

7.01 CHLORMETHINE HYDROCHLORIDE

Gel 160 micrograms per g, 60 g,

Ledaga[®],

Juniper Biologics Pty Ltd.

1 Purpose of submission

- 1.1 The Standard Re-entry resubmission requested a Section 85, Authority Required listing for chlormethine hydrochloride gel (hereafter referred to as chlormethine gel) for the topical treatment of mycosis fungoides-type cutaneous T-cell lymphoma (MF-CTCL). The listing was requested for patients with no more than 25% of body surface area (BSA) involved, who have failed, are intolerant of or have a contraindication to treatment with topical corticosteroids. The Pharmaceutical Benefits Advisory Committee (PBAC) previously considered chlormethine gel for the same indication in March 2023.
- 1.2 Listing was requested on the basis of a cost-minimisation approach (CMA) versus phototherapy.

Table 1: Key components of the clinical issue addressed by the submission (as stated in the resubmission)

Component	Description
Population	Patients with mycosis fungoides-type cutaneous T-cell lymphoma in adult patients with less than 25% BSA impacted.
Intervention	Chlormethine 160 microgram/g topical gel tube, 60g.
Comparator	Skin directed therapies including phototherapy (5% psoralen plus ultraviolet A radiation [PUVA], 95% ultraviolet B [UVB]).
Outcomes	Derived primary outcome: Restricted mean duration of response (complete response). Health-related quality of life (PROVe Study).
Clinical claim	Chlormethine is non-inferior in terms of effectiveness and has similar safety compared to phototherapy.

Source: Table 1-1, p10 of the resubmission.

BSA = Body surface area.

Blue shading indicates information previously seen by the PBAC.

- 1.3 The clinical claim made by the resubmission was that chlormethine gel is non-inferior in terms of effectiveness and has similar safety compared to phototherapy. This differed from the claim made in the March 2023 submission, that chlormethine gel was non-inferior in terms of effectiveness as measured by restricted mean duration of response (rmDOCR), superior in terms of effectiveness based on health-related quality of life (HRQoL) and had similar safety compared to phototherapy.

2 Background

Registration status

- 2.1 Chlormethine gel is registered for use in Australia, having been listed on the ARTG since 22 June 2021 for the topical treatment of MF-CTCL in adult patients.

Chlormethine gel was designated orphan status on 15 August 2019 and granted an extension of orphan status on 4 December 2019.

Previous PBAC consideration

- 2.2 A summary of the key matters of concern from the previous PBAC consideration (March 2023) and how they are addressed in the November 2023 resubmission is presented in Table 2.

Table 2: Summary of key matters of concern

Key issues in previous March 2023 submission	How the resubmission addresses it
Clinical evidence	
Clinical claim of superior effectiveness in term of health-related quality of life (HRQoL) was not supported by the clinical evidence (para 7.1, chlormethine gel, PSD, March 2023 PBAC meeting).	Partially addressed, the clinical claim for effectiveness in terms of HRQoL was revised to a claim of non-inferiority.
Clinical evidence	
The PBAC previously considered that a resubmission for chlormethine gel should provide a robust justification for the claim of non-inferior comparative effectiveness versus phototherapy (para 7.10, chlormethine gel, PSD, March 2023 PBAC meeting). Inconclusive statistical results added to concerns about whether the ITC had satisfactorily established non-inferiority to phototherapy (in terms of restricted mean duration of complete response) (para 7.4, chlormethine gel, PSD, March 2023 PBAC meeting).	Not addressed, the clinical claim for effectiveness in terms of restricted mean duration of complete response was non-inferiority. No further justification or additional clinical evidence was provided in support of the non-inferiority claim.
Economic evaluation	
The use of a CUA was not supported by clinical evidence (para 7.7, chlormethine gel, PSD, March 2023 PBAC meeting). A CMA against phototherapy should be provided in any resubmission (para 7.10, chlormethine gel, PSD, March 2023 PBAC meeting).	Addressed, a CMA was provided.
Utilisation and financial impact	
The utilisation and financial estimate were based on a complex approach, a prevalence approach should be applied (para 6.61, chlormethine gel, PSD, March 2023 PBAC meeting)	Partially addressed, a prevalence approach was utilised, however the evaluation considered the estimates remained subject to considerable uncertainty with regard to the estimated number of patients and the extent of use.
Uncertain eligible population, a review of data sources is needed to inform prevalence and consider age, gender distribution and BSA proportions (para 6.61, chlormethine gel, PSD, March 2023 PBAC meeting)	An additional search for prevalence data was performed by the resubmission, however no new evidence was identified.
Likely higher uptake rate due to convenience of topical therapy (para 6.60, chlormethine gel, PSD, March 2023 PBAC meeting)	Partially addressed, a higher uptake rate was applied in Years 1 and 2.
Underestimated dose of chlormethine gel of no more than two tubes per month of chlormethine gel (para 6.60, chlormethine gel, PSD, March 2023 PBAC meeting)	Addressed, higher dose estimated at 1 tube per month for 0%-10% BSA involvement and 2 tubes per month for 10%-25% BSA involvement.
The financial estimates assumed patients would receive 48 months of chlormethine gel treatment. No data were provided regarding the duration of use and efficacy beyond the 10-month follow-up in Study 201 (para 6.60, chlormethine gel, PSD, March 2023 PBAC meeting)	Not addressed, the resubmission maintained the application of the 48 months duration of treatment. No new data were presented to support the assumed treatment duration.
Overestimated cost-offset of phototherapy by assuming that each year of chlormethine gel would replace a full year of phototherapy. Ongoing annual treatment of phototherapy treatment is unlikely (the comparator trials only administered phototherapy for 12 to 24 weeks of approximately 40 sessions) (para 6.60, chlormethine gel, PSD, March 2023 PBAC meeting).	Addressed, a treatment duration of 39 sessions (13 weeks) for phototherapy was applied.
Did not consider displacement of phototherapy or combination use of chlormethine gel with phototherapy (para 6.60, chlormethine gel, PSD, March 2023 PBAC meeting and para 7.9, chlormethine gel, PSD, March 2023 PBAC meeting)	Partially addressed, the resubmission assumed that the proportions of concurrent use and replacement are ■■■% and ■■■% respectively. The resubmission did not consider the displacement of phototherapy.

Source: developed during the evaluation.

BSA = body surface area; CUA = cost-utility analysis; CMA = cost-minimisation approach; HRQoL = health-related quality of life; ITC = indirect treatment comparison; PBAC = Pharmaceutical Benefits Advisory Committee; PSD = public document summary.

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

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 pack	product	Dispensed Price Max quantity	PBS item code	Max. qty packs	Max. qty units	No. of Rpts	Available brands
chlormethine (160 microgram/g) gel, 60 g	0.016%	\$ published (\$ \$ effective (\$	NEW	24	24	5	Ledaga Juniper Biologics
Restriction Summary [new] / Treatment of Concept: [new]							
Category / Program: General Schedule (Code GE)							
Prescriber type: <input checked="" type="checkbox"/> Medical Practitioners							
Restriction type: <input checked="" type="checkbox"/> Authority Required (telephone/online PBS Authorities system)							
Condition: Mycosis fungoides cutaneous T-cell Lymphoma							
Indication: Mycosis fungoides cutaneous T-cell Lymphoma							
Treatment Phase: Initial treatment							
Clinical criteria:							
The condition must be any of: (i) Stage IA, (ii) IIA, (iii) IB mycosis fungoides cutaneous T-cell Lymphoma							
AND							
Clinical criteria:							
The condition must have been confirmed through a diagnostic lesion biopsy from an Approved Pathology Authority							
AND							
Clinical criteria:							
Patients must have either of which: (i) failed treatment with topical corticosteroids, OR (ii) have intolerance/contraindication to topical corticosteroids.							
AND							
The condition must cover no more than 10% of the patient's body surface area. <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>							
Treatment criteria:							
Patient must be treated by a dermatologist or haematologist							
AND							
<i>The treatment must be approved for 1 unit if the condition is no more than 10% of the patient's body surface area to provide 4 weeks of treatment per script; OR</i>							
<i>The treatment must be approved for 2 units if the condition is no more than 25% of the patient's body surface area to provide 4 weeks of treatment per script</i>							
Population criteria:							
Patient must be at least 18 years of age;							
Prescribing Instructions:							
The medical practitioner should request 1 pack for patients with no more than 10% of the patients body surface affected.							
Prescribing Instructions:							

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

Price in brackets updated by the evaluation based on the mark-ups effective 1 July 2023 and calculated using the pricing calculator effective from 1 July 2023.

MEDICINAL PRODUCT medicinal product pack	PBS item code	Max. qty pk	Max. qty un	No. of Rpts	Available brands
chlormethine 0.016% (160 microgram/g) gel, 60 g	NEW	2	2	5	Ledaga Juniper Biologics
Restriction Summary [new] / Treatment of Concept: [new]					
Concept ID (for internal Dept. use)	Category / Program: General Schedule (Code GE)				
	Prescriber type: <input checked="" type="checkbox"/> Medical Practitioners				
	Restriction type: <input checked="" type="checkbox"/> Authority Required – immediate/real time assessment by Services Australia (telephone/online PBS Authorities system)				
	Indication: Mycosis fungoides cutaneous T-cell Lymphoma				
	Treatment Phase: Initial treatment				
	Clinical criteria:				

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	The condition must be any of: (i) Stage IA, (ii) IIA, (iii) IB mycosis fungoides cutaneous T-cell Lymphoma, AND
	Clinical criteria:
	The condition must have been confirmed through a diagnostic lesion biopsy from an Approved Pathology Authority, AND
	Clinical criteria:
	Patients must have either: failed treatment with topical corticosteroids, OR have intolerance/contraindication to topical corticosteroids, AND
	The condition must cover no more than 10-25% of the patient's body surface.
	Treatment criteria:
	Patient must be treated by a dermatologist or haematologist
	Population criteria:
	Patient must be at least 18 years of age
	Prescribing Instructions:
	The medical practitioner should request 2 packs for patients with no more than 25% of the patient's body surface area affected to provide 4 weeks of treatment. Confirmation of eligibility for treatment with diagnostic reports must be documented in the patient's medical records.
	Administrative Advice: Applications for authorisation under this restriction may be made in real time using the Online PBS Authorities system (see www.servicesaustralia.gov.au/HPOS) or by telephone by contacting Services Australia on 1800 888 333.
	Category / Program: General Schedule (Code GE)
	Prescriber type: <input checked="" type="checkbox"/> Medical Practitioners
	Restriction type: <input checked="" type="checkbox"/> Authority Required (STREAMLINED)
	Indication: Mycosis fungoides cutaneous T-cell Lymphoma
	Treatment Phase: Continuing treatment
	Treatment criteria:-
	Clinical criteria:
	Patient must have previously received PBS subsidised treatment with this drug for this condition, AND
	Clinical criteria:
	Patient must not have developed disease progression while receiving PBS subsidised treatment with this drug for this condition, AND
	The condition must cover 10-25% of the patient's body surface.
	Population criteria:
	Patient must be at least 18 years of age.
	Prescribing Instructions:
	The medical practitioner should request 2 packs for patients with no more than 25% of the patient's body surface to provide 4 weeks of treatment.
	Administrative Advice: Applications for authorisation under this restriction may be made in real time using the Online PBS Authorities system (see www.servicesaustralia.gov.au/HPOS) or by telephone by contacting Services Australia on 1800 888 333.

- 3.2 The resubmission proposed a special pricing arrangement with an effective AEMP of \$| per tube and a published AEMP of \$| per tube. The effective AEMP was |% lower than proposed in the March 2023 pre-PBAC response (\$| per tube).
- 3.3 Each tube contains 60 grams of chlormethine gel. The resubmission specified separate restrictions for patients with disease that affected no more than 10% or 10% to 25% BSA involvement, to facilitate the greater quantity required to treat larger BSA involvement. The PBAC previously considered that 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 (para 3.3, chlormethine gel, Public Summary Document (PSD), March 2023 PBAC meeting). The resubmission argued that two separate restrictions (based on levels of BSA involvement) is more appropriate as this approach is one that clinicians are already used to with other PBS-listed skin directed treatments (e.g. betamethasone dipropionate and methylprednisolone acetonate). The Pre-Sub-Committee Response (PSCR) stated the sponsor is amenable to a combined listing that includes both patients with a BSA involvement of no more than 10% and 10% to 25%.

- 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.
- 3.5 The PBAC previously considered that the data provided in the March 2023 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 (para 7.9, chlormethine gel, PSD, March 2023 PBAC meeting). However, based on the individual patient data from Study 201 provided in the resubmission, 13.64% of patients with BSA involvement $\leq 25\%$ would require more than 2 tubes of chlormethine gel per month, exceeding the proposed maximum quantity. Prescribers will have the option of requesting a larger maximum quantity (via special Authority for increased maximum quantities) for those patients requiring more than 2 tubes per month.
- 3.6 The proposed criteria restrict use to patients with $\leq 25\%$ 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. The PBAC previously considered that patients with no more than 25% affected BSA was likely the most appropriate subgroup to benefit from treatment (para 7.8, chlormethine gel, PSD, March 2023 PBAC meeting).

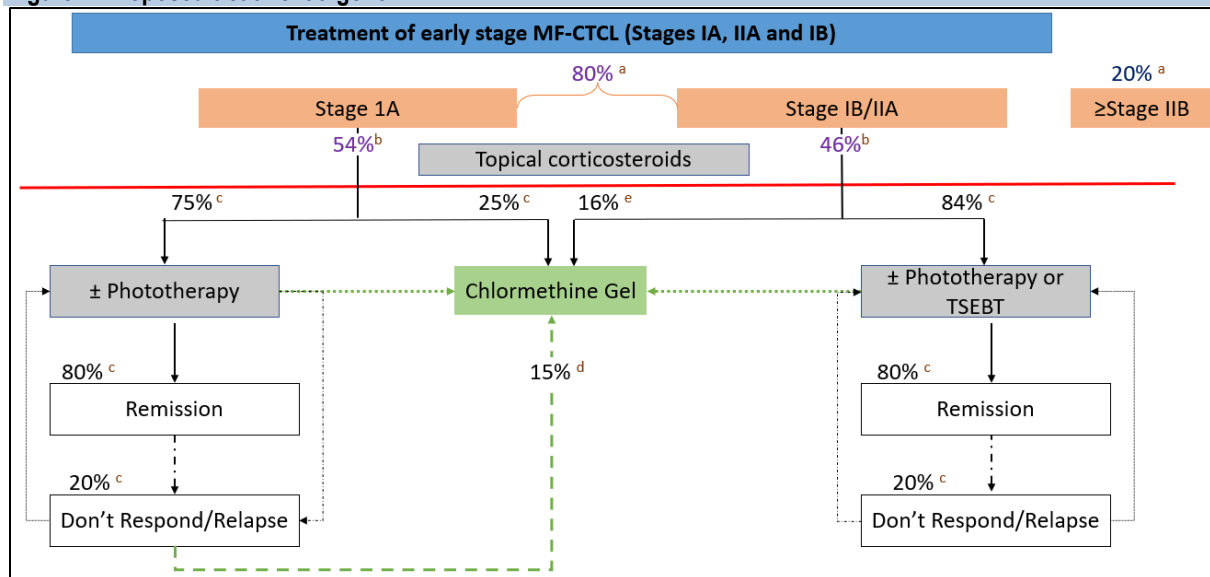
For more detail on PBAC's view, see section 7 PBAC outcome.

4 Population and disease

- 4.1 The description of the population and disease provided by the resubmission was unchanged from the March 2023 submission. Primary cutaneous lymphomas are a heterogenous 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. 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 resubmission stated the estimated incidence 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. Two measures were referred to for assessment of MF-CTCL severity:
- The Composite Assessment of Index Lesion Severity (CAILS) 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, 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 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 resubmission requested listing of chlormethine gel for MF-CTCL in adult patients who have no more than 25% of their BSA involved.
- 4.5 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, p6, chlormethine gel, PSD, March 2023 PBAC meeting.

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

a Based on US incidence rates taken from the National Cancer Institute between 1972 and 2001 and PROCLIP registry; b As reported in the model based on study 201; c Australian specialist input; d Estimated 15% ($=0.2 \times 0.75$) of Stage IA patients; e Estimated 16% ($=0.25 \times 0.63$) 63% ($=34/54$) of Stage IIA and IB patients had $\leq 25\%$ of their body surface area affected - Study 201 individual patient data analysis. Blue shading indicates information previously seen by the PBAC

4.6 The proposed treatment algorithm does not provide a comprehensive overview of treatments for MF-CTCL in Australia; a recent Australian Clinical Practice Statement¹ 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.

Systemic treatments (potentially in combination with skin-directed therapy) may be considered in patients who are refractory to skin-directed therapy alone.

4.7 The pre-PBAC response stated that skin directed therapies, including chlormethine gel and phototherapy, are recommended as primary treatment options for early stage MF-CTCL with limited skin involvement in the Australian and NCCN treatment guidelines as they can provide disease control without major cumulative toxicities. The pre-PBAC response argued that there is a particular disadvantage of phototherapy for people with limited skin disease (disease covering less than 10% of BSA), because the whole skin is exposed to UV radiation, which carries a long term risk of inducing skin cancer. The pre-PBAC response also stated that chlormethine gel would provide an alternative topical therapy option for patients with hairy area's involved (scalp, beard etc.), those living in rural areas that have limited access to phototherapy, patients who are claustrophobic and for those who have patches and plaques on body surface areas that are difficult to treat with phototherapy (e.g. groin area, under the breast) or those not responding to phototherapy.

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

5 Comparator

5.1 The resubmission nominated phototherapy (both PUVA and NB UVB) as the main comparator. The nominated comparator was consistent with the March 2023 submission and was previously considered by the PBAC to be reasonable. The PBAC also noted that some patients may use chlormethine gel concurrently with

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

phototherapy or after phototherapy (para 7.2, chlormethine gel, PSD, March 2023 PBAC meeting). The Economic Sub-Committee (ESC) considered the comparator was appropriate.

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

6 Consideration of the evidence

Sponsor hearing

6.1 There was no hearing for this item.

Consumer comments

6.2 The PBAC noted and welcomed the input from a health care professional (1) and an organisation (1) via the Consumer Comments facility on the PBS website. The comments from the health care professional described the impact of MF-CTCL on patients' quality of life noting it can be highly visible and uncomfortable. The health care professional also outlined the advantage of an easy to use pre-prepared topical preparation, especially for patients with smaller areas of skin involved. The comments from Rare Cancers Australia also emphasised the impact of MF-CTCL on patients' quality of life and described chlormethine as having an improved adverse effect profile (including lower risk of alopecia, nausea and vomiting) compared to other available treatments. The PBAC noted the consumer comments concurred with those received in March 2023 (para 6.2, chlormethine gel, PSD, March 2023 PBAC meeting).

Clinical trials

6.3 No new clinical evidence was presented in the resubmission. Instead, the resubmission provided a brief summary of trial results presented in the March 2023 submission.

6.4 The resubmission re-presented an analysis of clinical trials studying the use of chlormethine gel and phototherapy in patients with early-stage MF-CTCL. The two studies for chlormethine gel were Study 201, a randomised controlled trial (chlormethine ointment as control), and PROVe, a prospective observational study. Three randomised controlled trials were included for phototherapy (El-Mofty 2012, Whittaker 2012, and Vieyra-Garcia 2019).

6.5 These studies did not include a common reference arm that would have permitted an anchored indirect treatment comparison (ITC) of chlormethine gel against phototherapy. As such, the resubmission re-presented an unanchored 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.

6.6 Details of the trials presented in the resubmission are provided in Table 3.

Table 3: Trials and associated reports presented in the March 2023 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>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>July 2010</p> <p>JAMA dermatology 2013; 149(1): 25-32</p> <p>Retrieved Sept 2022 https://clinicaltrials.gov/ct2/show/NCT00168064.</p> <p>EORTC 2022. Madrid Spain.</p> <p>Clinical Lymphoma, Myeloma and Leukemia 2021; 21(2): 119-124.</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 https://www.tga.gov.au/sites/default/files/auspar-chlormethine-hydrochloride-210902.pdf.</p> <p>Retrieved Sept 2022, from https://www.ema.europa.eu/en/documents/assessment-report/ledaga-epar-public-assessment-report_en.pdf.</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>Retrieved Sept 2022, from https://clinicaltrials.gov/show/NCT02296164.</p> <p>Am J Clin Dermatol 2021; 22(3): 407-411.</p>

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Trial ID	Protocol title/ Publication title	Publication citation
	Kim, E., E. Gilmore, B. Poligone and C. Querfeld. Chlormethine Gel for Mycosis Fungoides T-cell Lymphoma: Recent Real-World Data.	EMJ 2020; 5(2): 37-41.
Phototherapy trials		
EI-Mofty 2012	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. Medical University of Graz. (2012). "NCT01686594: PUVA Maintenance Therapy in Mycosis Fungoides"	Photodermatol Photoimmunol Photomed 2012; 28(5): 274-277. Retrieved Sept 2022, from https://ClinicalTrials.gov/show/NCT01686594 .
Vieyra-Garcia 2019	Vieyra-Garcia, P., R. Fink-Puches, S. Porkert, R. Lang, S. Pochlauer, G. Ratzinger, A. Tanew, S. Selhofer, S. Paul-Gunther, A. Hofer, A. Gruber-Wackemagel, 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.	JAMA dermatology 2019; 155(5): 538-547.
	Anonymous. "Wording Errors in Abstract, Numeric Errors in Results, and Labeling Errors in Figure 2"	JAMA Dermatol 2019; 155(5): 638. Correction to Vieyra-Garcia 2019
	Vieyra-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.	Journal of Investigative Dermatology 2018; 138(5 Suppl 1): S98.
	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-Wackemagel, 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-Wackemagel, 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 https://www.clinicaltrials.gov/ct2/show/NCT00056056 .

Trial ID	Protocol title/ Publication title	Publication citation
	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, pp9-11, chlormethine gel, PSD, March 2023 PBAC meeting.

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

Blue shading indicates information previously seen by the PBAC.

6.7 The key features of the included studies are summarised in Table 4.

Table 4: Key features of the included evidence

Trial	N	Design/ duration	Treatment regimen	Risk of bias	Patient population	Outcomes	Use in CMA
Chlormethine							
Study 201	260	R, SB 12 mths	Daily	Low-Moderate	Stage IA-IIA MF-CTCL	CR, PR, DoR, SD, PD, TFR, safety	Used (dose)
PROVe	298	P, OS 24 mths	Not available	High	Stage IA-IV MF-CTCL	ORR ^a , QoL, safety	Not used
Phototherapy							
El-Mofty 2012	30	R, DB 36 mths	PUVA 3 sessions/week for 40 sessions	Low	Stage IA-IB MF-CTCL	CR, safety	Not used
Whittaker 2012	93	R, SB 76 mths	PUVA 3 sessions/week for up to 16 weeks	Low-Moderate	Stage IB-IIA MF-CTCL	CR, PR, SD, PD, TTR, DoR, safety	Not used
Vieyra-Garcia 2019	27	R, DB 60 months	PUVA 2 sessions/week for 12 to 24 weeks	Low-Moderate	Stage IA-IB MF-CTCL	CR, PR, TTR, safety	Not used

Source: Table 3, p12 of chlormethine gel, PSD, March 2023 PBAC meeting, Table 2.4.3, pp70-71 of the March 2023 evaluation report, p539 Vieyra-Garcia 2019, p680 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; PUVA = psoralen ultraviolet; 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.

Blue shading indicates information previously seen by the PBAC.

6.8 The risk of bias in Study 201, El-Mofty 2012, Vieyra-Garcia 2019 and Whittaker 2012 was low to moderate, with PROVe having a high likelihood of high selection, performance, and detection bias. The ITC was based on the single arms of Study 201, El Mofty 2012, Whittaker 2012 and Vieyra-Garcia 2019.

6.9 The primary efficacy endpoint in Study 201 was a $\geq 50\%$ improvement in the CAILS score (i.e., a partial response (PR) or a complete response (CR)) compared to baseline. The phototherapy studies used different measures for assessment (treatment

response including CR, PR and duration of response), with Vieyra-Garcia 2019 reporting 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 March 2023 submission conducted an analysis using rmDOCR, a bespoke outcome measure derived for the purposes of the submission. The rmDOCR was defined by CR occurrence and duration of response measured in the respective intention to treat (ITT) analyses. The ESC previously considered that while the empirical application of rmDOCR appeared statistically sound, there were transitivity concerns regarding its use in the ITC (para 6.11, chlormethine gel, PSD, March 2023 PBAC meeting).
- 6.11 As for the March 2023 submission, the resubmission did not nominate a non-inferiority margin for rmDOCR. The non-inferiority finding in the unanchored 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.

Comparative effectiveness

- 6.12 A summary of the results for the primary outcome measures is presented in Table 5. In Study 201 the confirmed response rate (CR+PR) was higher for chlormethine gel (58.5%) compared to chlormethine ointment (47.7%). In the phototherapy studies, the CR rate varied from 22.2% in Whittaker 2012 to 70.4% in Vieyra-Garcia 2019 and 73.3% in El-Mofty 2012. The PR rate reported was 48.9% in Whittaker 2012 and 29.6% in Vieyra-Garcia 2019.

Table 5: Results of complete response and partial response across the single-arm studies

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

Source: Table 5, p16 of chlormethine gel, PSD, March 2023 PBAC meeting.

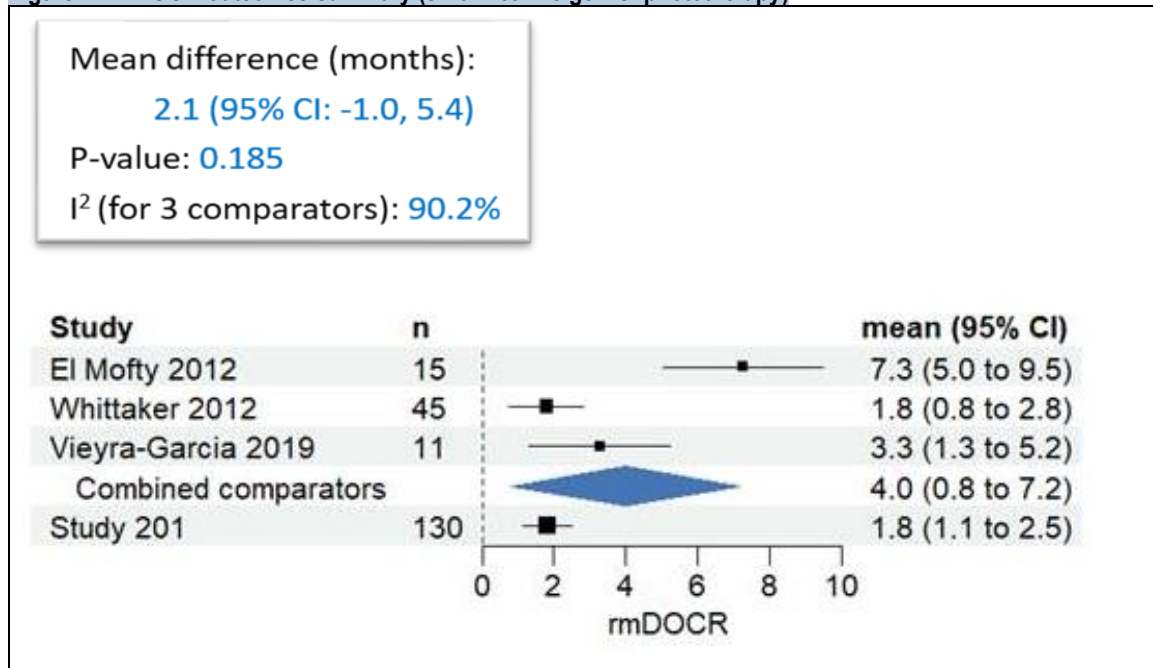
CAILS = Composite Assessment of Index Lesion Severity index; CR=complete response; mSWAT = The modified Severity Weighted Assessment Tool; n=number of participants with event; N=total participants in group; PR=partial response; PUVA= psoralen ultraviolet A.

^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

Blue shading indicates information previously seen by the PBAC.

6.13 A summary of the results from the unanchored ITC are presented in Figure 2.

Figure 2: rmDOCR outcomes summary (chlormethine gel vs. phototherapy)



Source: Figure 3, p18 of chlormethine gel, PSD, March 2023 PBAC meeting.

I²=heterogeneity statistic; CI=confidence interval; n = number of participants with event; rmDOCR=restricted mean duration of complete response

Blue shading indicates information previously seen by the PBAC.

6.14 The results of the ITC indicated no statistically significant difference in rmDOCR between the treatments (mean difference in months = 2.1; 95% CI: -1.0 to 5.4; p=0.185). However, as noted in the March 2023 evaluation, the results from the ITC is difficult to interpret due to the nature of the comparison, variability in response definitions, and high study heterogeneity (I² > 90%).

6.15 The March 2023 evaluation noted the following decisions biased the ITC in favour of chlormethine gel:

- Differences in duration of follow-up: the analysis was limited to a 10-month follow-up for Study 201, while comparator studies had longer follow-ups (20, 36, and 76 months), that were censored at 10 months in the ITC (para 6.18, chlormethine gel, PSD, March 2023 PBAC meeting).
- Differences in response assessment: In Study 201 the classification of CR was based on CAILS scores, 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, meaning patients may be classified as a ‘complete responder’ by the CAILS score, but not mSWAT CR. The March 2023 PSCR 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, and that 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 reiterated its March 2023 advice that the use of 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 (para 6.18, chlormethine gel, PSD, March 2023 PBAC meeting).

- Conduct of the ITC: The ITC classified 28 (21.5%) chlormethine gel patients as 'complete responders' – 10 more than reported in Study 201. The ESC previously considered the 10 patients classified as having a CR during the post hoc analysis of Study 201 should be excluded from the analysis (para 6.18, chlormethine gel, PSD, March 2023 PBAC meeting).

6.16 HRQoL was not investigated in Study 201. The resubmission re-presented the results from the PROVe study for chlormethine gel and Graier 2020 (a publication arising from the same study as Veiyra-Garcia 2019) 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 2020). In March 2023, the ESC noted the statements in the PSCR that the submission included the best available data on HRQoL. However, at that time the ESC remained concerned about the validity of the HRQoL comparison between chlormethine and phototherapy, given it relied on different questionnaires from single-arm studies (para 6.20, chlormethine gel, PSD, March 2023 PBAC meeting).

Comparative harms

6.17 A summary of the safety outcomes from the March 2023 submission is presented in Table 6. There were comparable treatment emergent adverse events (TEAEs) between chlormethine gel and chlormethine ointment (21% versus 17%). The most frequent adverse events (AEs) in Study 201 were skin-related, characterised mainly as local dermatitis (skin irritation), pruritis and erythema. AEs reported in the phototherapy studies included nausea, pruritus, dryness, and photosensitivity, sometimes requiring steroid use or dose reduction. The PBAC previously noted that it was difficult to compare chlormethine gel and phototherapy AE profiles given the different frequencies of administration and duration (para 7.6, chlormethine gel, PSD, March 2023 PBAC meeting).

Table 6: Summary of key adverse events in Study 201 (safety set)

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

Source: Table 7, p18 of chlormethine gel, PSD, March 2023 PBAC meeting.

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

^a Fisher's exact test.

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

^c No SAEs were considered possibly, probably or definitely related to study drug.

^d 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.

^e This was reported as an SAE not related to study drug

Blue shading indicates information previously seen by the PBAC.

Benefits/harms

6.18 A benefits and harms table was not presented as the resubmission made a claim of non-inferiority.

Clinical claim

6.19 The resubmission's clinical claim was that chlormethine gel is non-inferior in effectiveness and has similar safety to phototherapy. This differed from the claim in the March 2023 submission, which asserted non-inferiority in terms of effectiveness based on rmDOCR and superiority in terms of HRQoL compared to phototherapy.

6.20 In March 2023, the PBAC considered that there were issues of transitivity affecting the comparability of the studies included in the unanchored ITC 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. At that time, the PBAC considered 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 differences in the classification of CR across the trials. In addition, in March 2023 the PBAC noted that although the ITC result was not statistically significant ($p=0.185$), the point estimate favoured phototherapy (mean difference in rmDOCR = 2.1 months) with a wide confidence interval (-1.0, 5.4). The PBAC previously considered that non-inferiority to phototherapy was difficult to definitively establish given the limited available data for this rare condition (para 7.4, chlormethine gel, PSD, March 2023 PBAC meeting).

- 6.21 The PBAC previously suggested that a resubmission for chlormethine gel should provide a robust justification for the claim of non-inferior comparative effectiveness versus phototherapy (para 7.10, chlormethine gel, PSD, March 2023 PBAC meeting). The resubmission did not provide any new clinical evidence or further justification to support its claim of non-inferior effectiveness in terms of rmDOCR. The ESC considered that without any change in the clinical data or analysis, the resubmission has not robustly justified the claim of non-inferior clinical efficacy to phototherapy. The ESC considered that a claim of non-inferior effectiveness based on rmDOCR may be appropriate in this rare condition but it remained highly uncertain.
- 6.22 The PBAC previously considered that it was difficult to compare chlormethine gel and phototherapy AE profiles given the different frequencies of administration and duration. In March 2023, the PBAC advised 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 (para 7.6, chlormethine gel, PSD, March 2023 PBAC meeting).
- 6.23 The PBAC agreed with the ESC (see paragraph 6.21) that the claim of non-inferior comparative effectiveness was highly uncertain but likely reasonable in this rare condition.
- 6.24 The PBAC considered that the claim of non-inferior comparative safety was not adequately supported by the data but reaffirmed its March 2023 advice that the safety of chlormethine gel was manageable, given the intended use.

Economic analysis

- 6.25 The resubmission presented a CMA comparing chlormethine gel with phototherapy. The presentation of a CMA aligns with the PBAC's previous advice that a CMA should be provided in a subsequent submission for chlormethine gel (para 7.10, chlormethine gel, PSD, March 2023 PBAC meeting).
- 6.26 The key components and assumptions of the CMA are presented in Table 7.

Table 7: Key components and assumptions of the cost-minimisation approach

Component	Claim or assumption
Therapeutic claim: effectiveness	Chlormethine gel is non-inferior in terms of effectiveness compared to phototherapy.
Therapeutic claim: safety	Chlormethine gel has similar safety compared to phototherapy.
Evidence base	Unanchored indirect treatment comparison of restricted mean duration of complete response between one study for chlormethine gel (Study 201) vs three studies for phototherapy (El Mofty 2012, Whittaker 2012, Veyra-Garcia 2019), naïve comparison of health-related quality of life (HRQoL) between PROVe for chlormethine gel and Graier 2020 for phototherapy.
Equi-effective doses	26.90 grams/month of chlormethine gel is equivalent to 13.04 sessions/month of phototherapy.
Direct costs	Phototherapy at a cost of \$727.35 per month.
Other costs or cost offsets	None included.

Source: Compiled during the evaluation based on Table 1-1, p10; pp20-22; Table 3-1 p25 of the resubmission.

- 6.27 The resubmission estimated equi-effective doses of 26.90 grams/month of chlormethine gel and 13.04 phototherapy sessions per month. The equi-effective dose of chlormethine gel was underestimated for the following reasons:
- The resubmission did not consider the mean duration of treatment, thereby assuming equivalent and ongoing treatment of chlormethine gel and phototherapy. The Drug Utilisation Sub-Committee (DUSC) previously considered it was unlikely that a year of chlormethine gel would replace a full year of phototherapy and noted the comparator trials only administered phototherapy for 12 to 24 weeks with an approximation of 40 sessions, and that in Study 201, the mean duration of treatment was 9 months (para 6.60, chlormethine gel, PSD, March 2023 PBAC meeting). The financial estimates assumed the duration of treatment to be 13 weeks (39 sessions) for phototherapy and 48 months for chlormethine gel. The PSCR argued that both the chlormethine gel and phototherapy are intended for an ongoing treatment, and therefore the use of steady state dose is more relevant. The PSCR stated that the treatments are taken as long as they are tolerated because neither phototherapy, nor chlormethine, provide therapeutic benefits once treatments are ceased. The PSCR also noted that the duration of response to phototherapy was 9.7 months in Whittaker 2012 but argued that phototherapy ceases earlier than chlormethine gel due to safety concerns rather than cure. The ESC considered that given the limitations of the available clinical evidence it was not possible to reliably account for the comparative treatment duration of chlormethine and phototherapy in the CMA.
 - The resubmission assumed patients would receive 3.44 administrations per week of chlormethine gel, based on the French Temporary Use Authorization study. The evaluation considered this resulted in a potential double counting of the dose reductions in Study 201 as the dose reported in Study 201 is the average daily dose and therefore already accounts for any reductions in frequency of administration. The PSCR argued that there is no double counting of dose reductions as Study 201 mandated daily application of chlormethine. The ESC noted that 39.2% of patients in Study 201 did not apply chlormethine gel every day (Table 11, p62 of the Study 201 CSR). As such, the ESC agreed with the evaluation that any reductions in frequency are already accounted for in the calculation of the average daily dose from Study 201. The pre-PBAC response stated that 60.8% of patients in Study 201 applied chlormethine gel daily, with a further 24.6% and 12.3% doing so between 4-6 times per week and 1-3 times per week respectively. The pre-PBAC response argued that using the mid-point of these ranges, the 130 patients applied chlormethine gel a weighted mean of 5.73 times per week.
- 6.28 A summary of the results from the CMA as conducted in the resubmission is presented in Table 8.

Table 8: Results of the resubmission’s cost-minimisation approach

Component	Chlormethine			Phototherapy
	Source	Estimate	Source	Estimate
Cost per phototherapy administration	-	-	MBS 14050	\$55.80
Mean dose	Study 201 (median dose)	1.80 g	-	-
Number of administrations per week	French ATU study	3.44	Guidelines	3 (sessions)
Number of weeks per month		4.35		4.35
Total monthly usage		26.90g		13.04 (sessions)
Cost per month		\$█		\$727.35
Cost per tube of 60 g chlormethine at published AEMP price		\$█		
Cost per tube of 60 g chlormethine at effective AEMP price		\$█		

Source: Table 3-1, p25 of the resubmission

AEMP = approved ex-manufacturer price; ATU = Temporary Use Authorization; g = gram; MBS = Medicare Benefit Schedule

- 6.29 The resubmission estimated a cost per month of phototherapy of \$727.35. Based on this, the resubmission estimated that the cost per month of chlormethine gel is \$█, equivalent to \$█ per 60 gram tube which the submission proposed to be a published AEMP. The resubmission proposed a █% reduction to the published AEMP resulting in an effective AEMP of \$█ per tube.
- 6.30 Threshold analyses conducted during the evaluation showed that an effective AEMP of \$█ per tube of chlormethine gel was equivalent to █ sessions per year (█ sessions per month) of phototherapy.
- 6.31 During the evaluation the cost-minimised price of chlormethine gel was re-estimated (Table 9) using a total of 40 phototherapy sessions, the mean dose of chlormethine gel for patients with a BSA ≤ 25% from Study 201 (1.84 grams per day), treatment duration from Study 201 (9 months) and assuming daily administration of chlormethine gel. In addition, the evaluation updated the fee for MBS item 14050, based on the MBS effective 1 July 2023. The AEMP re-estimated by the evaluation was \$█ per 60 gram tube. The ESC considered that the adjustments for the comparative treatment duration of chlormethine and phototherapy in the CMA were unreliable (see paragraph 6.27) and proposed the cost-minimised price of chlormethine be re-estimated using alternative inputs (see paragraph 6.32).

Table 9: Re-estimation of the CMA conducted by the evaluation

Component	Chlormethine gel		Phototherapy
	Per the resubmission (base case) ^a	Per the evaluation	
Cost per phototherapy administration	-	-	\$57.80
Mean dose	1.80 g	1.84 g	-
Number of administrations per week	3.44	7.00	3 (sessions)
Number of weeks per month	4.35	4.35	4.35
Total monthly usage	26.90 g	56.03 g	13.04 sessions
Cost per month	\$█	-	\$753.71
Duration of treatment	-	9 months	-
Total usage	-	504.25 g	40 sessions ^b
Cost-minimised per tube of 60 g chlormethine	\$█	\$█ ^c	-

Source: developed during the evaluation

AEMP = approved ex-manufacturer price; CMA = cost-minimisation approach; d = day; g = gram

^a with updated fee for MBS item 14050, based on the MBS effective 1 July 2023.

^b based on the comparator trials that administered phototherapy for approximately 40 sessions (para 6.60, chlormethine gel, PSD, Mar 2023 PBAC meeting).

^c cost-minimised price of chlormethine gel accounting for duration of treatment for both chlormethine gel and 40 sessions of phototherapy = \$█/g; total cost of phototherapy at 40 sessions = \$█/total usage of chlormethine gel of 504.25 g.

6.32 As outlined in paragraph 6.27, the ESC considered that given the limitations of the available clinical evidence it was not possible to consider the comparative treatment duration of chlormethine and phototherapy in the CMA. Instead, the ESC considered it would be reasonable to conduct the CMA over a one month period. As also outlined in paragraph 6.27, the ESC agreed with the evaluation that reductions in frequency are already accounted for in the calculation of the average daily dose from Study 201. Therefore, the ESC advised that a more appropriate approach would be to conduct the CMA over a one month period using the average daily dose from Study 201 (1.84 gram) administered on a daily basis. The ESC noted the resulting re-estimated cost-minimised price of chlormethine gel was \$█ per 60 gram tube (Table 10).

Table 10: Re-estimation of the CMA as requested by the ESC

Component	Chlormethine gel	Phototherapy
Cost per phototherapy administration	-	\$57.80
Mean dose	1.84 g	-
Number of administrations per week	7.00	3 (sessions)
Number of weeks per month	4.35	4.35
Total monthly usage	56.03 g	13.04 sessions
Cost per month	-	\$753.71
Cost-minimised per tube of 60 g chlormethine	\$█	-

Source: compiled during the development of the ESC Advice

CMA = cost-minimisation approach; d = day; g = gram

^a with updated fee for MBS item 14050, based on the MBS effective 1 July 2023.

Treatment cost/patient/month

6.33 A summary of treatment costs per patient per month is presented in Table 11. The treatment costs of chlormethine gel were inconsistent across the different sections of the resubmission with the cost per patient estimated to be \$█ in the financial estimates,

compared with \$█ in the CMA, and \$█ based on Study 201. The main reasons for the difference are the discrepancy in the mean dose and number of administrations per week.

Table 11: Drug cost per patient per month for chlormethine gel and administration cost per month for phototherapy

	Chlormethine gel			Phototherapy		
	Trial	CMA	Financial estimates	Trial	CMA	Financial estimates
Mean dose	1.84 g/day ^a	1.80 g	2.79 g/day	3 sessions	3 sessions	3 sessions
Frequency of application	Daily	3.44 times/week	Daily	Weekly	Weekly	Weekly
Mean duration	9 months	Not applied	39 months ^b	40 sessions ^c	Not applied	39 sessions
Cost/patient/month	█ ^d	█ ^d	█ ^d	\$753.71	\$753.71	\$753.71

Source: compiled during the evaluation.

CMA = cost-minimisation approach; g = gram.

^a daily dose based on Study 201 individual patient data (patients with BSA ≤ 25%) extracted from Sheet Study 201 of resubmission's Excel financial model.

^b 39.14 months based on assumption that 78.9% of patients receive treatment for 48 months and 21.1% of patients receive 6 months of treatment.

^c based on the comparator trials that administered phototherapy for approximately 40 sessions (para 6.60, chlormethine gel, PSD, Mar 2023 PBAC meeting)

^d based on the proposed effective AEMP of \$█ per tube

Estimated PBS usage & financial implications

6.34 This resubmission was not considered by DUSC. The resubmission applied a prevalence approach to estimate the financial implications of listing chlormethine gel. This approach was consistent with the DUSC advice for the March 2023 submission (para 6.61, chlormethine gel, PSD, March 2023 PBAC meeting). At that time, the PBAC considered that there was substantial uncertainty around the number of eligible patients, the uptake, and the mean time-on-treatment (para 7.9, chlormethine gel, PSD, March 2023 PBAC meeting). The approach adopted by the resubmission remained subject to uncertainty, particularly around the eligible number of patients, uptake rate and mean time-on-treatment. A summary of the key inputs relied on for the financial estimates for the March 2023 and this resubmission is presented in Table 12.

Table 12: Key inputs for financial estimates

Input	March 2023 submission	November 2023 (current) resubmission	Evaluation comments
Prevalence of MF-CTCL	8.09 per 100,000 adult population based on data from England and Wales	8.09 per 100,000 adult population based on data from England and Wales	Remains uncertain, no further evidence identified in an additional search performed by the resubmission.
Receiving skin directed monotherapy	Not applied	55.80% (D'Agostino et. al. 2019)	Reasonable, consistent with the rate noted in the March 2023 PSD (Table 13, chlormethine gel, PSD, March 2023 PBAC meeting).
Failing topical corticosteroids	Not applied	100% (assumption)	The March 2023 evaluation previously noted that 50.70% of patients failed topical corticosteroids in Study 201 (Table 13,

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			chlormethine gel, PSD, March 2023 PBAC meeting).									
Uptake	█% in Yr1, █% in Yr2, █% in Yr3, █% in Yr4, █% in Yr5, █% in Yr6	█% each year in Yr1 – Yr3 and █% each year in Yr4 – Yr6, resulting █% over the 6 years for the whole pooled-prevalence cohort (assumption)	Uptake rates in the first year may be underestimated. The ESC considered that the uptake rates may be reasonable.									
Mean dose	1 tube per month regardless of skin burden (60g/m) i.e. 12 tubes per year	Varied by skin burden (Study 201). On average of 17.78 tubes per year	The weighted dose of 2.79g/d is inconsistent with the mean dose used in the CMA of 1.80 g applied 3.44 times per week. The population weight by skin burden is not consistent with individual patient data provided from Study 201 (58.50% vs 67.59% ^a for BSA 0% <10% and 41.50% vs 32.41% ^a for 10% – 25%). The ESC considered that the mean dose of 1.84 g/day used in the re-estimated CMA may be an appropriate input for the financial estimates.									
		<table border="1"> <tr> <td>Skin burden (BSA)</td> <td>0% - <10%</td> <td>10% - 25%</td> </tr> <tr> <td>Tube/month</td> <td>1 (60 g/m)</td> <td>2 (120 g/m)</td> </tr> <tr> <td>Population weight (Study 201)</td> <td>58.50%</td> <td>41.50%</td> </tr> </table>		Skin burden (BSA)	0% - <10%	10% - 25%	Tube/month	1 (60 g/m)	2 (120 g/m)	Population weight (Study 201)	58.50%	41.50%
		Skin burden (BSA)		0% - <10%	10% - 25%							
		Tube/month		1 (60 g/m)	2 (120 g/m)							
Population weight (Study 201)	58.50%	41.50%										
Weighted dose	2.79 g/day, 84.90 g/m											
Proposed duration of treatment	48 months	48 months (assumption). Including 6 months of initiation and 42 months of continuation treatment.	Uncertain. No new data provided by the resubmission to support the treatment duration (after accounting for a discontinuation factor, the expected mean duration of treatment is 39.14 months ^b).									
Continuing treatment (after initial treatment)	Not applied	78.90% (i.e. 21.1% of patients in Study 201 discontinued chlormethine due to drug related adverse events).	May be reasonable.									
Chlormethine gel effective AEMP price per tube	\$█	Effective AEMP \$█	Cost per month in the financial estimates of \$█ per month is higher than estimated in the CMA of \$█ per month.									
Phototherapy (MBS item 14050)	\$55.80 per session with total of 287.32-sessions over 4 years	\$55.80 per session with 39-sessions over 3 months.	The fee for MBS item 14050 was updated to \$57.80 per session based on the MBS updated on 1st July 2023.									
	No displacement or concurrent use considered.	Assuming █% concurrent use and █% replacement (cost-offset). No displacement considered.	Partially addressed, the resubmission did not consider that phototherapy may be used subsequent to chlormethine gel.									

Source: Table 4-1, p29; Table 4-5, p39; of the resubmission; March 2023 evaluation report of chlormethine gel; chlormethine gel, PBAC Minutes, March 2023 PBAC meeting; chlormethine gel, PSD, March 2023 PBAC meeting.

AEMP = approved ex-manufacturer price; BSA = body surface area; CMA = cost-minimisation approach; DPMQ = dispensed price for maximum quantity; d= day; g = gram; m = month; Mar = March; MBS = Medicare Benefit Schedule; MF-CTCL= mycosis fungoides-type cutaneous T-cell Lymphoma; PBAC = Pharmaceutical Benefits Advisory Committee; PBS = Pharmaceutical Benefits Scheme; PSD = public document summary; Yr = year

^a calculated based on individual patient data provided in workbook 'Chlormethine – Ledaga – Section 4 – Base Case (Final) – Nov 2023 – 29 June 2023, worksheet 'Study 201' of the resubmission

^b 39.14 months based on assumption that 78.9% of patients receive treatment for 48 months and 21.1% of patients receive 6 months of treatment.

- 6.35 The DUSC previously considered that the uptake rates applied in the March 2023 submission may be higher due to the convenience of topical therapy (para 6.58, chlormethine gel, PSD, March 2023 PBAC meeting). The resubmission stated that a higher uptake rate was applied to address the concerns raised in March 2023. The evaluation considered the uptake rate in the first year of 1% may be underestimated. Uptake rates in Years 2 – 6 were applied to the total prevalent population. The ESC considered that, in the context of the resubmission’s prevalent approach, the uptake rates applied to Years 2 – 6 may be reasonable.
- 6.36 The resubmission assumed the proportion of patients failing topical corticosteroids and eligible to start chlormethine gel would be 100%. The resubmission did not apply the proportion of 50.7% noted in the March 2023 evaluation (Table 14, chlormethine gel, PSD, March 2023 PBAC meeting). The resubmission stated that this assumption relies on topical corticosteroids as a measure of treatment failure but argued that they are not considered effective for MF-CTCL and are used mainly for symptom relief. According to the Australian Clinical Practice Statement for MF and Sezary syndrome (July 2020), 63% of T1 patients (<10% BSA involvement) and 25% of T2 patients (≥10% BSA involvement) achieved complete clearance of their disease after using topical corticosteroids. These patients would subsequently transition into the 'watch and wait' category, which is consistent with the submission’s poster (D’Agostino, 2011) which showed 36% of Stage IA and 11% of Stage IB/IIA were not receiving active treatments. DUSC previously advised that sensitivity analyses should be presented using an upper estimate of 75% as the uptake proportion of patients who failed topical corticosteroids (p9, chlormethine gel, DUSC Advice to PBAC, March 2023 PBAC meeting). The PSCR argued that the resubmission had taken DUSC’s sensitivity analysis request a step further based on the assumption that at some point in time in the patient journey corticosteroids will fail and therefore chlormethine gel would be a treatment option for 100% of patients. The ESC noted that this approach effectively removes the requirement for patients to have failed topical corticosteroids and considered that this may be appropriate.
- 6.37 The resubmission assumed that the required dose of chlormethine gel for those with a skin burden of 0% - 10% BSA involvement was one tube per month and for those with a skin burden of 10% – 25% was two tubes per month. Based on the proportion of patients in each BSA involvement category from Study 201, 58.80% and 41.50% for 0% - 10% and 10% – 25% respectively, this resulted in an average of 17.78 tubes per year, higher than the estimate of 12 tubes per year in the March 2023 submission. The estimate of use presented in the financial estimates also resulted in a higher average dose (84.9 grams/month) than in either the resubmission CMA (26.90 grams/month) or Study 201 (55.97 grams/month). Furthermore, the applied proportion of patients in each skin involvement category was not consistent with individual patient data provided from Study 201 (58.50% vs 67.59% for BSA 0% - <10% and 41.50% vs 32.41% for 10% - 25%). This resulted in an overestimation of the number of tubes utilised. The PSCR argued that the CMA derived the equi-effective dose based on the volume (in

grams) of gel applied in a month, which was different from the financial estimates that utilised the number of tubes of gel needed. The ESC considered the resubmission overestimated the required dose of chlormethine gel in the financial estimates.

- 6.38 As per the March 2023 submission, the resubmission maintained a proposed duration of treatment of 48 months (39.14 months, after adjusting for 21.1% of patients discontinuing treatment at 6 months, based on Study 201) for chlormethine gel. At that time, the PBAC agreed with the DUSC that the March 2023 financial estimates were subject to substantial uncertainty around the mean time-on-treatment (para 7.9, chlormethine gel, PSD, Mar 2023 PBAC meeting). No new data were provided by the resubmission to support the assumed duration of treatment. The PSCR maintained that a treatment duration of 48 months was appropriate based on clinical experience. The ESC noted the duration of Study 201 was 12 months and the mean duration of treatment was 9 months. The ESC considered that use of duration of treatment assumptions from Study 201 in the financial estimates would likely be more appropriate than the 48 months proposed by the resubmission. The pre-PBAC response stated that, at the end of the Study 201 (12 months), only 37.7% (49/130) of patients had discontinued therapy, and argued this suggested a greater than 12 month duration of therapy. The PBAC noted the median duration of therapy in Study 201 was 12 months (Table 33, p92 of the Study 201 CSR).
- 6.39 The resubmission did not consider the displacement of phototherapy, previously considered by the DUSC to be likely for a proportion of patients (para 6.60, chlormethine gel, PSD, March 2023 PBAC meeting).
- 6.40 A summary of the estimated utilisation and financial implications of chlormethine gel is presented in Table 13. The resubmission estimated that over the first 6 years of listing 500 to < 5,000 patients would be treated with chlormethine gel, with a total of 10,000 to < 20,000 scripts dispensed. This is substantially lower than the March 2023 submission, where it was estimated 500 to < 5,000 patients would be treated with 50,000 to < 60,000 scripts dispensed.

Table 13: Estimated use and financial implications

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Estimated extent of use						
Initial treatment (patients)	1	1	1	1	1	1
Number of scripts dispensed	2	2	2	2	2	2
March 2023 submission						
Initial treatment (patients)	1	1	1	1	1	1
Scripts (total)	2	2	5	7	7	7
Estimated financial implications of chlormethine gel						
Cost to PBS/RPBS less co-payments	3	3	3	3	3	3
Net financial implications						
Net cost to PBS/RPBS	3	3	3	3	3	3
Net cost to MBS	4	4	4	4	4	4
Net cost to PBS/RPBS/MBS	3	3	3	3	3	3
March 2023 submission						
Net cost to PBS/RPBS	3	3	6	6	8	8

Source: Table 4-5, p39; Table 4-6, p41 of the resubmission; Table 3, p9 of DUSC Advice to PBAC, chlormethine gel, March 2023. Table 4-6, p 42; Table 4-8, p42 of the resubmission

MBS = Medicare Benefits Schedule; PBS = Pharmaceutical Benefits Scheme; RPBS = Repatriation Schedule of Pharmaceutical Benefits
Blue shading indicates information previously seen by the PBAC.

The redacted values correspond to the following ranges:

¹ < 500

² 500 to < 5,000

³ \$0 to < \$10 million

⁴ net cost saving

⁵ 5,000 to < 10,000

⁶ \$10 million to < \$20 million

⁷ 10,000 to < 20,000

⁸ \$20 million to < \$30 million

- 6.41 The total cost to the PBS/RPBS of listing chlormethine gel was estimated to be \$0 to < \$10 million in Year 6, and a total of \$30 million to < \$40 million in the first 6 years of listing.
- 6.42 The evaluation considered the financial estimates are uncertain and likely overestimated. There was a net cost to Government (PBS/RPBS/MBS) associated with the listing of chlormethine gel (\$30 million to < \$40 million in the first 6 years of listing). This was as a result of the financial estimates applying a higher dose of chlormethine gel than in the CMA and the application of a duration of treatment of 48 months for chlormethine gel and 3 months for phototherapy (which the CMA did not account for). The net cost also arises from the concurrent use of chlormethine gel with phototherapy.
- 6.43 The financial estimates in the resubmission are substantially lower than the estimates in the March 2023 submission. The key drivers for this difference are the lower number of patients receiving initial and continuing treatment and the lower price of chlormethine gel.
- 6.44 The ESC considered that the financial estimates from the resubmission were highly uncertain primarily due to assumptions regarding chlormethine dose and duration of therapy, resulting in a net cost to the Government despite being based on a CMA. The ESC considered that use of chlormethine dose and duration assumptions based on

Study 201 may reduce the uncertainty in the estimates. The ESC noted that the use of these assumptions along with the re-estimated cost-minimised price of chlormethine gel (\$ per 60 gram tube) resulted in significantly lower estimates for the net cost to Government (PBS/RPBS/MBS) than provided in the resubmission (Table 14).

Table 14: Change in net financial implications from the sensitivity analyses

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6	Total	Δ% from base case
Base case	1	1	1	1	1	1	2	
CMA price of \$ per 60 gram tube								
Parameters as per the resubmission	1	1	1	1	1	1	3	-26%
Dose as in the (re-estimated) CMA – 1.84 g daily	1	1	1	1	1	1	4	-47%
12 months duration of treatment (using resubmissions assumption re mean dose of 2.79 g/day)	1	1	1	1	1	1	1	-77%
9 months duration of treatment (using resubmissions assumption re mean dose of 2.79 g/day)	1	1	1	1	1	1	1	-83%
Dose as in the (re-estimated) CMA – 1.84 g daily PLUS 12 months duration of treatment	1	1	1	1	1	1	1	-84%
Dose as in the (updated) CMA – 1.84 g daily PLUS 9 months duration of treatment	1	1	1	1	1	1	1	-88%

Source: compiled during the development of the ESC Advice

CMA = cost-minimisation approach; g = gram

The redacted values correspond to the following ranges:

¹ \$0 to < \$10 million

² \$30 million to < \$40 million

³ \$20 million to < \$30 million

⁴ \$10 million to < \$20 million

Quality Use of Medicines

6.45 The resubmission noted the reimbursed supply of chlormethine gel for MF-CTCL in Australia would be supported by the Sponsor 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).

- 6.46 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 Share Arrangements

- 6.47 The resubmission did not provide a Risk Sharing Arrangement.

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

7 PBAC Outcome

- 7.1 The PBAC recommended the Section 85, Authority Required listing of chlormethine hydrochloride gel (hereafter chlormethine gel) for the topical 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. The PBAC acknowledged the clinical need for additional treatment options for patients with MF-CTCL. The PBAC considered that due to the limited data available for this rare condition the claim of non-inferior effectiveness was highly uncertain but likely reasonable. The PBAC's recommendation for listing was based on, among other matters, its assessment, that the cost-effectiveness of chlormethine gel would be acceptable if it were cost-minimised to phototherapy. The PBAC considered it would be appropriate for a small price premium to be applied to chlormethine gel over phototherapy due to the potential for improvement in accessibility and suitability for patients unable to be treated with phototherapy due to the areas involved.
- 7.2 The PBAC noted the input from a health care professional and Rare Cancers Australia, and recalled consumer comments from the March 2023 submission. The PBAC reaffirmed its March 2023 advice that there was a clinical need for a range of treatment options in this chronic disease (para 7.2, chlormethine gel, PSD, March 2023 PBAC meeting). The PBAC further acknowledged that there was an unmet clinical need for patients who have patches or plaques in areas that are difficult to manage with treatments currently available and for those who have difficulty accessing phototherapy or for whom it is not an option (see paragraph 4.7).
- 7.3 The PBAC considered that a combined listing that includes both patients with a BSA involvement of no more than 10% and 10% to 25% was appropriate. The PBAC noted that the prescribing instructions direct the dermatologist or haematologist to request 1 pack for patients with no more than 10% of BSA affected and 2 packs if 10% to 25%

of BSA affected. The PBAC agreed with the ESC that it was appropriate to remove the requirement for patients to have failed topical corticosteroids from the restriction and noted that this had been accounted for in the resubmission financial estimates. The PBAC considered that it would be appropriate for both initial and continuing therapy restrictions to be Authority Required (telephone/online) listings.

- 7.4 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.
- 7.5 The PBAC recalled that the March 2023 submission claimed chlormethine gel was non-inferior in terms of effectiveness as measured by restricted mean duration of response (rmDOCR) and superior in terms of effectiveness based on health-related quality of life (HRQoL). The PBAC noted the resubmission removed the superiority claim and retained the non-inferiority claim based on rmDOCR. No new clinical evidence was provided in the resubmission and hence the clinical claim remained based on 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). The results of the ITC indicated no statistically significant difference in rmDOCR between the treatments (mean difference in months = 2.1; 95% CI: -1.0 to 5.4; p=0.185). With the clinical evidence unchanged, the PBAC reaffirmed its March 2023 concerns regarding the transitivity issues affecting the comparability of the studies included in the ITC (see paragraph 6.20). The PBAC noted that no further justification was provided by the resubmission in support of the claim of non-inferior clinical effectiveness compared to phototherapy. However, the PBAC acknowledged that non-inferiority to phototherapy was difficult to definitively establish given the limited data available. Overall, the PBAC considered the claim of non-inferior effectiveness based on rmDOCR was highly uncertain but likely reasonable in this rare condition.
- 7.6 The PBAC reaffirmed its March 2023 advice 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 recalled that in March 2023 it had considered that chlormethine gel may be a useful additional therapeutic option for a niche group of patients and advised that a cost-minimisation approach (CMA) against phototherapy may be a potential way forward in this rare condition (para 7.8, chlormethine gel, PSD, March 2023 PBAC meeting). The PBAC noted the resubmission presented a CMA assuming an equi-effective dose of 26.90 grams/month of chlormethine gel is equivalent to 13.04 phototherapy sessions per month. The PBAC noted the equi-effective dose presented in the resubmission assumed patients would receive 3.44 administrations per week of chlormethine gel, based on the French Temporary Use Authorization study, rather than daily administration. The PBAC agreed with the ESC that appropriate reductions in frequency were accounted for in the calculation of the average daily dose from Study 201. The PBAC also acknowledged the limitations of the clinical evidence

available regarding treatment duration and agreed with the ESC that it would be reasonable to conduct the CMA over a one month period. The PBAC noted the re-estimated CMA requested by ESC was conducted over a one month period using the average daily dose from Study 201 (1.84 gram) and this resulted in a cost-minimised price for chlormethine gel of \$ per 60 gram tube (see Table 10). The PBAC considered the ESC re-estimated CMA was appropriate. The PBAC accepted 56.03 grams/month of chlormethine gel is equi-effective to 13.04 phototherapy sessions per month. The PBAC considered it would be appropriate for a price premium of up to % to be applied to chlormethine gel over phototherapy due to the potential for improvement in accessibility and suitability for patients unable to be treated with phototherapy due to the areas involved (see paragraph 7.2).

- 7.8 The PBAC noted that, as per the March 2023 DUSC advice, the resubmission applied a prevalence-based approach to the financial estimates. The PBAC noted the resubmission assumed that 100% of patients failed topical corticosteroids and considered this was appropriate given its advice to remove this requirement from the proposed restriction (see paragraph 7.3). The PBAC agreed with the ESC that the revised uptake rates presented in the resubmission were reasonable. However, the PBAC considered the assumptions regarding the mean dose and the duration of treatment of chlormethine gel were not appropriate. The PBAC considered the resubmission overestimated the required dose of chlormethine gel and recommended the mean dose from Study 201 (1.84 grams/day) be used. In terms of treatment duration, the resubmission provided financial estimates based on 48 months of treatment with chlormethine gel (an expected mean duration of 39.14 months after accounting for 21.1% discontinuing therapy at 6 months). The duration of Study 201 was 12 months. The PBAC noted the pre-PBAC response reported that only 37.7% (49/130) of patients had discontinued therapy at the end of Study 201, and therefore argued that the treatment duration was likely to be greater than 12 months. The PBAC noted that while the mean treatment duration in Study 201 was 9 months, the median treatment duration was 12 months. The PBAC agreed with the pre-PBAC response argument that, without censoring, the mean treatment duration is likely to be longer than 12 months. However, the PBAC did not accept the resubmission assumption based on 48 months of treatment. The PBAC advised that, while uncertain, a mean treatment duration of 24 months was likely appropriate for the financial estimates. The PBAC considered the MBS offsets for phototherapy proposed in the resubmission were appropriate. The PBAC noted the financial estimates need to be updated to incorporate the outcome of the Committees advice in paragraph 7.7 along with a mean dose of 1.84 grams/day and a mean treatment duration of 24 months.
- 7.9 The PBAC noted the resubmission did not propose a Risk Share Arrangement and considered this reasonable given the expected low use and financial implications, together with a low likelihood of use outside of the restriction.
- 7.10 The PBAC noted that its recommendation was on a cost-minimisation basis and advised that, because chlormethine is not expected to provide a substantial and

clinically relevant improvement in efficacy, or reduction of toxicity, over phototherapy, or not expected to address a high and urgent unmet clinical need given the presence of an alternative therapy, the criteria prescribed by the *National Health (Pharmaceuticals and Vaccines – Cost Recovery) Regulations 2022* for Pricing Pathway A were not met.

- 7.11 The PBAC advised that chlormethine is not suitable for prescribing by nurse practitioners.
- 7.12 The PBAC recommended that the Early Supply Rule should not apply.
- 7.13 The PBAC recommended that chlormethine should not be treated as interchangeable with any other drugs.
- 7.14 The PBAC noted that this submission is not eligible for an Independent Review as it received a positive recommendation.

Outcome:

Recommended.

8 Recommended listing

8.1 Add new item:

MEDICINAL PRODUCT medicinal product pack	PBS item code	Max. qty packs	Max. qty units	No.of Rpts	Available brands
CHLORMETHINE					
chlormethine 0.016% (160 microgram/g) gel, 60 g	NEW MP	2	2	5	Ledaga
Restriction Summary [new] / Treatment of Concept: [new]					
	Category / Program: General Schedule (Code GE)				
	Prescriber type: <input checked="" type="checkbox"/> Medical Practitioners				
	Restriction type: <input checked="" type="checkbox"/> Authority Required – (telephone/online PBS Authorities system)				
	Indication: Mycosis fungoides cutaneous T-cell Lymphoma				
	Treatment Phase: Initial treatment				
	Clinical criteria:				
	The condition must be any of: (i) Stage IA, (ii) IIA, (iii) IB mycosis fungoides cutaneous T-cell Lymphoma				
	AND				
	Clinical criteria:				
	The condition must have been confirmed through a diagnostic lesion biopsy from an Approved Pathology Authority				
	AND				
	Clinical criteria:				
	The condition must cover either of which: (i) no more than 10% of the patient's body surface area, (ii) no more than 25% of the patient's body surface area.				
	Treatment criteria:				
	Patient must be treated by at least one of the following prescriber types (i) dermatologist, (ii) haematologist				
	AND				

	Treatment criteria:
	The treatment must be approved for 1 unit if the condition is no more than 10% of the patient's body surface area to provide 4 weeks of treatment per script; OR
	The treatment must be approved for 2 units if the condition is no more than 25% of the patient's body surface area to provide 4 weeks of treatment per script
	Population criteria:
	Patient must be at least 18 years of age;
	Prescribing Instructions: Confirmation of eligibility for treatment with diagnostic reports must be documented in the patient's medical records.
	Administrative Advice: Applications for authorisation under this restriction may be made in real time using the Online PBS Authorities system (see www.servicesaustralia.gov.au/HPOS) or by telephone by contacting Services Australia on 1800 888 333.
	Indication: Mycosis fungoides cutaneous T-cell Lymphoma
	Treatment Phase: Continuing treatment
	Clinical criteria:
	Patient must have previously received PBS-subsidised treatment with this drug for this condition
	AND
	Clinical criteria:
	Patient must not have developed disease progression while receiving PBS-subsidised treatment with this drug for this condition
	Treatment criteria:
	Patient must be treated by at least one of the following prescriber types (i) dermatologist, (ii) haematologist
	AND
	Treatment criteria:
	The treatment must be approved for 1 unit if the condition is no more than 10% of the patient's body surface area to provide 4 weeks of treatment per script; OR
	The treatment must be approved for 2 units if the condition is no more than 25% of the patient's body surface area to provide 4 weeks of treatment per script
	Administrative Advice: Applications for authorisation under this restriction may be made in real time using the Online PBS Authorities system (see www.servicesaustralia.gov.au/HPOS) or by telephone by contacting Services Australia on 1800 888 333.

This restriction may be subject to further review. Should there be any changes made to the restriction the sponsor will be informed.

9 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.

10 Sponsor's Comment

The sponsor had no comment.