7.27	1.13	(5.05, 9.49)	Only summary data provided but clearly one patient relapsed at 9 months and the remaining lasted beyond 10 months
Whittaker 2012	45	35	1.80	0.54	(0.75, 2.85)	Patient level data extracted from Fig 4
Vieyra-Garcia 2019	11	3	3.29	1.00	(1.32, 5.25)	Patient Level data extracted from Fig 3B, actually 8 non-responders but reduced to 3 (+8 =11) to best approximate the actual rate of non-response of 8/27
<b>Combined</b>			<b>4.01</b>	<b>1.62</b>	<b>(0.84, 7.18)</b>	

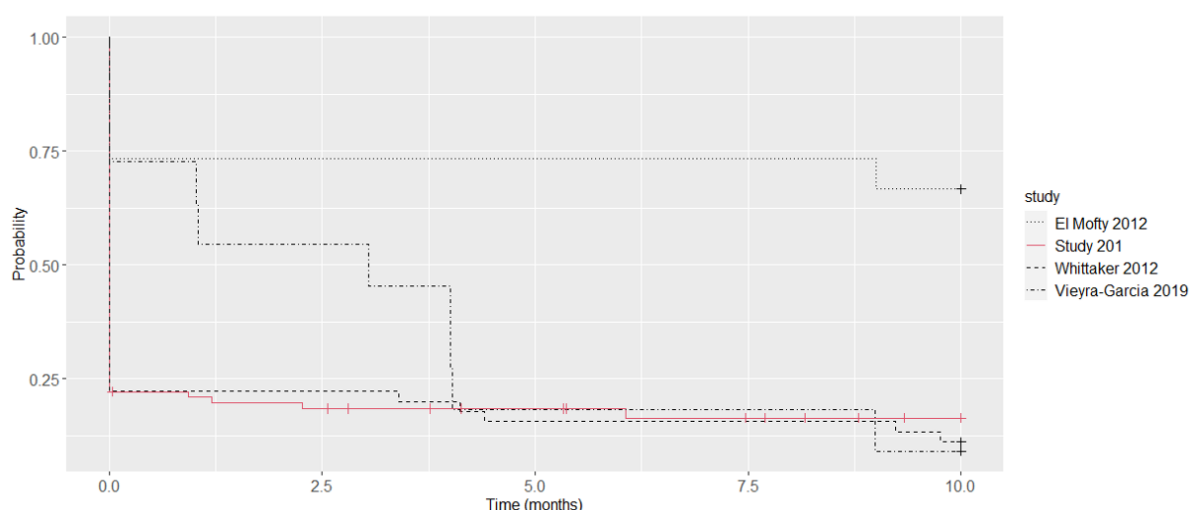
Source: Table 2-41 p140 of the submission

CI=confidence interval; CR=complete response; N=total participants in group; rmDOCR=restricted mean duration of complete response; SE=standard error. **The results showing restricted mean duration of complete response could not be verified during the evaluation**

6.19 The submission stated that in Study 201 chlormethine gel achieved a lower initial CR rate, but CR was generally maintained, whereas the phototherapy studies generally

showed initial higher response rates that decline over time (Figure 4). The submission's conclusion was not supported by the data in the plot which showed the curve for Study 201 to be consistent with that from Whittaker 2012 and Vieyra-Garcia 2019 from approximately 4 months, all of which were well below that of El-Mofty 2012.

Figure 4: KM curves for rmDOCR for chlormethine gel and phototherapy studies



Source: Figure 2-13 p140 of the submission

KM=Kaplan-Meier; rmDOCR=restricted mean duration of complete response

6.20 Health-related quality of life (HRQoL) was not investigated in Study 201. The submission reported HRQoL results from PROVe for chlormethine gel and from a publication arising from the same study as Vieyra-Garcia 2019 (Graier et al. 2020) for phototherapy. These studies used different disease-specific instruments for the assessment of quality of life in patients with MF-CTCL (Skindex-28 questionnaire in PROVe and the Dermatology Life Quality Index (DLQI) in Graier et al 2020). Hence the results in Graier 2020 cannot be directly compared with the HRQoL outcomes reported with chlormethine gel in PROVe. The results from Graier 2020 and PROVe did not inform the economic evaluation presented in the submission. The ESC noted the statements in the PSCR that the submission included the best available data on HRQoL. However, ESC remained concerned about the validity of the HRQoL comparison between chlormethine and phototherapy, given it relied on different questionnaires from single-arm studies.

### Comparative harms

6.21 A summary of the safety outcomes in Study 201 is presented in Table 7. The overall incidence of treatment emergent adverse events (TEAEs) was comparable across treatment groups (21% versus 17%). The submission concluded that overall, chlormethine gel is generally well tolerated and AEs are manageable by dose interruption, dose reduction and/or standard medical therapy.

**Table 7: Summary of key adverse events in Study 201 (safety set)**

AEs, n (%)	Chlormethine gel (N=128)	Chlormethine ointment (N=127)	p-value <sup>a</sup>
AEs	108 (84.4)	115 (90.6)	0.19
Drug-related AEs <sup>b</sup>	79 (61.7)	64 (50.4)	0.08
Grade 3-4 drug-related AEs	36 (28.1)	22 (17.3)	0.05
SAEs <sup>c</sup>	14 (10.9)	11 (8.7)	0.67
Discontinuation due to AEs <sup>d</sup>	28 (21.9)	23 (18.1)	0.53
Discontinuation due to drug related AEs <sup>d</sup>	27 (21.1)	22 (17.3)	0.53
Deaths <sup>e</sup>	1 (0.01)	0 (0.0)	-

Source: Table 2-34 p125, Table 2-36 p127 of the submission,

AE=adverse event; N=total participants in group; SAE=serious adverse event;

<sup>a</sup> Fisher's exact test.

<sup>b</sup> AEs with relation to drug of 'Yes, related', 'Probably related', 'Possibly related' or where such a relationship was not specified.

<sup>c</sup> No SAEs were considered possibly, probably or definitely related to study drug.

<sup>d</sup> Patients were categorised as 'Discontinued' if the course of action following an AE included 'Study Discontinuation'. Three patients, two on the chlormethine gel arm and one on the chlormethine ointment arm met this criterion. The reasons for withdrawal checked on the CRF were categorised as follows: 1. "Other": need for prohibited chemotherapy (Xeloda) for recurrence of metastatic squamous cell carcinoma originating on the scalp (untreated area); the AE was recurrent SCC, not related to study drug. 2. "Lack of Efficacy": the AE listed with action discontinued was "skin pain" which was "probably related" to study drug. 3. "Withdrew Consent": the AE was itching on lesion (severe) probably related to study drug.

<sup>e</sup> This was reported as an SAE not related to study drug

- 6.22 The most frequent AEs in Study 201 were skin-related, characterised mainly as local dermatitis (skin irritation), pruritis and erythema. Skin irritation occurred in 32 patients (25.0%) and 18 patients (14.2%) in the chlormethine gel and chlormethine ointment groups, respectively (p=0.040). The submission noted that topical steroids, which may be applied to treat dermatitis in clinical practice, were not permitted in Study 201. The data from Study 201 indicated that 5% (n=13) of patients were receiving topical corticosteroids while on chlormethine gel treatment.
- 6.23 The submission reported that after 2 years of follow-up in PROVE, the incidence of AEs was lower than those seen in Study 201 (44.6% versus 84.4%, respectively). The submission provided a Periodic Safety Update Report (PSUR, 26 October 2021) which covered the period from the 23 August 2020 to 22 August 2021 on potential safety concerns beyond those identified in the clinical trials. No new safety concerns have arisen during the reporting period. The results from longer-term studies and clinical use indicated that the safety profile of chlormethine gel was largely consistent with the safety results presented in Study 201.
- 6.24 The submission reported that AEs in the phototherapy studies included nausea, pruritus, dryness and photosensitivity that sometimes necessitated topical steroids or treatment dose reduction.
- 6.25 The submission stated it was difficult to compare the AE profiles of a topical therapy applied daily on multiple days per week with a phototherapy that patients attend three weekly sessions over studies of different duration, with different levels of AE monitoring intensity. Overall, the submission considered both therapies were tolerable with acceptable discontinuation rates. Given these results are based on a

naïve comparison of single arms from the included studies, it was not possible to use the event rates in a common reference arm to form a meaningful indirect comparison.

### **Benefits/harms**

- 6.26 While the submission included a superiority claim, this was not supported by the clinical evidence presented with respect to response (rmDOCR), HRQoL or safety. Accordingly, a benefits/harms table has not been presented.

### **Clinical claim**

- 6.27 The submission described chlormethine gel as having non-inferior efficacy in terms of rmDOCR and improved effectiveness in terms of HRQoL and has similar safety compared to phototherapy.
- 6.28 The claim of non-inferior efficacy in terms of rmDOCR was based on the results of a naïve ITC. The evaluation considered the therapeutic conclusion with respect to both efficacy and safety presented in the submission was not supported by the evidence presented for the following reasons:
- There were significant transitivity issues between the included trials, mainly pertaining to the duration of the studies, differences in the definition of response, the time and location of conduct, gender, prior treatment and study sample size. The PSCR (p2) stated that the transitivity issues largely arose from the low-quality phototherapy studies.
  - The ITC was biased in favour of chlormethine gel, through the use of data for different definitions of 'complete response' and the addition of 10 'complete responders' from the chlormethine gel arm, who did not meet the Study 201 protocol definition of 'complete responder'. The PSCR argued inclusion of Study 201 patients who reported any response (i.e. including the additional 10 patients) would allow a more consistent comparison with the phototherapy studies (see paragraph 6.18).
  - There was a high degree of heterogeneity identified in the phototherapy studies for which estimates of effect were compared ( $I^2 > 90\%$ ).
  - The comparison lacked a common reference, without a non-inferiority bound, and therefore the conclusion of non-inferiority based on the absence of a statistically significant difference is poorly supported.
- 6.29 The ESC acknowledged the difficulty in developing an evidence base for treatments for rare diseases such as MF-CTCL and agreed with the PSCR that the phototherapy studies were of low quality. However, the ESC considered that the issues raised by the evaluation about the comparability of the measured endpoints and the inclusion/exclusion of patients in the ITC added to concerns about the validity of the ITC. The ESC further noted that, although the ITC result was not statistically significant ( $p=0.185$ ), the point estimate favoured phototherapy (mean difference in rmDOR = 2.1 months) with a wide confidence interval (-1.0, 5.4). The ESC advised these

inconclusive statistical results further added to concerns about whether the ITC had satisfactorily established non-inferiority to phototherapy.

- 6.30 The submission claimed that chlormethine gel provided improved effectiveness compared to phototherapy with respect to HRQoL. The ESC considered this claim was not supported by the clinical trial evidence presented in the submission. HRQoL was derived from single arm data from two non-randomised studies which reported different HRQoL instruments and was considered inconclusive. HRQoL data were not used in the ITC.
- 6.31 The PBAC considered that the claim of superior comparative effectiveness compared to phototherapy with respect to HRQoL was not adequately supported by the data. The PBAC considered that the claim of non-inferior comparative effectiveness versus phototherapy was subject to much uncertainty.
- 6.32 The PBAC considered that the claim of non-inferior safety was not adequately supported by the data but that the safety of chlormethine gel was manageable, given the intended use.

### ***Economic analysis***

- 6.33 The submission presented a modelled economic evaluation; a CUA, comparing chlormethine gel with phototherapy (PUVA) based on data from one arm of Study 201 for chlormethine gel and one arm each of three studies for the nominated comparator, PUVA. The CUA resulted in an estimated difference in HRQoL in favour of chlormethine gel arising from patients treated with chlormethine gel spending less time in the initial health states, inferring a better and more durable response to therapy than achieved with phototherapy. The ESC considered the clinical evidence did not provide a reliable basis for a CUA with the claim that chlormethine gel provided improved effectiveness compared to phototherapy with respect to HRQoL not supported (see paragraph 6.30).
- 6.34 A summary of the model structure is presented in Table 8.

**Table 8: Summary of model structure, key inputs and rationale**

Component	Summary
Treatments	Chlormethine gel versus phototherapy
Time horizon	Lifetime- 46 years in the model base case. This was not reasonable given that disease-specific survival data used in the model were based on a study (Agar et al. 2010) with a median follow-up of 5.9 years. Response rates were sourced from Study 201, with a maximum follow-up of 12 months.
Outcomes	LYG and QALYs.
Methods used to generate results	State transition (Markov) cohort model
Health states	24 health states; each within a defined a MF-CTCL disease stage. The defined health states were: Stage IA, Stage IB/IIA, Stage IIB+ (<10% BSA) and Stage IIB+ (>10% BSA). Each disease stage had 6 health states defined per skin burden.
Cycle length	1 month
Transition probabilities	Transition probabilities between disease stages was derived from Agar et al. 2010 and Wernham et al. 2015. Transition probabilities within disease stages (degree of skin burden) were derived from mSWAT response rates from Study 201, Kim et al. 2003 and Phan et al. 2019 Transition to death was derived from Agar et al. 2010 and PROCLIP 2019.
Extrapolation method	No methods of extrapolation were presented by the submission. This was not appropriate given that the time horizon utilised in the model is beyond the trial time horizon from which the effectiveness data were drawn.
Health related quality of life	Utility values were derived from a vignette study describing twelve patients in different MF-CTCL disease stages with varying levels of skin burden. The vignettes covered the range of health states used in the model with clinicians used as proxies to determine EQ-5D-5L values. This was not appropriate. The utility values derived from the vignette study was used to estimate utility values for the 24 health states in the model. The same utility values were used for all the health states in the chlormethine gel and phototherapy arms of the model, thus the utility values used were independent of treatment group

Source: Compiled during the evaluation using information from Table 3-1, pp151-152; text, pp170-180; Workbook 'Chlormethine – Ledaga – Section 3 – Economic Model (Final)', worksheets 'Utility Calculations' of the submission.

BSA = body surface area; LYG = life years gained; m SWAT = modified severity-weighted assessment tool; PROCLIP = Prospective Cutaneous Lymphoma International Prognostic Index; QALYs = quality adjusted life years.

- 6.35 The submission claimed it presented early-stage MF-CTCL patients as their base case in the economic model. During the evaluation, it was observed that patients with early-stage MF-CTCL transitioned to some health states in Stage IIB+ with high burden, thus accruing costs and outcomes contributing to the estimated ICER. There was no clinical evidence presented on the rate of progression to later stage disease arising from the use of either chlormethine gel or phototherapy.
- 6.36 Patients entered the model either with a low skin burden (<10% BSA) or high skin burden (10-80% BSA). The entry point for patients into the model does not reflect the population in the proposed PBS criteria – patients who have no more than 10% or 25% of their BSA involved. As Study 201 included 14% of patients with BSA >25%, and there is no evidence of a difference in efficacy based on BSA affected, the results of the economic evaluation may be relevant in the context of a BSA agnostic listing. While the number and description of health states was reasonable, the categorisation of low/high skin burden under which patients enter the model in each health state did not align with the requested population (<10% BSA for low skin burden and 10-80% BSA for high skin burden for the model compared to no more than 10% or 25% BSA in the requested population). The ESC noted the PSCR (p5) provided a revised economic

- model that excluded patients with a BSA >25%. However, the ESC considered the overarching concerns raised regarding the reliability of the economic model also applied to the revised version provided with the PSCR (see paragraph 6.33).
- 6.37 The application of a lifetime time horizon on the basis of slow disease progression of MF-CTCL was not reasonable given that disease-specific survival data used in the model were based on a study (Agar et al. 2010) with a median follow-up of 5.9 years. Response rates were sourced from Study 201, with a maximum follow-up of 12 months (compared with overall model horizon of 46 years). The model does not have the functionality to assess the ICER per QALY gained over 12 months; the maximum follow-up for Study 201.
- 6.38 The submission did not present any methods of extrapolation even though the time horizon utilised in the model was beyond the time horizon of the trial from which the data were drawn. The absence of information on how the data have been extrapolated beyond the trial-based time-horizon (12 months in Study 201) or that of the supplementary material (5.9 years in Agar et al, 2010) to a 46 year time horizon renders this aspect of the model, and its impact on the resulting estimate of cost-effectiveness, unevaluable. Essentially, the model assumed that the treatment effects and associated transitions between health states remained constant over the entirety of the 46-year time horizon. This is not appropriate in the context of the treatment of MF-CTCL for which patients are likely to experience severe symptoms as disease progresses hence treatment effects are likely to vary with disease progression.
- 6.39 Transition probabilities were derived from Study 201 and other published studies identified through a systematic literature search. The use of efficacy and HRQoL data in the economic analysis which were not presented as part of the clinical evidence introduced a disconnect in the evidence base between what has been evaluated with respect to the clinical claim and that presented for the cost-effectiveness claim. The PSCR stated that comparable HRQoL data were not collected in Study 201 or in the phototherapy included studies and therefore could not be evaluated in the naïve ITC. Instead, the PSCR noted a comparison of HRQoL during long-term therapy was made via the modelled economic evaluation that included utility assessments derived from HRQoL outcomes. The PSCR argued that outcome results from the economic evaluation support a claim of superior HRQoL outcomes with use of chlormethine gel vs. phototherapy. The ESC reiterated that an overarching concern was that the CUA was based on a claim of superior HRQoL that was not supported by the clinical evidence provided in the submission.
- 6.40 The submission derived transition probabilities between disease stages from Agar et al. 2010. Information on the types of treatment patients in Agar et al 2010 were receiving was not presented; thus, it remains unclear if the transition probabilities arising from those data reflect treatment with either chlormethine gel or phototherapy. Data presented by Agar et al 2010 were for both MF and Sézary syndrome (SS) variants of CTCL. The submission assumed that the probability of a patient progressing from an earlier to a more advanced disease stage was treatment

independent. Thus, the model assumed no difference between chlormethine gel and phototherapy with respect to the impact on disease progression; this was consistent with the claim of non-inferior clinical efficacy.

- 6.41 The HRQoL data (Skindex-29) from PROVe presented as part of the clinical evidence were not used in the economic model. The submission did not provide a justification for the exclusion of those data. There have been recent efforts to map the Skindex-29 measure to health state utility values; the results from those mapping exercises were not considered by the submission<sup>5</sup>. The PSCR (4) stated the recent attempt to map the Skindex-29 measure to health state utility values concluded that applying published mapping algorithms to PROVe data appeared to result in overestimation compared with existing literature and that more research is required to understand the applicability of existing mapping algorithms and to develop new mapping algorithms in MF-CTCL.
- 6.42 The submission conducted a de novo utility study using clinicians as proxies by reasoning that this approach was necessary due to restricted access to patients and ethical considerations within the submission timeframe. While the use of clinicians as proxies may be expedient, the submission has not outlined why such a study may be considered more ethical in nature. In the absence of patient specific HRQoL elicitation, indirect utility elicitation studies could have been conducted that may have better reflected preference-based assessments of HRQoL from a population perspective.
- 6.43 The methodological approach used by the submission to derive utility values from the vignette study for each health state relied on multiple steps and assumptions, each of which introduced scope for variability in the resulting values. The ESC agreed with the evaluation that there were a number of issues with how the submission estimated the utility weights including:
- The submission used clinicians to elicit utility values for use in the model and for the base case evaluation. The PBAC Guidelines v5 note that methods used to elicit expert opinion should be well-designed and may vary from large, published questionnaires and surveys with statistical analysis to a summary of interviews with a panel of clinical experts (PBAC Guidelines v5, p181-182): the submission presented an opinion from only one UK clinical expert for development of the vignettes, elicitation of results from seven experts, and only one expert in the field of utility valuation for input on the choice of instruments. In addition, the PBAC Guidelines v5 note that where scenario-based methods using vignettes are used to indirectly elicit utility weights, these should usually be administered to a representative general population using accepted preference-based methods

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<sup>5</sup> Meregaglia M, Tarricone R. Feasibility of Deriving Health State Utilities in Mycosis Fungoides Cutaneous T-Cell Lymphoma Using Mapping Algorithms. *Pharmacoecon Open*. 2022 Jul;6(4):595-603. doi: 10.1007/s41669-022-00326-6. Epub 2022 Feb 19. PMID: 35182375; PMCID: PMC9283626.

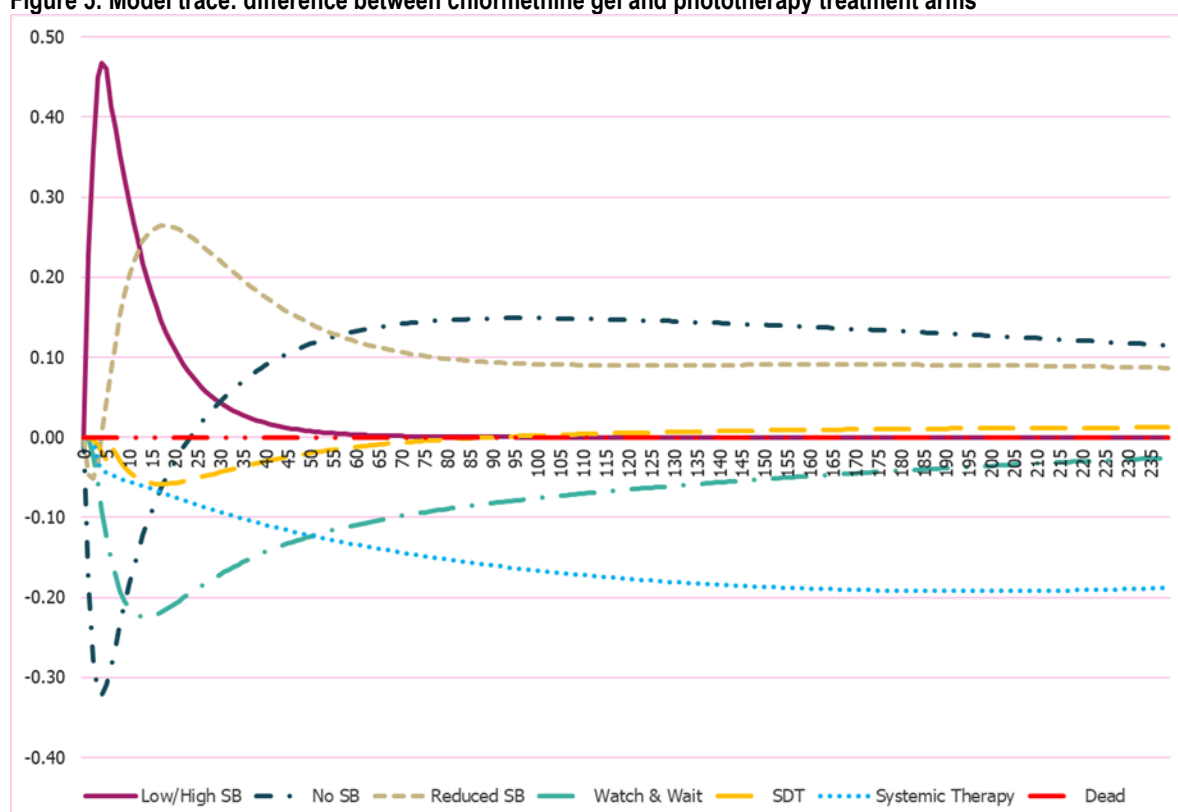
such as standard gamble, time trade-off and discrete choice experiments (PBAC Guidelines v5, p78).

- The submission did not provide justification for the choice of specific descriptions of the vignette used to elicit the HRQoL data. The descriptions of disease conditions in the vignette did not capture every aspect of MF-CTCL that could affect patients' quality of life. For example, the area of the patient's body that is affected by the symptom was not included.
  - The use of a UK based value set scoring algorithm to derive utility weights without providing justification of its use over the Australian scoring algorithm was inappropriate. The PBAC Guidelines v5 state the use of Australian-based preference weights as the preferred scoring algorithm to calculate utility weights (PBAC Guidelines v5, p77).
  - By assigning utility values derived from the vignette studies to mSWAT scores from Study 201, the submission assumed a linear relationship between mSWAT scores and HRQoL; such a linear relationship has not been validated. Moreover, by relying on the mSWAT, the submission has introduced a disconnect from the evidence presented as the basis for the calculation of the rmDOCR for chlormethine gel which relied on the CAILS index.
  - The mSWAT ranges nominated by the submission as representative of different disease burden under each disease stage were not justified. The mSWAT ranges used were not representative of the TNMB classification system of skin burden used to determine patient entry into the model. For example, the four mSWAT ranges assigned to Stage IA disease (classified as <10% BSA affected) included: 0; 1-10, 11-20, >20.
  - The approach used by the submission (using the NormDIST function in Excel) to derive the proportion of patients in each mSWAT range introduced uncertainties into the estimate of utility value applied to the overall health state in the model.
- 6.44 The ESC noted the evaluation was not able to provide a meaningful evidence-based assessment of the impact of the issues outlined above with respect to the estimation of utility values on the estimated base ICER. This was due to the approach in the model structure to deriving the utility weights, along with the lack of evidence supporting the description of health states in the vignette study and lack of evidence supporting assumptions made in deriving the utility values.
- 6.45 Even though not stated in the submission, it appears the same utility values were used for all the health states in the chlormethine gel and phototherapy arms of the model, thus the utility values used were independent of treatment group.
- 6.46 The submission presented a model trace for each health state according to skin burden derived from plotting the sum of the transition probabilities for a particular disease burden state under each disease stage. The submission claimed the model traces demonstrated a significant incremental benefit for chlormethine gel compared to

phototherapy, noting that the benefit from reduced skin burden and longer period of no skin burden were evident.

- 6.47 The difference between the model traces for the proportion of patients in each health state for chlormethine gel and phototherapy (i.e., chlormethine gel – phototherapy) is shown in Figure 5. This shows that there was no difference between the two treatments with regards to mortality. Patients on chlormethine gel spent more time in the no skin burden and reduced skin burden states, whilst patients receiving phototherapy treatment spent more time in the watch and wait and systemic therapy states.

Figure 5: Model trace: difference between chlormethine gel and phototherapy treatment arms



Source: Plotted during the evaluation using data from Workbook 'Chlormethine – Ledaga – Section 3 – Economic Model (Final), Worksheet 'Clinical Results'

SB = skin burden; SDT = skin directed therapy.

- 6.48 The submission applied the median dose (1.8 g) of chlormethine gel from Study 201 to the model. Using the mean dose for the safety set population (1.77 g for low skin burden and 4.28 g for high skin burden) and the mean ITT dose (an average of 2.21 g) resulted in a high impact on the ICER (224% and 90% change from the base case ICER respectively).
- 6.49 The model assumed that chlormethine gel will be applied on average, every second day as observed in the French Temporary Use Authorization real world data. Application of chlormethine gel on a daily basis as stipulated in the Australian product

information will result in a high impact on the estimated ICER (416% change from the base case ICER).

- 6.50 Based on current guidelines and clinical expert opinion, the submission assumed that PUVA was administered 3 times weekly for a maximum of 13 weeks and UVB 2 times weekly for a maximum of 13 weeks. Patients in the low skin burden health state received phototherapy for up to 40 weeks (including systemic phototherapy) and patients in the reduced skin burden, SDT and systemic therapy health states received phototherapy throughout the model. The model also assumed that patients with no skin burden would receive phototherapy weekly as maintenance therapy once the maximum 13-week limit applied to the model had been reached. Maintenance phototherapy is not supported by Australian clinical practice guidelines given that there is no supporting evidence for its use<sup>6</sup>.
- 6.51 The key drivers of the model are presented in Table 9.

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<sup>6</sup> Bhabha, F.K., et al (2021), Mycosis fungoides and Sézary syndrome: Australian clinical practice statement. *Australas J Dermatol*, 62, p. e12

Table 9: Key drivers of the model

Description	Method/Value	Impact Base case: \$1/QALY gained
Usage of chlormethine gel	In the base case, chlormethine gel was applied on average every second day as observed in the French ATU real world data.	High, favours chlormethine gel. Use of daily application of gel as stipulated in the Australian PI increased the ICER to \$ <sup>2</sup> /QALY gained.
Time horizon	Base case evaluation was over a lifetime time horizon	High, favours chlormethine gel. Use of 20 and 10-year time horizons increased ICER to \$ <sup>3</sup> /QALY and \$ <sup>4</sup> /QALY gained, respectively. The use of a 5-year time horizon makes phototherapy dominant.
Chlormethine gel dose	Base case used median chlormethine gel dose from Study 201 (1.8 g); 0.99 g for low skin burden and 2.93 g for high skin burden.	High, favours chlormethine gel. Use of mean safety set population dose: 1.77 g for low skin burden and 4.28 g for high skin burden increased the ICER to \$ <sup>5</sup> /QALY gained. The use of Study 201 mean ITT dose (average 2.21 g) increased the ICER to \$ <sup>6</sup> /QALY gained.
Subsequent treatment	Base case included costs due to subsequent treatment.	High, favours chlormethine gel. Exclusion of costs of subsequent treatment increases the ICER to \$ <sup>6</sup> /QALY gained.
Transition probabilities	Relapse post-CR and post-PR sourced from Whittaker et al. 2012 and assumed equal to initial PD.	High, favours chlormethine gel. Use of values sourced from Phan et al. 2019 increased ICER to \$ <sup>6</sup> /QALY gained.
Utilities	Base case analysis used baseline mSWAT score from Study 201.	Moderate, favours chlormethine gel Use of baseline mSWAT score from the PROCLIP registry increases the ICER to \$ <sup>7</sup> QALY/gained.
Definition of response	The base case used the definition of time point for response for effectiveness of chlormethine gel from Study 201 to derive transition probabilities within the disease stages.	High, favours phototherapy Use of definition of time point of response from 2 phototherapy studies (used to inform the ITC in comparative effectiveness section) to recode chlormethine gel response reported in Study 201, and derived new transition probabilities decreased the ICER to \$ <sup>8</sup> QALY/gained. The submission did not identify which 2 of the 3 phototherapy studies were used.
Effectiveness of phototherapy	Effectiveness of phototherapy was estimated as a weighted average of CR and PR rates from studies used to inform ITC in comparative effectiveness section.	High, favours phototherapy. Use CR and PR rates from the PROCLIP registry decreased ICER to \$ <sup>8</sup> /QALY gained.
Treatment duration of chlormethine gel	Chlormethine gel was applied throughout the model time horizon in the base case	High, favours phototherapy Applied a 12-month stopping rule to chlormethine gel and assumed no change in efficacy of gel post stopping rule. This resulted in chlormethine gel being dominant.

Source: Table 3-37 to 3-44, p221-227 and Workbook 'Chlormethine – Ledaga – Section 3 – Economic Model (Final)', worksheets 'Treatment Acquisition Costs', 'Settings' of the submission.

ATU = temporary use authorization; CR = complete response; ICER = incremental cost effectiveness ratio; ITC = indirect treatment comparison; PI = product information; PR = partial response; PD = progressive disease; PROCLIP = Prospective Cutaneous Lymphoma International Prognostic Index; QALY = quality adjusted life years; mSWAT = modified severity weighted assessment tool.

The redacted values correspond to the following ranges:

- <sup>1</sup> \$55,000 to < \$75,000
- <sup>2</sup> \$355,000 to < \$455,000
- <sup>3</sup> \$95,000 to < \$115,000
- <sup>4</sup> \$255,000 to < \$355,000

- <sup>5</sup> \$155,000 to < \$255,000
- <sup>6</sup> \$115,000 to < \$135,000
- <sup>7</sup> \$75,000 to < \$95,000
- <sup>8</sup> \$15,000 to < \$25,000

6.52 The base case ICER was \$55,000 to < \$75,000 per QALY gained (Table 10). The submission did not present the results of a stepped analysis. The results from a two-step analysis compiled from the model workbook (Table 10) show that an estimated difference arose in QALYs only; this was consistent with the assumption of no treatment effect on survival.

**Table 10: Results of the stepped economic evaluation**

Step and component	Chlormethine gel	Phototherapy	Increment
<b>Step 1: Costs and outcomes in life years</b>			
Costs	\$█	\$133,522	\$█
LYG	12.97	12.97	0.00
Incremental cost/extra LYG			\$█ <sup>1</sup>
<b>Step 2: Utility weights applied</b>			
Costs	\$█	\$133,522	\$█
QALYs	10.26	10.01	0.25
<b>Incremental cost/extra QALY gained (base case)</b>			\$█ <sup>2</sup>

Source: Table 3-35, p217 of the submission

ICER = incremental cost effectiveness ratio; LYG = life years gained; QALY = quality adjusted life years.

The redacted values correspond to the following ranges:

<sup>1</sup> \$0 to < \$5,000

<sup>2</sup> \$55,000 to < \$75,000

6.53 The submission presented univariate sensitivity analyses, univariate/multivariate scenario analyses and a probabilistic sensitivity analysis. Selected scenario analyses specified by the submission and additional analyses of relevance specified during the evaluation are presented in Table 11. These results show that the model was most sensitive to the time horizon (phototherapy dominant, \$255,000 to < \$355,000 and \$95,000 to < \$115,000 for 5, 10 and 20 years' time horizon respectively), the effectiveness of phototherapy (\$115,000 to < \$135,000 and \$15,000 to < \$25,000), treatment duration of chlormethine gel (chlormethine gel dominant), the definition of response rate applied to chlormethine gel (\$15,000 to < \$25,000), dose of chlormethine gel (\$155,000 to < \$255,000 and \$115,000 to < \$135,000), frequency of application of chlormethine gel (\$355,000 to < \$455,000) and subsequent treatment costs (\$115,000 to < \$135,000). Overall, the estimated ICER is not robust given that it is very sensitive to variations in most of the parameters used to inform the model.

Table 11: Sensitivity analyses

Analyses	Incremental cost (\$)	Incremental QALY	ICER	% change
<b>Base case</b>		<b>0.25</b>		
Usage of chlormethine gel (base case: application of gel on average every second day as observed in the French ATU real world data). Application of gel as stipulated in the Australian PI; daily application		0.25		416%
Time horizon (base case lifetime - 46 years)				
20 years		0.18		47%
10 years <sup>a</sup>		0.07		304%
5 years <sup>a</sup>		-0.01	Phototherapy dominant	-
Chlormethine gel dose (base case: median dose 1.8 g; 0.99 g for low skin burden and 2.93 g for high skin burden from Study 201).				
Mean dose of 1.77 g for low skin burden and 4.28 g for high skin burden from Study 201 safety set population		0.25		224%
Mean dose of 2.21 g from Study ITT		0.25		90%
Subsequent treatment costs (base case: included). Costs excluded		0.25		87%
Relapse post-CR and post-PR (base case sourced from Whittaker et al. 2012 and assumed equal to initial PD). Use values from Phan et al. 2019		0.17		85%
Utilities: (base case - mSWAT score from Study 201). Using baseline mSWAT score from the PROCLIP registry <sup>a</sup> .		0.22		15%
Discount rate (base case: 5%) <sup>a</sup>				
0%		0.60		-59%
3.5%		0.32		-22%
Definition of time point of response used to inform effectiveness of chlormethine gel to derive transition probabilities within disease stages (base case sourced from Study 201). Use of response used in 2 phototherapy studies (used to inform the ITC) to recode chlormethine gel response reported in Study 201, and derived new transition probabilities <sup>a</sup> . The submission did not identify which 2 of the 3 phototherapy studies were used.		0.34		-66%
Effectiveness of phototherapy (base case: weighted average of CR and PR rates from studies used to inform ITC). Applied CR and PR rates for phototherapy from PROCLIP registry		0.50		-69%
Treatment duration of chlormethine gel (base case: applied throughout the model time horizon). 12 months stopping rule to chlormethine gel and assumed efficacy of gel post stopping rule to be same as Study 201 (no change) <sup>a</sup> .		0.27	Chlormethine gel dominant	-

Source: Table 3-37 to 3-44, p221-227 and Workbook 'Chlormethine – Ledaga – Section 3 – Economic Model (Final)', worksheets 'Treatment Acquisition Costs', 'Settings' of the submission.

ATU = temporary use authorization; CR = complete response; ICER = incremental cost effectiveness ratio; ITC = indirect treatment comparison; PI = product information; PR = partial response; PD = progressive disease; PROCLIP = Prospective Cutaneous Lymphoma International Prognostic Index; QALY = quality adjusted life years; mSWAT = modified severity weighted assessment tool.

<sup>a</sup> sensitivity analysis was conducted during evaluation using drop-down box or changing a single clearly labelled cell.

The redacted values correspond to the following ranges:

<sup>1</sup> \$55,000 to < \$75,000

<sup>4</sup> \$255,000 to < \$355,000

<sup>7</sup> \$75,000 to < \$95,000

<sup>2</sup> \$355,000 to < \$455,000

<sup>5</sup> \$155,000 to < \$255,000

<sup>8</sup> \$25,000 to < \$35,000

<sup>3</sup> \$95,000 to < \$115,000

<sup>6</sup> \$115,000 to < \$135,000

<sup>9</sup> \$15,000 to < \$25,000

6.54 The ESC acknowledged the difficulty in populating an economic model for a rare disease but advised that the clarifications in the PSCR did not provide reassurance about the appropriateness of undertaking a CUA or the reliability of the model presented. The ESC considered that chlormethine may be a useful additional therapeutic option for a niche group of patients. With phototherapy considered an appropriate comparator the ESC considered a cost-minimisation analysis against phototherapy may be a potential way forward in this rare condition. The pre-PBAC response stated that the suggested cost-minimisation analysis is unlikely to facilitate a result which would allow chlormethine gel to be made available in Australia.

### Treatment cost/patient/year

6.55 The treatment cost per patient per year is presented in Table 12. The cost associated with phototherapy is not a drug cost but an administration cost for phototherapy. The results in Table 12 show that the submission estimated a higher cost per patient per year in the CUA and financial estimates compared to the trial-based use for either intervention; with a higher difference seen in the chlormethine gel arm. There are also differences in the costs calculated for the CUA and financial estimates for both chlormethine gel and phototherapy.

**Table 12: Treatment cost per patient for chlormethine gel and phototherapy**

	Chlormethine gel			Phototherapy		
	Trial dose and duration	Model	Financial estimates	Trial dose and duration	Model	Financial estimates
Mean dose	2.81 g/day	Not used	1.8 g/day	NR	NR	NR
Mean duration	12 months	272 months	48 months	13 weeks	272 months	48 months
Cost/patient/month	\$ [redacted] <sup>a</sup>	\$ [redacted] <sup>b</sup>	\$ [redacted] <sup>c</sup>	\$727.35 <sup>d</sup>	\$721.82 <sup>e</sup>	\$577.26 <sup>f</sup>
Cost/patient/year	\$ [redacted] <sup>g</sup>	\$ [redacted] <sup>h</sup>	\$ [redacted] <sup>i</sup>	\$2,176.20 <sup>j</sup>	\$4,012.30 <sup>k</sup>	\$3,209.84 <sup>l</sup>

Source: compiled during the evaluation using information from Table 2-14 p92; Workbook 'Chlormethine – Ledaga – Section 3 – Economic Model (Final)', worksheets 'Treatment Acquisition Costs', 'Trace\_ChormethineGel', 'Trace\_Phototherapy', of the submission of the submission; p275 EI-Mofly 2012

NR = not reported; SB = skin burden

<sup>a</sup> calculated as mean dose per day reported in Study 201 \* 3 applications per week to derive weekly dosage. Weekly dosage \* 4.345 weeks to derive monthly dosage; cost/patient/month calculated as monthly dose \* price per dose

<sup>b</sup> sum of cost per chlormethine gel per month for low skin burden (0.99 g) and high skin burden (2.93 g) using 14.96 dose frequency per month

<sup>c</sup> estimated as cost per patient per year/12

<sup>d</sup> calculated as cost per PUVA session \* number of sessions per week \* number of weeks in a month

<sup>e</sup> calculated as the weighted average of monthly cost of PUVA and UVB presented in the model

<sup>f</sup> calculated as the weighted average of cost PUVA session per month and UVB sessions per month. 80% applied as cost offset.

<sup>g</sup> estimated as weekly dose \* cost per dose \* maximum use in the trial (51.9 weeks [0.995 year])

<sup>h</sup> cost per patient per month \* 12

<sup>i</sup> estimated as average (submission's estimated cost of chlormethine gel per year/number of patients in a year)

<sup>j</sup> cost of phototherapy per session (80% applied given co-pay) \* 3 sessions per week \* 13 weeks

<sup>k</sup> sum of 'cost of weighted sessions of PUVA and UVB for 3 months (32.8)' and 'once weekly maintenance session for 9 months'.

<sup>l</sup> sum of 'cost of weighted sessions of PUVA and UVB for 3 months (32.8)' and 'once weekly maintenance session for 9 months'. 80% applied as cost offset applied to phototherapy cost

6.56 The pre-PBAC response offered a [redacted] % price reduction reducing the proposed EMP to \$ [redacted] per tube.

## Estimated PBS usage & financial implications

6.57 This submission was considered by DUSC. It presented an epidemiological approach to estimate anticipated script volumes and costs to Government. A summary of the key inputs relied on for the financial estimates is presented in Table 13.

**Table 13: Key inputs for financial estimates**

Parameter	Value applied and source	Comment
Prevalent Population	The submission applied mid-2018 prevalence data in the UK to 2021 census data for England and Wales: 3,515 MF-CTCL patients and 43,432,100 adults in England and Wales = prevalence rate of 8.09 per 100,000 adult population.	This is overestimated, as the census data did not match the year of the prevalence data, and excluded the populations of Northern Ireland and Scotland, which were included in the prevalence. Census data recorded 52,383,965 adults in the UK in mid-2018, <sup>7</sup> which would produce a prevalence rate of 6.71 per 100,000 adult population.  The PSCR argued that the commentary was incorrect and DUSC considered that the prevalence figure of 8.09 per 100,000 was correctly applied
Incident Population	The submission did not estimate the incident population; instead, it applied the prevalence rate to the ABS projections of the Australian population from 2022 to 2028.	This double-counted most of the prevalent population in subsequent years. The submission stated that in England, the age-standardised incidence rate of MF-CTCL was 0.42 and 0.29 per 100,000 for males and females respectively; this would be a more appropriate estimate after Year 1 of listing.  DUSC commented that the submission did not need to estimate the incident population.  DUSC noted that the prevalent approach was not necessarily incorrect. The double counting arose due to the sponsor applying a duration of use greater than one year to the prevalent population which led to double to counting.
% who meet the proposed PBS criteria	Proportion of patients with early-stage disease (IA, IB and IIA): 79.6% - based on the PROCLIP dataset.  Proportion of patients with <25% BSA: 85.27% - based on the population of Study 201.	The submission's two proportions are reasonable, but it failed to consider: - The proportion of patients receiving skin-directed monotherapy (55.8% as described by D'Agostino 2019) <sup>8</sup> - The proportion of patients who failed topical corticosteroids (50.7% as described in Figure 1-4, p 49 of the submission)
Uptake Rate	█% in year 1 increasing to █% in year 6.	Submission's assumption

<sup>7</sup> Data from the Office for National Statistics (2019), accessed 25/11/2022:

<https://www.ons.gov.uk/peoplepopulationandcommunity/populationandmigration/populationestimates/bulletins/annualmidyearpopulationestimates/mid2018>

<sup>8</sup> D'Agostino, P., Kent, A., Sharp, E., Schmidt, F. and Turini, M. (2019). Mycosis fungoides-type cutaneous T-cell lymphoma (MF-CTCL) epidemiology in UK: New insights for an accurate estimation. Unpublished conference abstract presented as an attachment to the submission.

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Parameter	Value applied and source	Comment
Compliance and use in practice	The submission assumed each patient treated with chlormethine gel would receive 4 years of therapy (i.e. 100% compliance over 48 months). This meant that the submission estimated an 11-fold increase in patients on treatment, from 116 in Year 1 to 1,322 in Year 6.	This is a substantially longer treatment time than recorded in Study 201, which had a median duration of treatment of 9 months. It is unlikely that all patients who initiate chlormethine gel would continue treatment for 4 years.
Dose	The submission estimated 1 x 60 g tube per month would be required, citing the mean dose of 1.8 g daily from Study 201.	This is an underestimate; in Study 201, the mean daily use for Stage IA patients was 1.8 g, however stage IB/IIA patients required 4.3 g per day, which would require over 2 tubes per month.
Offsets for comparator	The submission proposed MBS Item 14050 (phototherapy) would be replaced by chlormethine gel. It estimated 71.83 services would be offset per year, multiplied by 4 years per patient treated with chlormethine gel. This was informed by the comparator PUVA trials, which had 2 to 3 PUVA sessions weekly for the first 13 weeks, followed by an assumed once-weekly maintenance therapy for the rest of each year.	The number of annual services is an overestimate; the comparator trials administered PUVA three-times weekly for a maximum of 13 to 16 weeks, and one administered PUVA twice-weekly for 12 to 24 weeks. Therapy was stopped once a CR was achieved. A recent Australian Clinical Practice Statement indicated there is no evidence to support the use of maintenance phototherapy. <sup>9</sup> The submission did not consider phototherapy may be used in conjunction with, or subsequent to, chlormethine gel.

Source: Data extracted from Section 4 of the submission.

ABS = Australian Bureau of Statistics; BSA = body surface area; CR = complete response; PROCLIP = Prospective Cutaneous Lymphoma International Prognostic Index; PUVA = psoralen ultraviolet A; UK = United Kingdom.

6.58 The submission's estimated patient numbers are compared to the evaluation revised estimates in Table 14. The revised estimates take into account the corrected prevalence rate, the proportion of patients who are treated with skin-directed monotherapy, and the proportion of patients who failed topical corticosteroids. These result in an estimated number of patients receiving chlormethine gel that was approximately 1% of the submission's base case (< 500 versus 500 to < 5,000 patients over 6 years).

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<sup>9</sup> Australian Clinical Practice Statement for mycosis fungoides and Sézary syndrome (2020), Australasian Lymphoma Alliance, p. 22.

**Table 14: Submission's financial estimates, compared to a revised estimate compiled during the evaluation**

		2023	2024	2025	2026	2027	2028	Source
<b>Submission's estimate</b>								
MF-CTCL patients (n)		█ <sup>1</sup>	█ <sup>1</sup>	█ <sup>1</sup>	█ <sup>1</sup>	█ <sup>1</sup>	█ <sup>1</sup>	Prevalence rate of 8.09
Patients with Early-Stage Disease (IA, IB and IIA: %)		79.6%	79.6%	79.6%	79.6%	79.6%	79.6%	PROCLIFI Dataset
Patients with <25% BSA (%)		85.3%	85.3%	85.3%	85.3%	85.3%	85.3%	Study 201
<b>Eligible patients</b>								
Uptake rate		█ <sup>1</sup> %	█ <sup>1</sup> %	█ <sup>1</sup> %	█ <sup>1</sup> %	█ <sup>1</sup> %	█ <sup>1</sup> %	Submission's assumption
Initiating Patients		█ <sup>2</sup>	█ <sup>2</sup>	█ <sup>2</sup>	█ <sup>2</sup>	█ <sup>2</sup>	█ <sup>2</sup>	Total over 6 years: █ <sup>1</sup>
<b>Revised estimate compiled during the evaluation</b>								
A	Number of MF-CTCL patients	█ <sup>1</sup>	█ <sup>2</sup>	█ <sup>2</sup>	█ <sup>2</sup>	█ <sup>2</sup>	█ <sup>2</sup>	Prevalence rate of 6.71 for year 1; incidence rate of 0.42 and 0.29 for males and females, respectively, in subsequent years.
B	Patients with Early-Stage Disease (IA, IB and IIA; %)	79.6%	79.6%	79.6%	79.6%	79.6%	79.6%	PROCLIFI Dataset
C	Patients with <25% BSA (%)	85.3%	85.3%	85.3%	85.3%	85.3%	85.3%	Study 201
D	Patients receiving skin directed monotherapy (%)	55.8%	55.8%	55.8%	55.8%	55.8%	55.8%	D'Agostino et. al. 2019 <sup>a, b</sup>
E	Patients who failed topical corticosteroids (%)	50.7%	50.7%	50.7%	50.7%	50.7%	50.7%	Figure 1-4, p 49 of the submission <sup>a</sup>
F = A*B*C* D*E	<b>Eligible patients</b>	█ <sup>2</sup>	█ <sup>2</sup>	█ <sup>2</sup>	█ <sup>2</sup>	█ <sup>2</sup>	█ <sup>2</sup>	
G	<b>Carry-over from prior year</b>	-	█ <sup>2</sup>	█ <sup>2</sup>	█ <sup>2</sup>	█ <sup>2</sup>	█ <sup>2</sup>	Assumed carry-over of eligible patients from prior year <sup>c</sup>
H	Uptake rate	█ <sup>1</sup> %	█ <sup>1</sup> %	█ <sup>1</sup> %	█ <sup>1</sup> %	█ <sup>1</sup> %	█ <sup>1</sup> %	Submission's estimate
I = H* (F + G)	Initiating Patients	█ <sup>2</sup>	█ <sup>2</sup>	█ <sup>2</sup>	█ <sup>2</sup>	█ <sup>2</sup>	█ <sup>2</sup>	Total over 6 years: █ <sup>2</sup>

Source: Table 4-3, p 233 of the submission.

CHM = chlormethine; MF-CTCL = mycosis fungoides-type cutaneous T-cell lymphomas; PROCLIFI = Prospective Cutaneous Lymphoma International Prognostic Index

<sup>a</sup> Weighted averages used, based on the Study 201 population where 58.5% had Stage IA disease, and 41.5% had Stage IB/IIA disease.

<sup>b</sup> The proposed restriction allows for CHM gel use in combination with other therapies; 3% and 15% of Stage IA and IB/IIA respectively received combination therapies. A proportion of these may receive CHM gel, however the submission specified clinical evidence with monotherapy treatments only, so they have been omitted from these estimates.

<sup>c</sup> It is reasonable to assume that a proportion of the prevalent patient population would carry across to subsequent years, from four pools: (i) Patients who have failed phototherapy and/or another skin directed monotherapy, (ii) Patients who had been in 'watch and wait' who decide to seek treatment (these patients must first fail corticosteroids to become eligible for CHM gel), (iii) Patients who had previously achieved a complete response with CHM gel but experience disease recurrence, who would be eligible for a repeat course of CHM gel therapy, and (iv) some patients may receive CHM gel in combination with another therapy. To account for these patients, the eligible prevalent patients who did not initiate CHM gel have been carried over to subsequent years (e.g. carry-over to year 2024 = < 500 - < 500 = < 500).

Figures rounded from 7 decimal places in Microsoft Excel.

The redacted values correspond to the following ranges:

<sup>1</sup> 500 to < 5,000

<sup>2</sup> < 500

- 6.59 The submission anticipated the net cost to Government to increase in the first 6 years, from approximately \$0 to < \$10 million in year 1 to \$20 million to < \$30 million in year 6. Due to large overestimates in the submission's projection of initiating and continuing patients, and phototherapy offsets (as described in Table 13 and Table 14 above), the evaluation stated the estimated financial implications presented by the submission have not been reproduced on the basis that they cannot be meaningfully evaluated and are uninformative for decision-making.
- 6.60 DUSC considers the estimates presented in the submission to be uncertain. The main issues were:
- DUSC noted that the estimates for the prevalent population relied on a conference presentation from the United Kingdom. DUSC considered that the numbers for the eligible patient population presented in the submission were unreliable and more sources should be reviewed.
  - The financial estimates assumed patients would receive 48 months of chlormethine gel. In Study 201, the median duration of treatment was 9 months, and no data were provided regarding the duration of use and efficacy beyond the 10-month follow-up. Also, the amount of chlormethine gel used by the average patient is subject to uncertainty and the amount could vary over time.
  - DUSC noted that submission incorrectly assumed that all patients would use no more than two tubes per month of chlormethine gel. The evaluation stated that based on the average daily use in the key trial, Stage IA patients required 1.77 g/day and Stage IB/IIA required 4.28 g/day (see paragraph 3.4). As such, most patients with Stage IB/IIA disease would require over two tubes per month. The submission did not provide a breakdown of prevalence by BSA, making the number of tubes used per patient uncertain. DUSC considered the number of tubes, and therefore costs, were underestimated. The pre-PBAC response noted the economic model provided Study 201 individual patient data including the average daily grams of chlormethine gel used by participants. The pre-PBAC response argued that this data indicated the vast majority of patients would be adequately served by the proposed maximum quantity of 2 tubes per month.
  - DUSC considered it likely that uptake will be higher due to the convenience of topical therapy, and considered that the uptake rate does not account for treatment failure (i.e. treatment of corticosteroids or watchful waiting) required in the listing.
  - DUSC considered that patient numbers are highly dependent on the assumptions regarding the place in practice of chlormethine gel and the likelihood of replacing phototherapy.
  - DUSC considered that the cost offset applied to phototherapy was overestimated. The evaluation noted the submission overestimated phototherapy replacement in three ways, which underestimated the projected net cost of chlormethine gel:

- The submission assumed each year of chlormethine gel would replace a full year of phototherapy. DUSC considered this to be unlikely. The comparator trials only administered phototherapy for 12 to 24 weeks (approximately 40 sessions).
  - Each patient treated with chlormethine gel would save 4 years of phototherapy (287.32 phototherapy sessions per patient). There is no evidence to support the use of maintenance phototherapy (Australasian Lymphoma Alliance, 2020), and phototherapy was ceased once patients achieved a complete response in the comparator trials.
  - The submission did not consider that for a proportion of patients, chlormethine gel may displace or be used in combination with phototherapy.
- 6.61 DUSC considered the utilisation and financial estimates presented in this submission were complex and require substantial changes. DUSC advised that the estimates should be recalculated using a prevalence approach. A review of data sources should be undertaken to inform prevalence and consider age, gender distribution and BSA proportions. In addition, DUSC considered sensitivity analyses should be undertaken as the epidemiology of the disease is not well understood, as well as uncertainty in uptake.

### ***Quality Use of Medicines***

- 6.62 The Sponsor will support the reimbursed supply of chlormethine gel for MF-CTCL in Australia through provision of educational material for targeted clinicians and pharmacists (including information for patients/carers on appropriate administration, storage and safe disposal). Patient education leaflets will be provided in addition to the information provided in the PI and Consumer Medication Information (CMI).
- 6.63 Compliance with chlormethine gel may be affected by the potential inconvenience of the daily administration regimen; in Study 201, patients were instructed to cover all affected lesions (Stage IA) or apply a full body application for Stage IB or IIA disease. As MF-CTCL patches or plaques commonly occur in areas that are infrequently exposed to sunlight (such as the back), self-application may be challenging, considering most patients are over 65 years old. Application of the gel to the patient by a care giver required use of disposable gloves and washing with soap and water if any gel contacted their skin. Patients were instructed not to cover the applied area for 5-10 minutes after administration, and not wash off the chlormethine gel for a minimum of 4 hours.

### ***Financial Management – Risk Sharing Arrangements***

- 6.64 The submission did not propose a risk sharing arrangement.

## 7 PBAC Outcome

- 7.1 The PBAC did not recommend the listing of chlormethine hydrochloride gel (hereafter chlormethine gel) for the treatment of mycosis fungoides-type cutaneous T-cell lymphoma (MF-CTCL) in adult patients who have no more than 25% of their body surface area (BSA) involved, have failed, are intolerant of or have a contraindication to treatment with topical corticosteroids. The PBAC acknowledged the clinical need for additional treatment options for patients with MF-CTCL. However, the PBAC considered that the clinical evidence presented did not adequately support the claim that chlormethine gel provides improved effectiveness compared to phototherapy with respect to health-related quality of life (HRQoL) and hence the cost-utility analysis (CUA) based on this claim did not support that chlormethine gel was cost-effective.
- 7.2 The PBAC noted the input from an individual, health care professionals and Lymphoma Australia and acknowledged that there was a clinical need for a range of treatment options in this chronic disease.
- 7.3 The PBAC considered that the proposed comparator of phototherapy was reasonable. The PBAC also noted that some patients may use chlormethine gel concurrently with phototherapy or after phototherapy.
- 7.4 The PBAC noted the submission described chlormethine gel as having non-inferior efficacy in terms of restricted mean duration of complete response (rmDOCR) and improved effectiveness in terms of HRQoL and considered this was an unusual approach. The submission presented an unanchored indirect treatment comparison (ITC) of evidence extracted from the single arms of studies for chlormethine gel (Study 201) and phototherapy (El Mofty 2012, Whittaker 2012 and Vieyra-Garcia 2019) to support a claim of non-inferior efficacy for the outcome of rmDOCR. The PBAC considered there were issues of transitivity affecting the comparability of these studies due to differences in: the definition of response, prior treatments, sample sizes, time and location at which the studies were conducted, and the duration of the studies being compared. The PBAC agreed with the PSCR that the transitivity issues largely arose from the low-quality phototherapy studies and acknowledged the difficulty in developing an evidence base for treatments for rare diseases. However, the PBAC considered that the ITC was biased in favour of chlormethine gel primarily due to the differences in the classification complete response (CR) evident across the trials (see paragraph 6.18). In addition, the PBAC noted that although the ITC result was not statistically significant ( $p=0.185$ ), the point estimate favoured phototherapy (mean difference in rmDOR = 2.1 months) with a wide confidence interval (-1.0, 5.4). The PBAC agreed with the ESC that these inconclusive statistical results further added to concerns about whether the ITC had satisfactorily established non-inferiority to phototherapy. The PBAC considered that non-inferiority to phototherapy was difficult to definitively establish given the limited available data for this rare condition.

- 7.5 The PBAC noted that the impact of chlormethine gel on HRQoL was not investigated in Study 201 with the submission instead reporting results from the PROVe study. The submission used the results from Graier et al. 2020 for phototherapy. The PBAC noted these two single-arm studies used different disease-specific instruments for the assessment of quality of life in patients with MF-CTCL (see paragraph 6.20) and advised that no valid conclusions could be drawn from this comparison. As such, the PBAC considered that the claim of superior comparative effectiveness compared to phototherapy with respect to HRQoL was not adequately supported by the data.
- 7.6 The PBAC noted the most frequent adverse events (AEs) in Study 201 were skin-related, characterised mainly as local dermatitis, pruritis and erythema. The PBAC agreed with the submission that it was difficult to compare chlormethine gel and phototherapy AE profiles given the different frequencies of administration and duration (see paragraph 6.25). As such, the PBAC considered that the claim of non-inferior safety was not adequately supported by the data but that the safety of chlormethine gel was manageable, given the intended use.
- 7.7 The PBAC noted that the CUA relied on the claim that chlormethine gel was superior with respect to HRQoL versus phototherapy. This claim was based on an assumed difference in quality of life in favour of chlormethine gel from a comparison of HRQoL during long-term therapy via the modelled economic evaluation. The HRQoL data informing the economic model was based on data derived from a de novo vignette study. As outlined in paragraph 7.5, the PBAC considered the claim of superior comparative effectiveness with respect to HRQoL was not supported by data from the PROVe and Graier et al. 2000 studies. The PBAC further considered the approach taken by the submission introduced a disconnect in the evidence base between that evaluated with respect to the clinical claim and that presented for the cost-effectiveness claim. The PBAC acknowledged the difficulty in populating an economic model for a rare disease however, concluded that the economic model was not reliable for decision making as the clinical evidence presented did not provide a reliable basis for undertaking a CUA and hence the cost-effectiveness of chlormethine gel could not be assessed.
- 7.8 The PBAC agreed with the ESC that chlormethine gel may be a useful additional therapeutic option for a niche group of patients. The PBAC considered that use in patients with no more than 25% affected BSA was likely the most appropriate subgroup to benefit from treatment. With phototherapy considered an appropriate comparator the PBAC agreed with the ESC that a cost-minimisation analysis against phototherapy may be a potential way forward in this rare condition.
- 7.9 The PBAC agreed with the DUSC that the financial estimates in the submission were subject to substantial uncertainty around the number of eligible patients, the uptake, and the mean time-on-treatment. The PBAC considered that the data provided in the pre-PBAC response on the average daily grams of chlormethine gel used by participants in Study 201 provided some reassurance that the majority of patients would be adequately served by the proposed maximum quantity of 2 tubes per month

(see paragraph 6.61). However, the PBAC considered that the cost offsets applied to phototherapy were overestimated, given that for a proportion of patients chlormethine gel is likely to be used as an option in addition to phototherapy, not as a substitute for phototherapy. Overall, the PBAC agreed with the DUSC that the utilisation and financial estimates presented in this submission were complex and require substantial changes.

7.10 The PBAC considered a resubmission for chlormethine gel should address the following issues:

- Provide a robust justification for the claim of non-inferior comparative effectiveness versus phototherapy.
- Provide a cost-minimisation analysis against phototherapy as outlined in paragraph 7.8.
- Provide revised financial estimates that address the concerns raised by DUSC as outlined in paragraphs 6.60 and 6.61.

7.11 The resubmission may be lodged at any future standard due date for PBAC submissions using the standard re-entry pathway.

7.12 The PBAC noted that this submission is eligible for an Independent Review.

**Outcome:**

Not recommended

## **8 Context for Decision**

The PBAC helps decide whether and, if so, how medicines should be subsidised through the Pharmaceutical Benefits Scheme (PBS) in Australia. It considers applications regarding the listing of medicines on the PBS and provides advice about other matters relating to the operation of the PBS in this context. A PBAC decision in relation to PBS listings does not necessarily represent a final PBAC view about the merits of the medicine or the circumstances in which it should be made available through the PBS. The PBAC welcomes applications containing new information at any time.

## **9 Sponsor's Comment**

The sponsor had no comment.