NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Chlormethine gel for treating mycosis fungoides-type cutaneous T-cell lymphoma [ID1589]

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Chlormethine gel for treating mycosis fungoides-type cutaneous T-cell lymphoma [ID1589]

Contents:

The following documents are made available to consultees and commentators:

Any information supplied to NICE which has been marked as confidential, has been redacted. All personal information has also been redacted.

Appraisal title

Single Technology Appraisal

Response to consultee, commentator and public comments on the Appraisal Consultation Document (ACD)

Type of stakeholder:

Consultees – Organisations that accept an invitation to participate in the appraisal including the companies, national professional organisations, national patient organisations, the Department of Health and Social Care and the Welsh Government and relevant NHS organisations in England. Consultees can make a submission and participate in the consultation on the appraisal consultation document (ACD; if produced). All non-company consultees can nominate clinical experts and/or patient experts to verbally present their personal views to the Appraisal Committee. Company consultees can also nominate clinical experts. Representatives from NHS England and clinical commissioning groups invited to participate in the appraisal may also attend the Appraisal Committee as NHS commissioning experts. All consultees have the opportunity to consider an appeal against the final recommendations, or report any factual errors, within the final appraisal document (FAD).

Clinical and patient experts and NHS commissioning experts – The Chair of the Appraisal Committee and the NICE project team select clinical experts and patient experts from nominations by consultees and commentators. They attend the Appraisal Committee meeting as individuals to answer questions to help clarify issues about the submitted evidence and to provide their views and experiences of the technology and/or condition. Before they attend the meeting, all experts must either submit a written statement (using a template) or indicate they agree with the submission made by their nominating organisation..

Commentators – Commentators can participate in the consultation on the ACD (if produced), but NICE does not ask them to make any submission for the appraisal. Non-company commentator organisations can nominate clinical experts and patient experts to verbally present their personal views to the Appraisal Committee. Commentator organisations representing relevant comparator technology companies can also nominate clinical experts. These organisations receive the FAD and have opportunity to report any factual errors. These organisations include comparator technology companies, Healthcare Improvement Scotland any relevant National Collaborating Centre (a group commissioned by NICE to develop clinical guidelines), other related research groups where appropriate (for example, the Medical Research Council and National Cancer Research Institute); other groups such as the NHS Confederation, the NHS Commercial Medicines Unit, the Scottish Medicines Consortium, the Medicines and Healthcare Products Regulatory Agency, the Department of Health and Social Care, Social Services and Public Safety for Northern Ireland).

Public – Members of the public have the opportunity to comment on the ACD when it is posted on the Institute's web site 5 days after it is sent to consultees and commentators. These comments are usually presented to the appraisal committee in full, but NICE reserves the right to summarise and edit comments received during consultations, or not to publish them at all, where in the reasonable opinion of NICE, the comments are voluminous, publication would be unlawful or publication would be otherwise inappropriate.

Please note: Comments received in the course of consultations carried out by NICE are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the submissions that NICE has received, and are not endorsed by NICE, its officers or advisory committees.

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
1	Professional group	United Kingdom Cutaneous Lymphoma Group (UKCLG)	Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity? Chlormethine gel has proven efficacy for MF-CTCL without any real comparator. It provides a convenient, effective therapy for those not responding to potent topical steroids, without the need for hospital based treatment nor monitoring, This cost saving may be difficult to determine on paper but significantly reduces the burden of patient treatment from the hospital and the improvement in skin allowing patients to return to work with less days of work lost / sick benefits claimed. Not recommending Chlormethine gel for treatment of MF-CTCL will contribute to the overall discrimination that affects patients who develop a rare cancer. While this type of discrimination may not be 'unlawful' it has significant impact on the lives of patients with this condition. Chlormethine gel for MF-CTCL was granted orphan designation by the Committee for Orphan Medicinal Products in 2012 due to the rarity of the disease. Incidence estimates in England derived from Public Health England National Cancer Registration Analysis between 2009-2013 found an average annual incidence of 332 cases for all types of CTCL; of which the estimate for mycosis fungoides type was **182 cases per year** (55%)[1]. Compare this to the incidence of breast cancer in the UK of 55, 000 cases per year[2]. At every stage of their journey patients with CTCL are disadvantaged: **Recognition**: GPs are unlikely to be familiar with the condition or presentation and typically misdiagnose as benign skin disease. Chlormethine gel should be limited to prescribing at expert MF-CTCL centres. **Referral:** There is no 2 week-wait referral pathway suitable for CTCL patients unlike common cancers. GPs may be reluctant to refer patients with a skin condition to secondary care for some time; patients may be given ineffective topical treatments. Waiting times are long in many regions of the UK due to the high prevalence of skin disease in general and a shortage of Consultant dermatologists. Due to tendering out of dermatology services in some regions patients may be referred to community services who do not employ practitioners with the necessary training or experience to recognise CTCL. The median delay from onset of symptoms to diagnosis is 3 years (ref Scarisbrick JJ, Quaglino P,	Comments noted. The committee took these comments into consideration along with the company's updated models and the updated discount. Chlormethine gel is recommended for early stage MF-CTCL.

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			Prince HM et al. The PROCLIPI international registry of early stage mycosis fungoides identifies substantial diagnostic delay in most patients. Br J Dermatol. 181(2):350-357, 2019.[3] **Diagnosis**: Even when assessed by an appropriate clinician who suspects CTCL diagnosis is not always straight forward; this often requires multiple skin biopsies over time, specialist laboratory assessments and careful clinicopathological correlation. There are only 10 supra-regional multidisciplinary teams in the UK specialising in diagnosis and management of CTCL and patients may not be referred to one of these teams, particularly in early stages. Delay in diagnosis can affect health related quality of life and patients may progress or receive inappropriate treatments.. **Treatments**: There are few licensed treatments available for CTCL. Although UK, European and International clinical guidelines exist for management, there has been paucity of data from randomised clinical trials conducted on which to make evidenced based decisions due to the rarity of the disease, the need for multinational collaboration and the inevitable expense in setting up and monitoring such studies. Most guidelines rely on low quality evidence from retrospective studies, case series or expert opinion, particularly in early stage disease (stage IA-IIA). **UK disparity**: Topical Chlormethine gel is one of the few licensed treatments available for early stage MF-CTCL. Historically Nitrogen mustard has been used extensively over 50 years as a standard therapy worldwide and there is good evidence of its effectiveness from retrospective studies. The multicentre randomised prospective clinical trial (Lessin 2013 [4]) which led to its approval in the USA by the FDA (approved August 23, 2013, under Trade name Valchlor) and in Europe approved by the EMA for the treatment of mycosis fungoides-type cutaneous T-cell lymphoma (22 Dec 2016). Objective end points were used to measure skin disease response compared to the original product in use at the time. There are clear advantages in using Chlormethine gel (Ledaga) compared to the original Nitrogen Mustard product, which became impossible to source in the UK in the last decade and in addition required expensive extemporaneous preparation in specialist pharmacy units. Failure to recommend Chlormethine gel for MF-CTCL in the NHS further disadvantages UK patients by limiting treatment choices compared to patients worldwide.	
2	Professional group	United Kingdom Cutaneous Lymphoma Group (UKCLG)	**Has all of the relevant evidence been taken into account?** The committee state that there is no robust evidence of the effectiveness of Chlormethine gel compared with other treatments or showing if it is more effective for people with limited skin disease. We disagree with these statements but accept there is no true comparator making calculations difficult but provides a convenient , effective therapy (proven over many years) without the need for hospital based treatment nor monitoring. The committee discounts the Lessin 2013 study[4] as it compares Chlormethine gel to a treatment no longer used. This group believe this is unfair just because	Comments noted. The committee were unable to consider the evidence for chlormethine ointment but did take these comments into consideration during the meeting, along with the company's updated models and the updated discount. Chlormethine gel is recommended for early stage MF-CTCL.

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			the alternative is no longer available. The study clearly shows that Chlormethine gel was as effective as Nitrogen mustard ointment which was the **initial standard of care** for MF-CTCL in Stanford, USA, where the trial originates, as opposed to phototherapy. There was no inferiority of the gel compared to the ointment using either CAILS or mSWAT assessment: Response rates (RR) for gel and ointment were 59% vs. 48% by CAILS and 46.9% vs. 46.2% by mSWAT respectively in 260 patients. Subset analysis of the 201 study showed those with stage IA (n=141) had RR of 59% for Chlormethine gel vs. 57% with stage IB/IIA (n=119) using CAILS assessment of up to 5 index lesions. The mSWAT data is not reported. However, the historical evidence from Stamford shows that Nitrogen mustard ointment is more effective for people with limited skin disease. The 2003 study by Kim et al[5] reported on 203 patients who used nitrogen mustard as initial therapy. Patients with T1 or stage IA disease had better response rates and survival outcomes than patients with T2 or stage IB disease: T1 complete response (CR) rate of 65% vs. T2 CR rate of 34% and T1 overall response rate (ORR) of 93% vs. T2 ORR of 72%. Patients used nitrogen mustard alone without other concurrent therapy. As the Lessin 2013 study demonstrates no inferiority between Chlormethine gel or Nitrogen mustard ointment; it is entirely reasonable to extrapolate that Chlormethine gel would similarly be more effective in patients with early stage skin disease. There is additional historical data from other centres confirming that Nitrogen mustard is more effective in early stage disease. A retrospective study from Philadelphia of 331 patients showed CR of 80% in stage IA vs. CR of 68% in stage IB patients using aqueous nitrogen mustard, although other concurrent therapy was allowed[6]. A retrospective study from New York of 117 patients showed CR 75.8% in stage I vs. CR of 44.6% in stage II; in this study concomitant therapy was not allowed[7]. There are other unacknowledged potential benefits of using nitrogen mustard therapy. The Vonderheid 1989 study found **long lasting remission of greater than 8 years in 11%** (35 of 331 patients, 53% Stage IA) treated with nitrogen mustard, providing evidence that MF-CTCL might be eradicated or 'cured' by nitrogen mustard. Analyses of the large case series from Stamford have also demonstrated that complete responses to topical nitrogen mustard in early stage IA patients is associated with a lower risk of disease progression[5, 16]. **Nitrogen mustard may also have a unique effect on the immunopathogenesis of MF-CTCL**. Studies have shown that patients who develop a significant contact dermatitis (delayed type IV hypersensitivity reaction) may have a greater clinical response to Nitrogen mustard[5] suggesting that the mechanism of action of nitrogen mustard stems from both its alkylating properties but also via immune stimulation or interaction with the epidermal-Langerhans cell-T-call axis[8].	
3	Professional group	United Kingdom Cutaneous	**Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?**	Comments noted. The committee was presented with updated cost effectiveness modelling which it

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		Lymphoma Group (UKCLG)	The committee state the evidence used to estimate cost effectiveness is uncertain as it does not accurately reflect clinical practice. It is important to highlight that although published clinical guidelines exists there is no single 'gold standard' approach. Recommendations for initial treatment may depend on a variety of factors: burden or stage of skin disease, availability of therapy, clinician speciality, location and personal experience, and importantly patient preference. Clinical practice varies depending on who is seeing the patient: a local dermatologist is likely to only recommend therapy they have direct access to or experience of – such as phototherapy, whereas a dermatologist working in a superregional service may recommend all available options including Chlormethine gel and off label use of other topical treatments with published data. Prior use of nitrogen mustard in the UK was generally limited to a few clinicians working in specialist supra-regional centres in London and Manchester, as experts there had developed the required clinical experience or had direct experience of using nitrogen mustard from clinical fellowships in the USA. As there are so few available therapies for early stage disease the reality is that **patients will try all available treatment options before moving onto systemic therapy**. Many patients will cycle through the available skin directed therapies, with periods of active monitoring (watch and wait) between therapies until the severity of relapse requires a new cycle of treatment. The availability of Chlormethine gel will significantly improve the options for skin directed therapy for both clinician and patient. The committee highlight the limitations of using retrospective phototherapy studies as a comparator in the cost effectiveness models but prefer to use estimates based on the metanalysis by Phan et al[9]. The seven studies were observational, non-controlled, utilised varied methodology and did not use robust clinical assessment or disease end points. The designation of a 'CR' of only 80-95% clearance of skin lesions in some of the studies negates their validity as a comparator. The combined studies gave a CR rate for PUVA of 78%. The data from Whittaker et al[10] is discounted yet is more directly applicable to the UK population in addition to being a RCT with robust clinical assessment. The CR rate for PUVA was only 22%. This CR rate is much lower than reported by Phan et al and highlights the high risk of bias in the use of retrospective studies. The CR rate of 78% from the Phan metanalysis is more reliably comparable to the ORR of 71% in the Whittaker study. The efficacy of phototherapy will be overestimated in the comparator models compared to the use of Chlormethine gel. The committee states it prefers the ERG estimate of 2.8g Chlormethine gel daily	considers to better represent clinical practice. This was taken into consideration along with the company's updated models and the updated discount. Chlormethine gel is recommended for early stage MF-CTCL. Section 3.1 of the FAD had been amended to note that there is no gold standard approach and also to note that the decision for treatment will depend on different patients' factors including patient preference. The company's revised base case incorporates Phan et al. (2019) for all outcomes. The committee acknowledged that the efficacy of phototherapy may be optimistic in Phan et al. (2019) (see section 3.8). The company's revised base case uses a dose of 2.8g. Section 3.2 has been amended to clarify length of treatment for people who have no response, full response or partial response. The committee acknowledged the comments about previous use of nitrogen mustard and took this into account as part of its decision-making. Section 3.2 also now incorporates a comment that clinicians in the UK have experience using similar topic treatments as chlormethine gel.

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			in the cost effectiveness models yet there is no robust evidence that this estimate is more correct than the companies estimates from real world usage or the original Lessin trial. For UK use it is highly likely that the amount of gel used will be less as clinicians recommend application to individual lesions not whole or regional body use as was advocated in the Lessin trial. It is possible that UK clinicians may choose to follow protocols developed in Europe where Chlormethine gel is applied only twice weekly to reduce the risk of skin irritaion[11]**.** A better estimate of usage may relate to the stability data of Chlormethine gel with a fresh tube being required every 2 months – leading to 6 tubes per year for an average patient using treatment over a 12 month period. The assumption that Chlormethine gel may only be used for 4-6 months, or a maximum of 12 months, which increases costs in the company model is also not necessarily correct. The median time to a CR in the Kim 2003 study was 12 months[5.] Many patients used therapy for longer than 12 months with ongoing improvement. The extension study[12] for participants in the Lessin 2013 trial who had not yet achieved a CR showed that ongoing usage for 7 months of a Chlormethine gel 0.04% was well tolerated and led to further documented responses in 26.5% of patients (CR 6.1%; PR 20.4%). Personal experience of using nitrogen mustard ointment in the UK also confirms continued use and benefit longer than 12 months[13]. While there are clearly stated advantages to be able to offer Chlormethine gel to patients with limited stage IA skin disease compared to phototherapy, it should not be forgotten that nitrogen mustard has proven utility in patients with stage IB disease, to treat sanctuary sites missed by other skin directed therapies and to help with symptom control in patients with advanced disease who may still have significant skin disease burden. It has been shown to be equally effective as salvage therapy after initial relapse[5]. The issue of patient choice has not been fully taken into account when considering cost effectiveness of using Chlormethine gel. Although the model takes into account reference costs to the NHS of providing phototherapy the costs for the patient is not fully considered. These include inconvenience, traveling to hospital, car parking, loss of work and income, as well as lack of autonomy over a hospital based therapy. Phototherapy is provided as a limited course over 6-10 weeks, due to accumulative side effects of maintenance therapy and because it is a finite resource shared by all patients with serious benign skin disease. Patients are often anxious at the end of a treatment course especially if remission is not achieved. Chlormethine gel gives control back to the patient as treatment can be continued longer term while the skin is improving.	

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4	Professional group	United Kingdom Cutaneous Lymphoma Group (UKCLG)	**Are the recommendations sound and a suitable basis for guidance to the NHS?** Treatments for early MF-CTCL aim to relieve symptoms rather than provide a cure; this applies to all skin directed therapies. Therefore improving patient's quality of life assumes greater importance. A treatment such as Chlormethine gel which is convenient, home-based, with no monitoring requirements and documented efficacy and tolerability over many months should be made available to UK patient on the NHS. Controlling skin disease for as long as possible with topical therapies is important as it reduces the need for systemic treatment which is more expensive and associated with greater toxicity. Improved skin disease control is associated with improved quality of life for patients. The potential to offer a long term remission, reduce the risk of disease progression or delay the need for systemic therapy in a subset of early stage IA patients should not be dismissed from the evidence provided by historical data for nitrogen mustard. The committee acknowledge the need for alternative treatments for MF-CTCL and the unmet needs of patients with limited early stage disease – yet despite this fail to recommend Chlormethine gel for NHS use. This will leave patients with limited skin directed choices between topical steroids, phototherapy, radiotherapy or no specific therapy if the latter are unsuitable. Topical steroids have typically been tried by most patients with MF-CTCL prior to diagnosis. The treatment may improve symptoms in the short term by suppressing skin lesions, but unlike Chlormethine gel rarely clears them. Potent or super potent topical steroids are required and have significant side effects and risks over time: skin lesion rebound, skin atrophy, telangiectasia, striae and cutaneous infection. Recent data shows that long term use of potent topical steroids contribute to glucocorticoid induced osteoporosis[14]. Phototherapy is an inconvenient hospital based therapy, exposes the whole skin surface to the effects of UV light and has a finite recommended cumulative dose due to carcinogenicity. Radiotherapy is not suitable for young patients is also carcinogenic and is necessarily an expensive hospital based therapy to provide. In contrast a population based cohort study did not show that nitrogen mustard was associated with an increased risk of secondary cancers and comorbidities in MF-CTCL[15]. The committee have failed to recommend Chlormethine gel based on cost effectiveness models despite acknowledging that the assumptions used in these models are flawed. However, due to the rarity of MF-CTCL the **overall costs to the NHS** from recommending this therapy will be low compared to the costs of providing therapy for other common cancers.	Comments noted. The committee took these comments into consideration along with the company's updated models and the updated discount. Chlormethine gel is recommended for early stage MF-CTCL. Section 3.2 notes that the aim of all skin directed therapies is to relieve symptoms but has been amended to highlight that another skin-directed therapy could improve quality of life of patients. The impact of treatment with phototherapy (for example in reducing travel to hospital) is covered in section 3.1
5	Professional group	United Kingdom Cutaneous Lymphoma Group (UKCLG)	Lastly, the committee should not underestimate the effect of the Covid pandemic on the treatment choices for patient with MF-CTCL. During the first wave there was a disproportionate shutting down of dermatology services compared to other specialities. The effect of staff redeployment/shielding and self-isolation	Comments noted. The committee took these comments into consideration along with the company's updated models and the updated discount. Chlormethine gel is recommended for early stage MF-

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			led to many phototherapy units to shut completely. In some regions there are exceptionally long waiting times for UVB or PUVA treatment, some units are still not open or have shut again during the third wave of the pandemic. It will likely take several years for the effect of the Covid pandemic on phototherapy services to resolve. Chlormethine gel provides patients with a therapy which can be applied at home, reducing travel and footfall within hospitals. By not recommending Chlormethine gel for use in the NHS currently means that many patients with early stage disease have very limited access to specific therapy.	CTCL. The committee acknowledged the potential benefits of chlormethine gel in the context of COVID-19 in section 3.1.
6	Professional group	United Kingdom Cutaneous Lymphoma Group (UKCLG)	**References** 1. PHE. Cutaneous T-cell lymphoma short report NB241016, 2016. 2. Breast Cancer Statistic UK -World Cancer Research Fund. 3. The PROCLIPI international registry of early stage mycosis fungoides identifies substantial diagnostic delay in most patients. Scarisbrick J, Quaglino P, Prince HM et al. *Brit J Dermatol* 2019; **181**: 350-357. 4. Topical chemotherapy in cutaneous T-cell lymphoma: positive results of a randomised, controlled, multicentre trial testing the efficacy and safety of a novel mechlorethamine 0.02% gel in mycosis fungoides. Lessin SR, Duvic M, Guitart J et al. *JAMA Dermatol* 2013; 149: 25-32. 5. Topical nitrogen mustard in the management of mycosis fungoides: Update of the Stanford experience. Kim Y, Martinez G, Varghese A et al. *Arch Dermatol* 2003**; 39**: 165-173. 6. Long term efficacy, curative potential and carcinogenicity of topical mechlorethamine chemotherapy in cutaneous T-cell lymphoma. Vonderheid E, Tan E, Kantor A et al. *J Am Acad Dermatol* 1989; **20**: 416-428 7. Topical mechlorethamine therapy for early stage mycosis fungoides. Ramsay D, Halperin P, Zelenich-Jacquotte A. *J Am Acad Dermatol*. 1988; **19**: 684-691. 8. Recent clinical evidence for topical mechlorethamine in mycosis fungoides. Sahu J, Sepassi M, Nagato M et al. Clinical Investigation. *Clin Invest* 2014; **4**: 745–761.	Noted. No response required.
7	Company	Recordati Rare Diseases; Helsinn Healthcare SA	**When faced with uncertainty, the Committee preferences adopt a pessimistic view of chlormethine gel cost-effectiveness.** The company fully acknowledges that there is uncertainty with regards to a number of assumptions informing the economic analysis. However, we feel that the preferred analyses from the Evidence Review Group and National Institute for Health and Care Excellence Committee reflect a pessimistic estimate of the cost-effectiveness of chlormethine gel, and that this is not acknowledged in the interpretation of these analyses within the Appraisal Consultation Document. Notably, there are a number of decisions underpinning the cost-effectiveness	Comments noted. The committee acknowledged that there is considerable uncertainty in various inputs to the model (see section 3.8, 3.9). The FAD has been amended to acknowledge that the committee's preferred source for phototherapy may be optimistic for phototherapy and may have overestimated its effectiveness. Despite these uncertainties, the revised base case resulted in cost effectiveness estimates below what NICE normally considers an acceptable use of NHS

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			estimates where the National Institute for Health and Care Excellence Committee have stated a preference for inputs/assumptions that lead to the incremental cost-effectiveness ratio for chlormethine gel being a worst-case value. These include the use of dosing from the Valchor® summary of product characteristics (versus Study 201 individual patient data utilised by the company), the use of Phan *et al.* (2019) for all phototherapy efficacy estimates in the model (versus Whittaker *et al.* [2012] for duration of response or PROCLIPI data for complete/partial response rates) and, as per the Evidence Review Group's model, patients refractory to treatment with chlormethine gel were assumed to receive only one course of phototherapy before receiving systemic therapy.[1-3] A range of alternative scenarios and assumptions have been presented throughout the appraisal, reflecting the uncertainty in these parameters. We consider that there should be explicit acknowledgment that of this range of scenarios that have been presented, the preferences of the Evidence Review Group and the National Institute for Health and Care Excellence Committee stated in the Appraisal Consultation Document represent pessimistic scenarios with regards to cost-effectiveness of chlormethine gel.	resources and therefore chlormethine gel is recommended for early stage MF-CTCL. Section 3.6 of the FAD notes the concerns the company had with the committee's preferred assumptions which it included in its revised base case.
8	Company	Recordati Rare Diseases; Helsinn Healthcare SA	**The preference of the Committee for the Evidence Review Group's approach to modelling subsequent phototherapy following progressive disease with chlormethine gel is not aligned to clinical feedback; the company approach is more consistent with the likely clinical reality.** The company believes that the way in which the Evidence Review Group models the receipt of phototherapy following chlormethine gel for patients who do not respond to chlormethine gel in the first instance is a simplification that lacks face validity in representing clinical reality. In the Evidence Review Group model, following progressive disease with chlormethine gel, patients transition straight to the Systemic Therapy health state. The original 50:50 split between bexarotene and interferon-α in the Systemic Therapy state is adjusted to also include phototherapy in the treatment basket. Therefore, the Evidence Review Group have modelled a treatment distribution of bexarotene (44.65%), interferon-α (44.65%) and phototherapy (10.71%); this distribution aims to reflect an assumption that all patients entering this state receive a single course of phototherapy. The Evidence Review Group's approach was taken in order to create alignment between the chlormethine gel and phototherapy arms of the model in terms of patients progressing to Systemic Therapy upon an initial progressive disease. However, the company believes that this assumption does not accurately reflect clinical practice in the UK: • The approach taken by the Evidence Review Group does not account for the fact that patients can receive more than one cycle of phototherapy following chlormethine gel. Clinical expert feedback has indicated that the number of courses of phototherapy that patients would receive following progression on chlormethine gel is dependent on the type of phototherapy as well as the duration of response.	Comments noted. The committee were aware of the company's concerns with the ERG' s model. See section 3.6 of the FAD.

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			Psoralen-ultraviolet A and ultraviolet B have a limit of approximately seven courses and 11 courses, respectively due to carcinogenesis and skin cancer risk. With regards to duration of response, clinical experts have indicated that if a short duration occurs, then systemic therapy may be offered after 2–4 courses of phototherapy; however, if a longer duration is achieved, then patients may receive 1–2 courses per year, or a course every few years until the maximum number of courses has been reached. Therefore, assuming only one course of phototherapy following chlormethine gel is an underestimate.[4] • The approach taken by the Evidence Review Group is an oversimplification as it does not capture that patients may experience a range of responses to this phototherapy treatment. By maintaining the SDT health state, the company's model allows patients receiving treatment with phototherapy in this state to achieve complete response and subsequently enter the Watch and Wait health state, a partial response, transitioning to Reduced Skin Burden, or progressive disease, then progressing to Systemic Therapy, thereby aiming to reflect the potential pathway of patients following receipt of phototherapy. In contrast, the Evidence Review Group approach only captures the quality of life benefit of achieving a complete response to phototherapy. • The rationale for the Evidence Review Group's alternative approach was that the company approach "provides an unfair advantage for chlormethine gel by removing the direct transition to the systemic therapy state". It is true that the company approach is more favourable to chlormethine gel, but we do not consider that this is unfair; rather it is a correct reflection of clinical practice. Part of the value of chlormethine gel is providing a treatment option that delays the need for systemic therapies. Feedback from clinical experts in the UK has outlined that if patients experienced progressive disease with chlormethine gel, they would receive phototherapy before escalating to systemic therapy, whereas patients experiencing progressive disease with phototherapy would receive bexarotene or pegylated interferon-α (systemic therapies) straight away.[4] The company does, however, acknowledge that their approach may overestimate the utility that patients experience when receiving phototherapy following progressive disease on chlormethine gel. The SDT state in the company's model has a single utility value, and therefore implicitly assumes that the utility of patients who enter the SDT state following progressive disease to initial chlormethine gel treatment is the same as the utility of patients who have initially responded to chlormethine gel and subsequently relapsed. However, it may be more reasonable to assume that a patient who has experienced initial progressive disease and hence progressed to phototherapy would have	

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			reduced utility relative to a patient who has previously responded to chlormethine gel. Therefore, alternative analyses have been presented below (see **Error! Reference source not found.** and **Error! Reference source not found.**) whereby 1) the health state utility value of the SDT state for patients in the chlormethine gel arm is equivalent to the Systemic Therapy state and 2) the utility value for the SDT health state for patients in the chlormethine gel arm is a weighted average of the SDT health state (80%) and the Systemic Therapy health state (20%) in line with the proportion of patients who are the 'initial PD' patients and receive phototherapy in this health state (20%).	
9	Company	Recordati Rare Diseases; Helsinn Healthcare SA	**Mycosis fungoides-type cutaneous T-cell lymphoma is a rare disease with a poor evidence base for existing treatment options – uncertainty in the modelling approach is therefore inevitable and a greater degree of uncertainty should be accepted in this context.** The company acknowledge the underlying uncertainty associated with the cost-effectiveness estimates derived from the model. However, it is important to note that mycosis fungoides-type cutaneous T-cell lymphoma is a rare disease with a complex treatment pathway and very limited robust data for comparator therapies. Thus, modelling the decision problem for this submission in a way that reflects the clinical pathway is incredibly challenging with the available data. The company note that National Institute for Health and Care Excellence's ongoing methods review acknowledges such contexts, proposing that "a greater degree of uncertainty and risk should be accepted in defined circumstances, including conditions for which it is recognised that evidence generation is complex and difficult, such as rare diseases". In acknowledgement of the unavoidable uncertainty in this rare disease, the company has proposed revised and enhanced patient access schemes. Cost-effectiveness results with these patient access schemes incorporated are presented at the end of this document. As agreed through discussion with NHS England, a different level of discount is provided for the early-stage (Stage IA–IIA) population versus the Stage IA only population. Cost-effectiveness results from a series of alternative analyses have been presented, with the aim of demonstrating the effect of key model parameters on the incremental cost-effectiveness ratio for chlormethine gel versus phototherapy and providing the Committee with cost-effectiveness results corresponding to a range of assumptions previously discussed as part of this appraisal. Given the Appraisal Consultation Document suggests that the National Institute for Health and Care Excellence Committee would be interested in cost-effectiveness estimates for patients with Low Skin Burden as the most appropriate place in therapy for chlormethine gel, results for patients with early-stage disease and Stage IA disease only, respectively, have been presented. For transparency, it is important to note that the way in which the cost-effectiveness model has been developed means that explicitly modelling a Low	Comments noted. As the NICE's methods review is still ongoing, and the final methods are not yet agreed this approach cannot yet be adopted by the committee. Despite the uncertainties, the revised base case resulted in cost effectiveness estimates below what NICE normally considers an acceptable use of NHS resources and therefore chlormethine gel is recommended for early stage MF-CTCL.

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			Skin Burden population is not possible. However, the results presented for early-stage and Stage IA populations aim to provide the Committee and the Evidence Review Group with economic evidence that supports assessment of the cost-effectiveness of chlormethine gel in this Low Skin Burden population. Of note, according to the tumour-node-metastasis-blood classification system, all patients with Stage IA disease present with limited patches, papules and/or plaques covering <10% of the skin surface and can thus all be considered to have Low Skin Burden. All Stage IB patients present with patches, papules or plaques covering ≥10% of the skin surface and therefore many patients in this group may be considered to have High Skin Burden where lesions may vastly exceed ≥10% of the skin surface. Stage IIA patients may have Low or High Skin Burden (with data from the PROCLIPI registry suggesting that [redacted]% patients with Stage IIA disease have Low Skin Burden).[5, 6] The Stage IA results represent cost-effectiveness estimates for a population where 100% patients have Low Skin Burden. However, it is important to note that patients may have Low Skin Burden irrespective of disease stage, and hence the Stage IA population does not capture all patients with Low Skin Burden across disease stages (including other early-stage disease stages). Therefore, the results for the early-stage population have been presented to provide an analysis in a broader population that includes Low Skin Burden patients from multiple disease stages, in addition to some patients with High Skin Burden. It should be noted that the analysis of the early-stage population likely represents a conservative estimate of the cost-effectiveness of chlormethine gel in a population of patients with Low Skin Burden (either irrespective of disease stage, or a population defined as 'early-stage disease and Low Skin Burden'). This is because some patients in the early-stage population (most Stage IB patients and some patients with Stage IIA) would be considered to have High Skin Burden, leading to a higher consumption of chlormethine gel and therefore greater treatment costs. The company believes that it is in patients' best interests for chlormethine gel to be available for all early-stage patients, irrespective of disease stage within this, in order to allow physicians to use chlormethine gel to treat patients whom they consider as having Low Skin Burden. This would avoid a situation where patients for whom chlormethine gel is the most suitable treatment based on their level of skin burden are precluded from accessing this skin-directed therapy due to disease factors separate to the skin burden that influence disease stage classification (such as nodal involvement). Overall, as chlormethine gel is a treatment for the skin lesions associated with mycosis fungoides-type cutaneous T-cell lymphoma, limiting its use to a particular disease stage (rather than level of skin burden) would not be beneficial for patients, as skin burden is not the only factor influencing disease stage. Finally, with regards to the cost-effectiveness analyses presented in this	

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
			document, the availability of a confidential patient access scheme for bexarotene means that determining the cost-effectiveness estimates that the Committee will use in decision-making is a black box for the company. The company has provided results with an assumed bexarotene patient access scheme ([redacted]) as an illustrative example.	
10	Company	Recordati Rare Diseases; Helsinn Healthcare SA	**Additional comments on the wording of the Appraisal Consultation Document.** Lastly, the company would like to suggest revisions to the following statements in the Appraisal Consultation Document: • *However, because the comparator ointment is no longer used in clinical practice, the committee concluded that Study 201 does not show how effective chlormethine gel is compared with standard care. Moreover, no advanced stage patients were included in the trial so the effectiveness in people who have advanced disease or are also on chemotherapy is not known* o Although no advanced stage patients were included in Study 201, data from real-world evidence to support the use of chlormethine gel in this population are available.[7-9] The statement currently in the Appraisal Consultation Document is misleading as it implies that chlormethine gel has never been investigated in advanced stage patients. We would propose a rewording to *"Moreover, no advanced stage patients were included in the trial, so Study 201 does not provide evidence for the efficacy in people who have advanced disease"* • *The company also introduced a watch and wait state in its updated model for people who have an initial complete response. This was after patient input that, for people whose skin disease progressed after treatment, but whose symptoms are limited and are not affecting their functioning, a watch and wait approach is typical in practice before resuming treatment.* o For accuracy, the introduction of a Watch and Wait state was based on *clinical expert* input, though patient input would likely have been in agreement. • *In the chlormethine gel arm, if skin symptoms return after initial treatment 80% are offered a second round of chlormethine gel and the other 20% phototherapy. The ERG considered it likely that everyone whose disease responded to chlormethine gel would be offered it again.* o This statement misinterprets the role of the SDT state in the company model. In the company model, the SDT state captures patients who enter this state upon relapse following an initial response to chlormethine gel (these patients would receive repeat chlormethine gel) and patients who enter this	Comments noted. Since the company is no longer seeking a recommendation for advanced stage disease, this text has been removed. Section 3.4 now has a sentence that clarifies that no advanced stage patients were in the trial. This has been removed from the FAD which now focuses on the changes between the 2nd and 3rd meeting. As the company's model no longer has patients with refractory disease entering the SDT state and all patients with relapsed disease receive a second round of chlormethine gel, this text has been removed from the FAD.

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
			state following an initial progressive disease on chlormethine gel (these patients would receive phototherapy). The single SDT state with an assumed 80/20 split of chlormethine gel and phototherapy is a simplification to prevent the need for multiple SDT health states in the model based on prior treatment. The distribution of treatments applied within the health state (i.e. 80/20) is assumed to reflect the overall distribution of treatments that a patient cohort would receive as subsequent SDT in line with the different origin of treatments entering this state as described in the previous sentence (i.e. post progressive disease versus post relapse). The figure of 20% was based on the fact that 20% patients in Study 201 experienced progressive disease and would therefore likely receive phototherapy in clinical practice. The company agree that it is likely that everyone whose disease responded to chlormethine gel would be offered it again, but in the company model (which this section of the Appraisal Consultation Document is describing) the SDT state does not capture only these patients. This wording therefore misrepresents the company model, implying that the company model does not reflect that patients who respond to chlormethine gel would be offered it again, whereas in fact this assumption is accounted for in the company SDT state. • *The ERG was concerned about the quality of all sources of data for the effectiveness of phototherapy. It was particularly concerned with the company's use of Whittaker et al. (2012) because it had a small sample size and excluded people with stage 1A disease. The ERG preferred to use Phan et al. (2019) for all outcome measures because it ensured the same, consistent source of data for response rates and duration, reducing potential bias, and because it separates outcomes by type of phototherapy and stage of disease.* ○ The wording in the Appraisal Consultation Document highlights the limitations associated with Whittaker *et al.* (2012) here but does not mention those associated with Phan *et al.* (2019), leading to an unbalanced interpretation of the available sources.[1, 2] Some of the relevant limitations of Phan *et al.* (2019) are mentioned elsewhere in the Appraisal Consultation Document; however, the limitations of Phan *et al.* (2019) should be mentioned here for full transparency and balanced interpretation.[2] • *Comparison of symptom response rates from Study 201 and the phototherapy trials used in the model suggested that chlormethine gel may be less effective than phototherapy for treating skin symptoms.* ○ There is no mention within this statement that the response	As noted, the limitations of Phan et al were summarised earlier in section 3.6; so a cross-reference has been added to this section of the FAD. This text has been removed from the FAD.

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
			measures utilised in phototherapy trials are largely based on subjective measures, which may lead to overestimates of efficacy. This is important context for interpreting the comparison between response rates, and hence should be included to provide a reasonable interpretation of the evidence. Furthermore, as described previously by the company, complete and partial response data for phototherapy from the PROCLIPI registry (derived from UK clinical practice) support this argument, as response rates for phototherapy from PROCLIPI were lower than those reported in Phan *et al.* (2019), and were based on an objective response measure ([redacted]).[2, 5]	
11	Company	Recordati Rare Diseases; Helsinn Healthcare SA	**References** 1. Whittaker S, Ortiz P, Dummer R, et al. 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). Br J Dermatol 2012;167:678-87. 2. Phan K, Ramachandran V, Fassihi H, et al. Comparison of Narrowband UV-B With Psoralen–UV-A Phototherapy for Patients With Early-Stage Mycosis Fungoides: A Systematic Review and Meta-analysis. JAMA Dermatology 2019;155:335-341. 3. Food and Drug Administration (FDA). Valchor Summary of Product Characteristics (SmPC). August 2013. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2013/202317lbl.pdf [Last Accessed 04 February 2021]. 4. Recordati Rare Diseases/Helsinn Healthcare SA. Data on File. UK Clinical Validation. 2019-2021. 5. PROCLIPI Registry Data. 2019. 6. Olsen E, Vonderheid E, Pimpinelli N, et al. Revisions to the staging and classification of mycosis fungoides and Sezary syndrome: a proposal of the International Society for Cutaneous Lymphomas (ISCL) and the cutaneous lymphoma task force of the European Organization of	Noted. No response required.

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
			Research and Treatment of Cancer (EORTC). Blood 2007;110:1713-22. 7. Recordati Rare Diseases/Helsinn Healthcare SA. Data on file. Rapport de synthese pour valchlor™/ledaga® (chlorméthine ou méchloréthamine). 8. Bagot M, Beylot-Barry M, Grange F, et al. Use of chlormethine (CL) gel in the treatment of mycosis fungoides (MF) from the French early access program. EADV 2019 Oral Presentation 2019. 9. Kim EJ, Geskin LJ, Querfeld C, et al. Efficacy and quality of life (QoL) in patients with mycosis fungoides cutaneous T-cell lymphoma (MF-CTCL) treated with chlormethine gel and other therapies: results from the PROVe study. Abstract. European Journal of Cancer 2019;119:S39.	

NICE National Institute for Health and Care Excellence

Chlormethine gel for treating mycosis fungoides-type cutaneous T-cell lymphoma [ID1589]

Consultation on the appraisal consultation document – deadline for comments 5pm on Wednesday 17 February 2021 **email:** NICE DOCS

	Please read the checklist for submitting comments at the end of this form. We cannot accept forms that are not filled in correctly. The Appraisal Committee is interested in receiving comments on the following: • has all of the relevant evidence been taken into account? • are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? • are the provisional recommendations sound and a suitable basis for guidance to the NHS? NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the preliminary recommendations may need changing in order to meet these aims. In particular, please tell us if the preliminary recommendations: • could have a different impact on people protected by the equality legislation than on the wider population, for example by making it more difficult in practice for a specific group to access the technology; • could have any adverse impact on people with a particular disability or disabilities. Please provide any relevant information or data you have regarding such impacts and how they could be avoided or reduced**.**
Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	Recordati Rare Diseases; Helsinn Healthcare SA (Recordati/Helsinn; collectively 'the company')
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None.
Name of commentator person completing form:	[redacted]

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Chlormethine gel for treating mycosis fungoides-type cutaneous T-cell lymphoma [ID1589]

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Comment number	Comments Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
1	**When faced with uncertainty, the Committee preferences adopt a pessimistic view of chlormethine gel cost-effectiveness.** The company fully acknowledges that there is uncertainty with regards to a number of assumptions informing the economic analysis. However, we feel that the preferred analyses from the Evidence Review Group and National Institute for Health and Care Excellence Committee reflect a pessimistic estimate of the cost-effectiveness of chlormethine gel, and that this is not acknowledged in the interpretation of these analyses within the Appraisal Consultation Document. Notably, there are a number of decisions underpinning the cost-effectiveness estimates where the National Institute for Health and Care Excellence Committee have stated a preference for inputs/assumptions that lead to the incremental cost-effectiveness ratio for chlormethine gel being a worst-case value. These include the use of dosing from the Valchor® summary of product characteristics (versus Study 201 individual patient data utilised by the company), the use of Phan *et al.* (2019) for all phototherapy efficacy estimates in the model (versus Whittaker *et al.* [2012] for duration of response or PROCLIPI data for complete/partial response rates) and, as per the Evidence Review Group's model, patients refractory to treatment with chlormethine gel were assumed to receive only one course of phototherapy before receiving systemic therapy.[1-3] A range of alternative scenarios and assumptions have been presented throughout the appraisal, reflecting the uncertainty in these parameters. We consider that there should be explicit acknowledgment that of this range of scenarios that have been presented, the preferences of the Evidence Review Group and the National Institute for Health and Care Excellence Committee stated in the Appraisal Consultation Document represent pessimistic scenarios with regards to cost-effectiveness of chlormethine gel.
2	**The preference of the Committee for the Evidence Review Group's approach to modelling subsequent phototherapy following progressive disease with chlormethine gel is not aligned to clinical feedback; the company approach is more consistent with the likely clinical reality.** The company believes that the way in which the Evidence Review Group models the receipt of phototherapy following chlormethine gel for patients who do not respond to chlormethine gel in the first instance is a simplification that lacks face validity in representing clinical reality. In the Evidence Review Group model, following progressive disease with chlormethine gel, patients transition straight to the Systemic Therapy health state. The original 50:50 split between bexarotene and interferon-α in the Systemic Therapy state is adjusted to also include phototherapy in the treatment basket. Therefore, the Evidence Review Group have modelled a treatment distribution of bexarotene (44.65%), interferon-α (44.65%) and phototherapy (10.71%); this distribution aims to reflect an assumption that all patients entering this state receive a single course of phototherapy. The Evidence Review Group's approach was taken in order to create alignment between the chlormethine gel and phototherapy arms of the model in terms of patients progressing to Systemic Therapy upon an initial progressive disease. However, the company believes that this assumption does not accurately reflect clinical practice in the UK: • The approach taken by the Evidence Review Group does not account for the fact that patients can receive more than one cycle of phototherapy following chlormethine gel. Clinical expert feedback has indicated that the number of courses of phototherapy that patients would receive following progression on chlormethine gel is dependent on the type of phototherapy as well as the duration of response.

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	Psoralen-ultraviolet A and ultraviolet B have a limit of approximately seven courses and 11 courses, respectively due to carcinogenesis and skin cancer risk. With regards to duration of response, clinical experts have indicated that if a short duration occurs, then systemic therapy may be offered after 2–4 courses of phototherapy; however, if a longer duration is achieved, then patients may receive 1–2 courses per year, or a course every few years until the maximum number of courses has been reached. Therefore, assuming only one course of phototherapy following chlormethine gel is an underestimate.[4] • The approach taken by the Evidence Review Group is an oversimplification as it does not capture that patients may experience a range of responses to this phototherapy treatment. By maintaining the SDT health state, the company's model allows patients receiving treatment with phototherapy in this state to achieve complete response and subsequently enter the Watch and Wait health state, a partial response, transitioning to Reduced Skin Burden, or progressive disease, then progressing to Systemic Therapy, thereby aiming to reflect the potential pathway of patients following receipt of phototherapy. In contrast, the Evidence Review Group approach only captures the quality of life benefit of achieving a complete response to phototherapy. • The rationale for the Evidence Review Group's alternative approach was that the company approach "provides an unfair advantage for chlormethine gel by removing the direct transition to the systemic therapy state". It is true that the company approach is more favourable to chlormethine gel, but we do not consider that this is unfair; rather it is a correct reflection of clinical practice. Part of the value of chlormethine gel is providing a treatment option that delays the need for systemic therapies. Feedback from clinical experts in the UK has outlined that if patients experienced progressive disease with chlormethine gel, they would receive phototherapy before escalating to systemic therapy, whereas patients experiencing progressive disease with phototherapy would receive bexarotene or pegylated interferon-α (systemic therapies) straight away.[4] The company does, however, acknowledge that their approach may overestimate the utility that patients experience when receiving phototherapy following progressive disease on chlormethine gel. The SDT state in the company's model has a single utility value, and therefore implicitly assumes that the utility of patients who enter the SDT state following progressive disease to initial chlormethine gel treatment is the same as the utility of patients who have initially responded to chlormethine gel and subsequently relapsed. However, it may be more reasonable to assume that a patient who has experienced initial progressive disease and hence progressed to phototherapy would have reduced utility relative to a patient who has previously responded to chlormethine gel. Therefore, alternative analyses have been presented below (see **Error! Reference source not found.** and **Error! Reference source not found.**) whereby 1) the health state utility value of the SDT state for patients in the chlormethine gel arm is equivalent to the Systemic Therapy state and 2) the utility value for the SDT health state for patients in the chlormethine gel arm is a weighted average of the SDT health state (80%) and the Systemic Therapy health state (20%) in line with the proportion of patients who are the 'initial PD' patients and receive phototherapy in this health state (20%).
3	**Mycosis fungoides-type cutaneous T-cell lymphoma is a rare disease with a poor evidence base for existing treatment options – uncertainty in the modelling approach is therefore inevitable and a greater degree of uncertainty should be accepted in this context.** The company acknowledge the underlying uncertainty associated with the cost-effectiveness estimates derived from the model. However, it is important to note that mycosis fungoides-type cutaneous T-cell lymphoma is a rare disease with a complex treatment pathway and very limited robust

	data for comparator therapies. Thus, modelling the decision problem for this submission in a way that reflects the clinical pathway is incredibly challenging with the available data. The company note that National Institute for Health and Care Excellence's ongoing methods review acknowledges such contexts, proposing that "a greater degree of uncertainty and risk should be accepted in defined circumstances, including conditions for which it is recognised that evidence generation is complex and difficult, such as rare diseases". In acknowledgement of the unavoidable uncertainty in this rare disease, the company has proposed revised and enhanced patient access schemes. Cost-effectiveness results with these patient access schemes incorporated are presented at the end of this document. As agreed through discussion with NHS England, a different level of discount is provided for the early-stage (Stage IA–IIA) population versus the Stage IA only population. Cost-effectiveness results from a series of alternative analyses have been presented, with the aim of demonstrating the effect of key model parameters on the incremental cost-effectiveness ratio for chlormethine gel versus phototherapy and providing the Committee with cost-effectiveness results corresponding to a range of assumptions previously discussed as part of this appraisal. Given the Appraisal Consultation Document suggests that the National Institute for Health and Care Excellence Committee would be interested in cost-effectiveness estimates for patients with Low Skin Burden as the most appropriate place in therapy for chlormethine gel, results for patients with early-stage disease and Stage IA disease only, respectively, have been presented. For transparency, it is important to note that the way in which the cost-effectiveness model has been developed means that explicitly modelling a Low Skin Burden population is not possible. However, the results presented for early-stage and Stage IA populations aim to provide the Committee and the Evidence Review Group with economic evidence that supports assessment of the cost-effectiveness of chlormethine gel in this Low Skin Burden population. Of note, according to the tumour-node-metastasis-blood classification system, all patients with Stage IA disease present with limited patches, papules and/or plaques covering <10% of the skin surface and can thus all be considered to have Low Skin Burden. All Stage IB patients present with patches, papules or plaques covering ≥10% of the skin surface and therefore many patients in this group may be considered to have High Skin Burden where lesions may vastly exceed ≥10% of the skin surface. Stage IIA patients may have Low or High Skin Burden (with data from the PROCLIPI registry suggesting that [redacted]% patients with Stage IIA disease have Low Skin Burden).[5, 6] The Stage IA results represent cost-effectiveness estimates for a population where 100% patients have Low Skin Burden. However, it is important to note that patients may have Low Skin Burden irrespective of disease stage, and hence the Stage IA population does not capture all patients with Low Skin Burden across disease stages (including other early-stage disease stages). Therefore, the results for the early-stage population have been presented to provide an analysis in a broader population that includes Low Skin Burden patients from multiple disease stages, in addition to some patients with High Skin Burden. It should be noted that the analysis of the early-stage population likely represents a conservative estimate of the cost-effectiveness of chlormethine gel in a population of patients with Low Skin Burden (either irrespective of disease stage, or a population defined as 'early-stage disease and Low Skin Burden'). This is because some patients in the early-stage population (most Stage IB patients and some patients with Stage IIA) would be considered to have High Skin Burden, leading to a higher consumption of chlormethine gel and therefore greater treatment costs. The company believes that it is in patients' best interests for chlormethine gel to be available for all early-stage patients, irrespective of disease stage within this, in order to allow physicians to use chlormethine gel to treat patients whom they consider as having Low Skin Burden. This would avoid a

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	situation where patients for whom chlormethine gel is the most suitable treatment based on their level of skin burden are precluded from accessing this skin-directed therapy due to disease factors separate to the skin burden that influence disease stage classification (such as nodal involvement). Overall, as chlormethine gel is a treatment for the skin lesions associated with mycosis fungoides-type cutaneous T-cell lymphoma, limiting its use to a particular disease stage (rather than level of skin burden) would not be beneficial for patients, as skin burden is not the only factor influencing disease stage. Finally, with regards to the cost-effectiveness analyses presented in this document, the availability of a confidential patient access scheme for bexarotene means that determining the cost-effectiveness estimates that the Committee will use in decision-making is a black box for the company. The company has provided results with an assumed bexarotene patient access scheme ([redacted]) as an illustrative example.
4	**Additional comments on the wording of the Appraisal Consultation Document.** Lastly, the company would like to suggest revisions to the following statements in the Appraisal Consultation Document: • *However, because the comparator ointment is no longer used in clinical practice, the committee concluded that Study 201 does not show how effective chlormethine gel is compared with standard care. Moreover, no advanced stage patients were included in the trial so the effectiveness in people who have advanced disease or are also on chemotherapy is not known* ○ Although no advanced stage patients were included in Study 201, data from real-world evidence to support the use of chlormethine gel in this population are available.[7-9] The statement currently in the Appraisal Consultation Document is misleading as it implies that chlormethine gel has never been investigated in advanced stage patients. We would propose a rewording to *"Moreover, no advanced stage patients were included in the trial, so Study 201 does not provide evidence for the efficacy in people who have advanced disease"* • *The company also introduced a watch and wait state in its updated model for people who have an initial complete response. This was after patient input that, for people whose skin disease progressed after treatment, but whose symptoms are limited and are not affecting their functioning, a watch and wait approach is typical in practice before resuming treatment.* ○ For accuracy, the introduction of a Watch and Wait state was based on *clinical expert* input, though patient input would likely have been in agreement. • *In the chlormethine gel arm, if skin symptoms return after initial treatment 80% are offered a second round of chlormethine gel and the other 20% phototherapy. The ERG considered it likely that everyone whose disease responded to chlormethine gel would be offered it again.* ○ This statement misinterprets the role of the SDT state in the company model. In the company model, the SDT state captures patients who enter this state upon relapse following an initial response to chlormethine gel (these patients would receive repeat chlormethine gel) and patients who enter this state following an initial progressive disease on chlormethine gel (these patients would receive phototherapy). The single SDT state with an assumed 80/20 split of chlormethine gel and phototherapy is a simplification to prevent the need for multiple SDT health states in the model based on prior treatment. The distribution of treatments applied within the health state (i.e. 80/20) is assumed to reflect the overall distribution of treatments that a patient cohort would receive as subsequent SDT in line with the different origin of treatments entering this state as described in the previous sentence (i.e. post progressive disease

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	versus post relapse). The figure of 20% was based on the fact that 20% patients in Study 201 experienced progressive disease and would therefore likely receive phototherapy in clinical practice. The company agree that it is likely that everyone whose disease responded to chlormethine gel would be offered it again, but in the company model (which this section of the Appraisal Consultation Document is describing) the SDT state does not capture only these patients. This wording therefore misrepresents the company model, implying that the company model does not reflect that patients who respond to chlormethine gel would be offered it again, whereas in fact this assumption is accounted for in the company SDT state. • *The ERG was concerned about the quality of all sources of data for the effectiveness of phototherapy. It was particularly concerned with the company's use of Whittaker et al. (2012) because it had a small sample size and excluded people with stage 1A disease. The ERG preferred to use Phan et al. (2019) for all outcome measures because it ensured the same, consistent source of data for response rates and duration, reducing potential bias, and because it separates outcomes by type of phototherapy and stage of disease.* ○ The wording in the Appraisal Consultation Document highlights the limitations associated with Whittaker *et al.* (2012) here but does not mention those associated with Phan *et al.* (2019), leading to an unbalanced interpretation of the available sources.[1, 2] Some of the relevant limitations of Phan *et al.* (2019) are mentioned elsewhere in the Appraisal Consultation Document; however, the limitations of Phan *et al.* (2019) should be mentioned here for full transparency and balanced interpretation.[2] • *Comparison of symptom response rates from Study 201 and the phototherapy trials used in the model suggested that chlormethine gel may be less effective than phototherapy for treating skin symptoms.* ○ There is no mention within this statement that the response measures utilised in phototherapy trials are largely based on subjective measures, which may lead to overestimates of efficacy. This is important context for interpreting the comparison between response rates, and hence should be included to provide a reasonable interpretation of the evidence. Furthermore, as described previously by the company, complete and partial response data for phototherapy from the PROCLIPI registry (derived from UK clinical practice) support this argument, as response rates for phototherapy from PROCLIPI were lower than those reported in Phan *et al.* (2019), and were based on an objective response measure ([redacted]).[2, 5]

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- Complete the disclosure about links with, or funding from, the tobacco industry.
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Cost-effectiveness results

Cost-effectiveness analyses are presented below based on modelling the early-stage population and the Stage IA population. As described earlier, these analyses are presented in the absence of being able to model a Low Skin Burden population specifically; please see the company response above for discussion of the relationship of these analyses to a Low Skin Burden population. The patient access scheme for chlormethine gel applied for the modelled early-stage population is [redacted] and for the Stage IA population is [redacted]. The patient access scheme the company is able to offer is linked to expected number of patients, hence two different patient access schemes are presented depending on the population in question. This approach (having a different level of discount depending on the population considered) has been confirmed with NHS England. It should be noted that the [redacted] PAS would apply to a population defined as "early-stage" or a population defined as "Low Skin Burden" (either within early stage, or irrespective of stage). However, for a population restricted to Stage IA specifically, the company can only support a PAS of [redacted]. These patient access schemes represent a revised and enhanced offer relative to that considered at the 2nd Committee meeting. All results are presented with these patient access schemes for chlormethine gel. As described above, the results presented below also include a column specifying the net monetary benefit when a [redacted] patient access scheme for bexarotene is assumed. These are provided to illustrate the impact of a potential bexarotene patient access scheme, as a confidential discount for bexarotene is known to exist, but the value of this discount is not known by the company.

Economic analyses that adopt the Committee preferred assumptions from the 2nd Appraisal Consultation Document are provided below in **Error! Reference source not found.** and **Error! Reference source not found.**, in order to illustrate the impact of the revised patient access scheme and the focus on early-stage and Stage IA populations. The '2nd Appraisal Consultation Document Committee preferred' results are based on the following assumptions as outlined in the Appraisal Consultation Document:

- Patients who are disease refractory to chlormethine gel or phototherapy proceed to the Systemic Therapy health state; those in the chlormethine arm are assumed to have one course of phototherapy before moving on to systemic treatment
- Re-treatment with a skin-directed therapy is associated with the same efficacy as initial treatment
- Phan *et al.* (2019) is used to inform all phototherapy efficacy parameters[2]
- The mean daily dose for chlormethine gel was derived from the Valchor® summary of product characteristics[3]

As outlined in the company response, there are a number of areas where the company either disagrees with these Committee preferred assumptions or considers that the Committee preferred assumptions represent a pessimistic view and that it is important to also consider alternative analyses that reflect the range of uncertainty. Accordingly, variations from the Committee preferred assumptions are described in the "alternative analysis" tables below (see **Error! Reference source not found.** and **Error! Reference source not found.**).

It should be noted that the analysis of the early-stage population may represent a conservative estimate of the cost-effectiveness of chlormethine gel in a population of patients with Low Skin Burden (either irrespective of disease stage, or a population defined as early-stage disease and Low Skin Burden). This is because some patients in the early-stage population (most Stage IB patients and some patients with Stage IIA) would be considered to have High Skin Burden, leading to a higher consumption of chlormethine gel and therefore greater treatment costs.

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2nd Appraisal Consultation Document Committee preferred analyses with revised chlormethine gel patient access scheme

Early-stage disease

Table 1: Early stage – [redacted] chlormethine gel patient access scheme

	Total costs	Total LYs	Total QALYs	Incremental costs	Incremental LYs	Incremental QALYs	Chlormethine gel ICER (£/QALY)	NMB	NMB (with assumed [redacted] bexarotene PAS)
Chlormethine gel	[redacted]	12.37	[redacted]	-	-	-	-	-	-
Phototherapy (PUVA/UVB)	[redacted]	12.37	[redacted]	[redacted]	0.00	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ICER: incremental cost effectiveness ratio; LY: life year; NMB: net monetary benefit; PAS: patient access scheme; PUVA: psoralen-ultraviolet A; QALY: quality adjusted life year; UVB: ultraviolet B.

Stage IA

Table 2: Stage IA – [redacted] chlormethine gel patient access scheme

	Total costs	Total LYs	Total QALYs	Incremental costs	Incremental LYs	Incremental QALYs	Chlormethine gel ICER (£/QALY)	NMB	NMB (with assumed [redacted] bexarotene PAS)
Chlormethine gel	[redacted]	13.76	[redacted]	-	-	-	-	-	-
Phototherapy (PUVA/UVB)	[redacted]	13.76	[redacted]	[redacted]	0.00	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ICER: incremental cost effectiveness ratio; LY: life year; NMB: net monetary benefit; PAS: patient access scheme; PUVA: psoralen-ultraviolet A; QALY: quality adjusted life year; UVB: ultraviolet B.

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Alternative analyses

The alternative analyses presented below stem from the Committee preferred assumptions outlined above. However, as mentioned previously in this response, the company believe that the way in which the Evidence Review Group has modelled subsequent phototherapy following progressive disease with chlormethine gel (and the approach for which the Committee have indicated a preference) is not aligned to clinical feedback. The company consider that a model in which chlormethine gel patients who experience an initial progressive disease transition to the SDT state is more reflective of clinical reality. The company accept that there may be a need to adjust utility values applied in the SDT state to account for the fact that this approach may overestimate the utility that patients experience when receiving phototherapy following progressive disease on chlormethine gel. Therefore, further alternative analyses are presented below where this utility value is altered to 1) set the health state utility value of the SDT state for patients in the chlormethine gel arm equivalent to the Systemic Therapy state and 2) set the utility value for the SDT health state for patients in the chlormethine gel arm as a weighted average of the SDT health state (80%) and the Systemic Therapy health state (20%), in line with the proportion of patients who are the 'initial PD' patients and receive phototherapy in this health state (20%) compared to patients who have relapsed following an initial response to chlormethine gel (80%). As shown in **Error! Reference source not found.** and **Error! Reference source not found.** below, altering this utility value has a minimal impact on the cost-effectiveness results. Furthermore, alternative analyses have also been presented to demonstrate the effects of altering sources of phototherapy efficacy, as this represents a key unresolvable area of uncertainty in the appraisal and the company considers it important to reflect the impact of this uncertainty on cost-effectiveness results. The net monetary benefit from analyses where phototherapy efficacy inputs are altered varies from [redacted] in the early-stage population and [redacted] in the Stage IA population.

Early stage

Table 3: Alternative results for early-stage – ([redacted]) chlormethine gel patient access scheme

#	Description	Incremental costs	Incremental QALYs	Chlormethine gel ICER (£/QALY)	NMB	NMB (with assumed bexarotene PAS)
1.	• 'Committee preferred' assumptions	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
2.	• 'Committee preferred' assumptions • + PD chlormethine patients go to SDT health state	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
2.1.	• 'Committee preferred' assumptions • + PD chlormethine patients go to SDT health state • + HSUV SDT = Systemic Therapy (chlormethine gel arm)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
2.2.	• 'Committee preferred' assumptions • + PD chlormethine patients go to SDT health state	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

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	• + HSUV SDT = 80% SDT and 20% Systemic Therapy (chlormethine gel arm)					
3.	• 'Committee preferred' assumptions • + PD chlormethine patients go to SDT health state • + Company preferred source for relapse post-CR (Whittaker *et al.* [2012])[1]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
4.	• 'Committee preferred' assumptions • + Company preferred source for relapse post-CR (Whittaker *et al.* [2012])[1]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
5.	• 'Committee preferred' assumptions • + Company preferred source for relapse post-CR (Whittaker *et al.* [2012])[1] • + Company preferred source for relapse post-PR (assumed equal to initial PD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
6.	• 'Committee preferred' assumptions • + PD chlormethine patients go to SDT health state • + Company preferred source for relapse post-CR (Whittaker *et al.* [2012])[1] • + Company preferred source for relapse post-PR (assumed equal to initial PD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
7.	• 'Committee preferred' assumptions • + PROCLIPI efficacy for phototherapy CR/PR[5]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: CR: complete response; HSUV: health state utility value; ICER: incremental cost effectiveness ratio; LY: life year; NMB: net monetary benefit; PAS: patient access scheme; PD: progressive disease; PR: partial response; PUVA: psoralen-ultraviolet A; QALY: quality adjusted life year; SDT: skin-directed therapy; UVB: ultraviolet B.

Stage IA

Table 4: Alternative results for Stage IA – ([redacted]) chlormethine gel patient access scheme

#	Description	Incremental costs	Incremental QALYs	Chlormethine gel ICER (£/QALY)	NMB	NMB (with assumed bexarotene PAS)

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1.	• 'Committee preferred' assumptions (as per **Error! Reference source not found.**)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
2.	• 'Committee preferred' assumptions • + PD chlormethine patients go to SDT health state	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
2.1.	• 'Committee preferred' assumptions • + PD chlormethine patients go to SDT health state • + HSUV SDT = Systemic Therapy (chlormethine gel arm)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
2.2.	• 'Committee preferred' assumptions • + PD chlormethine patients go to SDT health state • + HSUV SDT = 80% SDT and 20% Systemic Therapy (chlormethine gel arm)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
3.	• 'Committee preferred' assumptions • + PD chlormethine patients go to SDT health state • + Company preferred source for relapse post-CR (Whittaker *et al.* [2012])[1]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
4.	• 'Committee preferred' assumptions • + Company preferred source for relapse post-CR (Whittaker *et al.* [2012])[1]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
5.	• 'Committee preferred' assumptions • + Company preferred source for relapse post-CR (Whittaker *et al.* [2012])[1] • + Company preferred source for relapse post-PR (assumed equal to initial PD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
6.	• 'Committee preferred' assumptions • + PD chlormethine patients go to SDT health state • + Company preferred source for relapse post-CR (Whittaker *et al.* [2012])[1]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

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	• + Company preferred source for relapse post-PR (assumed equal to initial PD)					
7.	• 'Committee preferred' assumptions • + PROCLIPI efficacy for phototherapy CR/PR[5]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: CR: complete response; HSUV: health state utility value; ICER: incremental cost effectiveness ratio; LY: life year; NMB: net monetary benefit; PAS: patient access scheme; PD: progressive disease; PR: partial response; PUVA: psoralen-ultraviolet A; QALY: quality adjusted life year; SDT: skin-directed therapy; UVB: ultraviolet B.

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References

1. Whittaker S, Ortiz P, Dummer R, et al. 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). Br J Dermatol 2012;167:678-87.

2. Phan K, Ramachandran V, Fassihi H, et al. Comparison of Narrowband UV-B With Psoralen–UV-A Phototherapy for Patients With Early-Stage Mycosis Fungoides: A Systematic Review and Meta-analysis. JAMA Dermatology 2019;155:335-341.

3. Food and Drug Administration (FDA). Valchor Summary of Product Characteristics (SmPC). August 2013. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2013/202317lbl.pdf [Last Accessed 04 February 2021].

4. Recordati Rare Diseases/Helsinn Healthcare SA. Data on File. UK Clinical Validation. 2019-2021.

5. PROCLIPI Registry Data. 2019.

6. Olsen E, Vonderheid E, Pimpinelli N, et al. Revisions to the staging and classification of mycosis fungoides and Sezary syndrome: a proposal of the International Society for Cutaneous Lymphomas (ISCL) and the cutaneous lymphoma task force of the European Organization of Research and Treatment of Cancer (EORTC). Blood 2007;110:1713-22.

7. Recordati Rare Diseases/Helsinn Healthcare SA. Data on file. Rapport de synthese pour valchlor™/ledaga® (chlorméthine ou méchloréthamine).

8. Bagot M, Beylot-Barry M, Grange F, et al. Use of chlormethine (CL) gel in the treatment of mycosis fungoides (MF) from the French early access program. EADV 2019 Oral Presentation 2019.

9. Kim EJ, Geskin LJ, Querfeld C, et al. Efficacy and quality of life (QoL) in patients with mycosis fungoides cutaneous T-cell lymphoma (MF-CTCL) treated with chlormethine gel and other therapies: results from the PROVe study. Abstract. European Journal of Cancer 2019;119:S39.

Single technology appraisal

Chlormethine gel for treating mycosis fungoides-type cutaneous T-cell lymphoma [ID1589]

Dear NICE technical team,

Please find below the responses from Recordati Rare Diseases Ltd and Helsinn Healthcare SA based on the additional ERG report ('ID1589 Chlormethine Gel ERG Critique of evidence post ACM2 v1.0 31.03.21 [ACIC]') developed and shared on 21st April 2021.

Kind regards,

xxxxx

1. One of the company's proposed discounts is to apply to 'a population defined as "early-stage" or a population defined as "Low Skin Burden'. The ERG have assumed this means that this will apply to 'early disease patients (i.e. stages IA, IB and IIA only) or a population defined on the basis of skin burden (<10% BSA affected)'. Please would you confirm if this is correct?

In the description of the cost-effectiveness modelling results as per our response to the second Appraisal Consultation Document (ACD) (4. ID1589 chlormethine gel ACD stakeholder comments form Jan21_RRD_Helsinn_12.03.21, page 8), the company mentions that *'It should be noted that the [redacted] PAS would apply to a population defined as "early-stage" or a population defined as "Low Skin Burden" (either within early stage, or irrespective of stage).'*

The ERG states that (ID1589 Chlormethine Gel ERG Critique of evidence post ACM2 v1.0 31.03.21 [ACIC], page 5) it *'… considers an assessment of cost-effectiveness defined according to disease staging to be more robust than one based on definitions of skin burden, as the latter cannot be demonstrated within the restriction of the current economic model structure. The ERG is concerned that assessments of cost-effectiveness based on definitions of skin burden (low or high) would be based on assumptions that cannot necessarily be verified using the company's economic model.'* The company concurs with this assessment and therefore accept that the [redacted] patient access scheme (PAS) discount can only be interpreted as referring to the full early-stage population without any skin burden restriction.

Therefore, the company would like to confirm that whilst the response to the second ACD stated that the *'PAS would apply to a population defined as "early-stage" or a population defined as "Low Skin Burden" (either within early stage, or irrespective of stage)',* the company has a preference for this discount to apply to the full early-stage disease population, i.e., including both Low and High Skin Burden in line with the wording from the ERG surrounding uncertainty in estimating cost-effectiveness based on skin burden.

The company confirms that we have to limit the confidential PAS discount to 40% in a case where NICE were to approve only the stage IA population.

2. The revised economic models submitted by the company no longer include an assessment of cost-effectiveness for later (stage IIB+) disease. Can we confirm with them that the company no longer wish NICE to pursue a decision for this population?

Overall, although chlormethine gel is licensed in the advanced stage population, the company is no longer pursuing a recommendation in advanced stage disease in line with feedback from NICE and the ERG as to the most suitable place in therapy for chlormethine gel.

The ERG is correct that in the submitted models (dated 15.10.20), patients with Stage IIB+ disease are not considered. The patient distribution across different health states is hard coded to be either 100% Stage IA or 100% Stage IA–IIA depending on the model. Therefore, even if the user selected "all stages" on the setting tab, no patients would be modelled in the Stage IIB+ health states.

The company revised the model in this way in response to wording outlined in the second ACD for this appraisal, whereby the NICE Committee stated that they would be interested in cost-effectiveness estimates for patients with Low Skin Burden as the most appropriate place in therapy for chlormethine gel. Given that modelling a Low Skin Burden population was not explicitly possible, analyses restricted to Stage IA and early-stage disease were considered to

provide the Committee and the ERG with the most useful economic evidence in support of an assessment of the cost-effectiveness of chlormethine gel in a Low Skin Burden population. In summary, and as described in the company's response to the second ACD for this appraisal, Stage IA results represent cost-effectiveness estimates for a population where 100% patients have Low Skin Burden. However, it is important to note that patients may have Low Skin Burden irrespective of disease stage, and hence the Stage IA population does not capture all patients with Low Skin Burden across disease stages (including other early-stage disease stages). Therefore, the results for the early-stage population were presented to provide an analysis in a broader population that includes Low Skin Burden patients from multiple disease stages, in addition to some patients with High Skin Burden. Equally, if thinking in terms of disease stages rather than level of skin burden, the submitted analyses provide an assessment of chlormethine gel in the disease stages in which it would most likely be used.

In summary, the company no longer wishes for chlormethine gel to be considered for Stage IIB+ MF-CTCL based on NICE appraisal feedback to date on the most suitable place in therapy for chlormethine gel, and in acknowledgement of the Study 201 evidence base.

3. The ERG have noted an additional undocumented change to the model related to the transition probability for underlying disease, which the company have not explained (see pages 5-6 of ERG critique). Please would you explain the reason for this change?

The company apologises for the confusion here. In the submitted model, the company have simplified the model to only model the disease stage or stages of interest (Stage IA or Stage IA–IIA) rather than modelling disease stage progression. This was taken as a necessary simplification to model the subgroups of interest in the time available; if the model had retained the functionality for patients to progress to an advanced disease stage, the model would have then also required further adaptations to remove chlormethine gel as a treatment from these advanced stages (e.g. the SDT health state) in order to accurately reflect a world in which chlormethine gel is not available for Stage IIB+ patients. These adaptations would have required structural changes and amending several inputs (including those which inform transition probabilities/efficacy). This was not deemed feasible in the time provided and therefore it was considered more appropriate to remove progression to advanced disease, rather than including this progression to advanced disease and hence modelling that patients could receive chlormethine gel in these advanced disease stages. This was deemed a reasonable simplification for the following reasons:

- The probability of disease progression in MF-CTCL is low (particularly at early stages of disease)[1]; therefore, relatively few patients in the model are impacted by this simplification

- The probability of disease progression is modelled as independent of treatment in the cost-effectiveness model; therefore, the simplification to ignore disease progression does not directly bias in favour of one treatment over another

- Later disease stages were not of interest for this latest response, in line with preferences indicated by the NICE committee (see response to question 2)

4. Reason why the QALYs for stage IA are negative – can we ask for the company's considerations for why this may be? (The ERG have noted on page 10 some of what might be contributing to this)

The main explanation for the negative incremental quality-adjusted life years (QALYs) in Stage IA is due to phototherapy efficacy estimates by disease stage.

For Stage IA patients receiving phototherapy, the initial transitions from Low Skin Burden to No Skin Burden and Reduced Skin Burden (i.e. complete [CR] and partial response [PR] rates) are better than the Stage IB/IIA CR and PR rates for phototherapy (i.e. the Phan *et al.* data indicates higher probability of response to phototherapy in Stage IA disease than Stage IB/IIA disease, both for PR and CR). Patients are more likely to experience a PD with phototherapy than with chlormethine gel in Stage IA, but the difference in probability of PD/failed response is only approximately 10%. Therefore, in the Stage IA model, phototherapy is modelled as a treatment more likely to result in a response (CR or PR) than chlormethine gel, and this is not offset by the difference in probability of a PD between the two treatments, resulting in negative QALYs.

However, in the Stage IB/IIA population, the probability of achieving response (CR or PR) with phototherapy reduces relative to Stage IA (whilst still being greater than the probability of response with chlormethine gel), while the probability of a PD increases (to a greater degree than the increase in the probability of PD with chlormethine gel). As a result, in the Stage IA–IIA population, the increased probability of PD with phototherapy offsets the higher CR and PR rates compared to chlormethine gel. Thus, overall, at Stage IB/IIA, phototherapy is not modelled as a more efficacious treatment, and therefore, in this population positive QALYs are generated for chlormethine gel.

Importantly, and as noted in various company responses, phototherapy efficacy (CR and PR rates) is likely overestimated by deriving response data from Phan *et al.* (2019), as response measures utilised in the phototherapy trials included in Phan *et al.* are largely based on subjective, rather than objective measures.[2] Furthermore, as has been noted previously, the clinician's risk benefit assessment for the use of phototherapy also takes into account the potential carcinogenicity that is associated with phototherapy, and which is not accounted for in the cost-effectiveness model other than through the restriction on the number of phototherapy administrations in light of this risk. Overall, the company consider that the model may overestimate the benefits associated with phototherapy.[3-5]

5. The ERG note that they are unable to produce the same results (see results in table 2) from the version of the model that was submitted by the company. Please would you check that the correct version was submitted? If so, please would you provide some further explanation for why this may have occurred? The ERG has highlighted several tables (table 3-5) related to key effectiveness parameters for information.

The company apologises for the confusion here. The correct versions of the cost-effectiveness models were submitted to the ERG (15.10.20 versions); however, it appears that the discrepancy may be due to whether or not transition probabilities to advanced disease stages are set to 0 when sub-populations are modelled, as discussed above in question 3. In the results extracted by the company, these transition probabilities are set to zero. However, the results derived by the ERG can be matched when the company uses the models submitted but then includes transition probabilities to other stages during the model according to data from Agar *et al.* (2010).[1] The reasoning for setting these transition probabilities to 0 is explained in the response to question 3 above.

Should the ERG wish to gain the results extracted by the company, the models have been shared again as part of this response. To achieve the company results, the ERG must open the models and apply the correct PAS for chlormethine gel. No further changes should be required.

References

1. Agar NS, Wedgeworth E, Crichton S, et al. Survival outcomes and prognostic factors in mycosis fungoides/Sezary syndrome: validation of the revised International Society for Cutaneous Lymphomas/European Organisation for Research and Treatment of Cancer staging proposal. J Clin Oncol 2010;28:4730-9.
2. Phan K, Ramachandran V, Fassihi H, et al. Comparison of Narrowband UV-B With Psoralen-UV-A Phototherapy for Patients With Early-Stage Mycosis Fungoides: A Systematic Review and Meta-analysis. JAMA Dermatol 2019;155:335-341.
3. Gilson D, Whittaker SJ, Child FJ, et al. British Association of Dermatologists and U.K. Cutaneous Lymphoma Group guidelines for the management of primary cutaneous lymphomas 2018. Br J Dermatol 2019;180:496-526.
4. Archier E, Devaux S, Castela E, et al. Carcinogenic risks of psoralen UV-A therapy and narrowband UV-B therapy in chronic plaque psoriasis: a systematic literature review. J Eur Acad Dermatol Venereol 2012;26 Suppl 3:22-31.
5. Ling TC, Clayton TH, Crawley J, et al. British Association of Dermatologists and British Photodermatology Group guidelines for the safe and effective use of psoralen-ultraviolet A therapy 2015. Br J Dermatol 2016;174:24-55.

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	Please read the checklist for submitting comments at the end of this form. We cannot accept forms that are not filled in correctly. The Appraisal Committee is interested in receiving comments on the following: • has all of the relevant evidence been taken into account? • are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? • are the provisional recommendations sound and a suitable basis for guidance to the NHS? NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the preliminary recommendations may need changing in order to meet these aims. In particular, please tell us if the preliminary recommendations: • could have a different impact on people protected by the equality legislation than on the wider population, for example by making it more difficult in practice for a specific group to access the technology; • could have any adverse impact on people with a particular disability or disabilities. Please provide any relevant information or data you have regarding such impacts and how they could be avoided or reduced.
Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	United Kingdom Cutaneous Lymphoma Group (UKCLG) [redacted]
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	none
Name of commentator person completing form:	[redacted]

Comment number	Comments

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	Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
Example 1	We are concerned that this recommendation may imply that ……..
1	Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity? Chlormethine gel has proven efficacy for MF-CTCL without any real comparator. It provides a convenient, effective therapy for those not responding to potent topical steroids, without the need for hospital based treatment nor monitoring, This cost saving may be difficult to determine on paper but significantly reduces the burden of patient treatment from the hospital and the improvement in skin allowing patients to return to work with less days of work lost / sick benefits claimed. Not recommending Chlormethine gel for treatment of MF-CTCL will contribute to the overall discrimination that affects patients who develop a rare cancer. While this type of discrimination may not be 'unlawful' it has significant impact on the lives of patients with this condition. Chlormethine gel for MF-CTCL was granted orphan designation by the Committee for Orphan Medicinal Products in 2012 due to the rarity of the disease. Incidence estimates in England derived from Public Health England National Cancer Registration Analysis between 2009-2013 found an average annual incidence of 332 cases for all types of CTCL; of which the estimate for mycosis fungoides type was **182 cases per year** (55%)[1]. Compare this to the incidence of breast cancer in the UK of 55, 000 cases per year[2]. At every stage of their journey patients with CTCL are disadvantaged: **Recognition**: GPs are unlikely to be familiar with the condition or presentation and typically misdiagnose as benign skin disease. Chlormethine gel should be limited to prescribing at expert MF-CTCL centres. **Referral:** There is no 2 week-wait referral pathway suitable for CTCL patients unlike common cancers. GPs may be reluctant to refer patients with a skin condition to secondary care for some time; patients may be given ineffective topical treatments. Waiting times are long in many regions of the UK due to the high prevalence of skin disease in general and a shortage of Consultant dermatologists. Due to tendering out of dermatology services in some regions patients may be referred to community services who do not employ practitioners with the necessary training or experience to recognise CTCL. The median delay from onset of symptoms to diagnosis is 3 years (ref Scarisbrick JJ, Quaglino P, Prince HM et al. The PROCLIPI international registry of early stage mycosis fungoides identifies substantial diagnostic delay in most patients. Br J Dermatol. 181(2):350-357, 2019.[3] **Diagnosis**: Even when assessed by an appropriate clinician who suspects CTCL diagnosis is not always straight forward; this often requires multiple skin biopsies over time, specialist laboratory assessments and careful clinicopathological correlation. There are only 10 supra-

	regional multidisciplinary teams in the UK specialising in diagnosis and management of CTCL and patients may not be referred to one of these teams, particularly in early stages. Delay in diagnosis can affect health related quality of life and patients may progress or receive inappropriate treatments.. **Treatments**: There are few licensed treatments available for CTCL. Although UK, European and International clinical guidelines exist for management, there has been paucity of data from randomised clinical trials conducted on which to make evidenced based decisions due to the rarity of the disease, the need for multinational collaboration and the inevitable expense in setting up and monitoring such studies. Most guidelines rely on low quality evidence from retrospective studies, case series or expert opinion, particularly in early stage disease (stage IA-IIA). **UK disparity**: Topical Chlormethine gel is one of the few licensed treatments available for early stage MF-CTCL. Historically Nitrogen mustard has been used extensively over 50 years as a standard therapy worldwide and there is good evidence of its effectiveness from retrospective studies. The multicentre randomised prospective clinical trial (Lessin 2013 [4]) which led to its approval in the USA by the FDA (approved August 23, 2013, under Trade name Valchlor) and in Europe approved by the EMA for the treatment of mycosis fungoides-type cutaneous T-cell lymphoma (22 Dec 2016). Objective end points were used to measure skin disease response compared to the original product in use at the time. There are clear advantages in using Chlormethine gel (Ledaga) compared to the original Nitrogen Mustard product, which became impossible to source in the UK in the last decade and in addition required expensive extemporaneous preparation in specialist pharmacy units. Failure to recommend Chlormethine gel for MF-CTCL in the NHS further disadvantages UK patients by limiting treatment choices compared to patients worldwide.
2	**Has all of the relevant evidence been taken into account?** The committee state that there is no robust evidence of the effectiveness of Chlormethine gel compared with other treatments or showing if it is more effective for people with limited skin disease. We disagree with these statements but accept there is no true comparator making calculations difficult but provides a convenient , effective therapy (proven over many years) without the need for hospital based treatment nor monitoring. The committee discounts the Lessin 2013 study[4] as it compares Chlormethine gel to a treatment no longer used. This group believe this is unfair just because the alternative is no longer available. The study clearly shows that Chlormethine gel was as effective as Nitrogen mustard ointment which was the **initial standard of care** for MF-CTCL in Stanford, USA, where the trial originates, as opposed to phototherapy. There was no inferiority of the gel compared to the ointment using either CAILS or mSWAT assessment: Response rates (RR) for gel and ointment were 59% vs. 48% by CAILS and 46.9% vs. 46.2% by mSWAT respectively in 260 patients. Subset analysis of the 201 study showed those with stage IA (n=141) had RR of 59% for Chlormethine gel vs. 57% with stage IB/IIA (n=119) using CAILS assessment of up to 5 index lesions. The mSWAT data is not reported. However, the historical evidence from Stamford

	shows that Nitrogen mustard ointment is more effective for people with limited skin disease. The 2003 study by Kim et al[5] reported on 203 patients who used nitrogen mustard as initial therapy. Patients with T1 or stage IA disease had better response rates and survival outcomes than patients with T2 or stage IB disease: T1 complete response (CR) rate of 65% vs. T2 CR rate of 34% and T1 overall response rate (ORR) of 93% vs. T2 ORR of 72%. Patients used nitrogen mustard alone without other concurrent therapy. As the Lessin 2013 study demonstrates no inferiority between Chlormethine gel or Nitrogen mustard ointment; it is entirely reasonable to extrapolate that Chlormethine gel would similarly be more effective in patients with early stage skin disease. There is additional historical data from other centres confirming that Nitrogen mustard is more effective in early stage disease. A retrospective study from Philadelphia of 331 patients showed CR of 80% in stage IA vs. CR of 68% in stage IB patients using aqueous nitrogen mustard, although other concurrent therapy was allowed[6]. A retrospective study from New York of 117 patients showed CR 75.8% in stage I vs. CR of 44.6% in stage II; in this study concomitant therapy was not allowed[7]. There are other unacknowledged potential benefits of using nitrogen mustard therapy. The Vonderheid 1989 study found **long lasting remission of greater than 8 years in 11%** (35 of 331 patients, 53% Stage IA) treated with nitrogen mustard, providing evidence that MF-CTCL might be eradicated or 'cured' by nitrogen mustard. Analyses of the large case series from Stamford have also demonstrated that complete responses to topical nitrogen mustard in early stage IA patients is associated with a lower risk of disease progression[5, 16]. **Nitrogen mustard may also have a unique effect on the immunopathogenesis of MF-CTCL**. Studies have shown that patients who develop a significant contact dermatitis (delayed type IV hypersensitivity reaction) may have a greater clinical response to Nitrogen mustard[5] suggesting that the mechanism of action of nitrogen mustard stems from both its alkylating properties but also via immune stimulation or interaction with the epidermal-Langerhans cell-T-call axis[8].
3	**Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?** The committee state the evidence used to estimate cost effectiveness is uncertain as it does not accurately reflect clinical practice. It is important to highlight that although published clinical guidelines exists there is no single 'gold standard' approach. Recommendations for initial treatment may depend on a variety of factors: burden or stage of skin disease, availability of therapy, clinician speciality, location and personal experience, and importantly patient preference. Clinical practice varies depending on who is seeing the patient: a local dermatologist is likely to only recommend therapy they have direct access to or experience of – such as phototherapy, whereas a dermatologist working in a superregional service may recommend all available options including Chlormethine gel and off label use of other topical treatments with published data. Prior use of nitrogen mustard in the UK was generally limited to a few clinicians working in specialist supra-regional centres in London and

Manchester, as experts there had developed the required clinical experience or had direct experience of using nitrogen mustard from clinical fellowships in the USA. As there are so few available therapies for early stage disease the reality is that **patients will try all available treatment options before moving onto systemic therapy**. Many patients will cycle through the available skin directed therapies, with periods of active monitoring (watch and wait) between therapies until the severity of relapse requires a new cycle of treatment. The availability of Chlormethine gel will significantly improve the options for skin directed therapy for both clinician and patient.

The committee highlight the limitations of using retrospective phototherapy studies as a comparator in the cost effectiveness models but prefer to use estimates based on the metanalysis by Phan et al[9]. The seven studies were observational, non-controlled, utilised varied methodology and did not use robust clinical assessment or disease end points. The designation of a 'CR' of only 80-95% clearance of skin lesions in some of the studies negates their validity as a comparator. The combined studies gave a CR rate for PUVA of 78%. The data from Whittaker et al[10] is discounted yet is more directly applicable to the UK population in addition to being a RCT with robust clinical assessment. The CR rate for PUVA was only 22%. This CR rate is much lower than reported by Phan et al and highlights the high risk of bias in the use of retrospective studies. The CR rate of 78% from the Phan metanalysis is more reliably comparable to the ORR of 71% in the Whittaker study. The efficacy of phototherapy will be overestimated in the comparator models compared to the use of Chlormethine gel.

The committee states it prefers the ERG estimate of 2.8g Chlormethine gel daily in the cost effectiveness models yet there is no robust evidence that this estimate is more correct than the companies estimates from real world usage or the original Lessin trial. For UK use it is highly likely that the amount of gel used will be less as clinicians recommend application to individual lesions not whole or regional body use as was advocated in the Lessin trial. It is possible that UK clinicians may choose to follow protocols developed in Europe where Chlormethine gel is applied only twice weekly to reduce the risk of skin irritaion[11]**.** A better estimate of usage may relate to the stability data of Chlormethine gel with a fresh tube being required every 2 months – leading to 6 tubes per year for an average patient using treatment over a 12 month period.

The assumption that Chlormethine gel may only be used for 4-6 months, or a maximum of 12 months, which increases costs in the company model is also not necessarily correct. The median time to a CR in the Kim 2003 study was 12 months[5.] Many patients used therapy for longer than 12 months with ongoing improvement. The extension study[12] for participants in the Lessin 2013 trial who had not yet achieved a CR showed that ongoing usage for 7 months of a Chlormethine gel 0.04% was well tolerated and led to further documented responses in 26.5% of patients (CR 6.1%; PR 20.4%). Personal experience of using nitrogen mustard ointment in the UK also confirms continued use and benefit longer than 12 months[13].

While there are clearly stated advantages to be able to offer Chlormethine gel to patients with limited stage IA skin disease compared to phototherapy, it should not be forgotten that nitrogen mustard has proven utility in patients with stage IB disease, to treat sanctuary sites missed by other skin directed therapies and to help with symptom control in patients with advanced disease who may still have significant skin disease burden. It has been shown to be equally effective as salvage therapy after initial relapse[5].

The issue of patient choice has not been fully taken into account when considering cost

	effectiveness of using Chlormethine gel. Although the model takes into account reference costs to the NHS of providing phototherapy the costs for the patient is not fully considered. These include inconvenience, traveling to hospital, car parking, loss of work and income, as well as lack of autonomy over a hospital based therapy. Phototherapy is provided as a limited course over 6-10 weeks, due to accumulative side effects of maintenance therapy and because it is a finite resource shared by all patients with serious benign skin disease. Patients are often anxious at the end of a treatment course especially if remission is not achieved. Chlormethine gel gives control back to the patient as treatment can be continued longer term while the skin is improving.
4	**Are the recommendations sound and a suitable basis for guidance to the NHS?** Treatments for early MF-CTCL aim to relieve symptoms rather than provide a cure; this applies to all skin directed therapies. Therefore improving patient's quality of life assumes greater importance. A treatment such as Chlormethine gel which is convenient, home-based, with no monitoring requirements and documented efficacy and tolerability over many months should be made available to UK patient on the NHS. Controlling skin disease for as long as possible with topical therapies is important as it reduces the need for systemic treatment which is more expensive and associated with greater toxicity. Improved skin disease control is associated with improved quality of life for patients. The potential to offer a long term remission, reduce the risk of disease progression or delay the need for systemic therapy in a subset of early stage IA patients should not be dismissed from the evidence provided by historical data for nitrogen mustard. The committee acknowledge the need for alternative treatments for MF-CTCL and the unmet needs of patients with limited early stage disease – yet despite this fail to recommend Chlormethine gel for NHS use. This will leave patients with limited skin directed choices between topical steroids, phototherapy, radiotherapy or no specific therapy if the latter are unsuitable. Topical steroids have typically been tried by most patients with MF-CTCL prior to diagnosis. The treatment may improve symptoms in the short term by suppressing skin lesions, but unlike Chlormethine gel rarely clears them. Potent or super potent topical steroids are required and have significant side effects and risks over time: skin lesion rebound, skin atrophy, telangiectasia, striae and cutaneous infection. Recent data shows that long term use of potent topical steroids contribute to glucocorticoid induced osteoporosis[14]. Phototherapy is an inconvenient hospital based therapy, exposes the whole skin surface to the effects of UV light and has a finite recommended cumulative dose due to carcinogenicity. Radiotherapy is not suitable for young patients is also carcinogenic and is necessarily an expensive hospital based therapy to provide. In contrast a population based cohort study did not show that nitrogen mustard was associated with an increased risk of secondary cancers and comorbidities in MF-CTCL[15]. The committee have failed to recommend Chlormethine gel based on cost effectiveness models despite acknowledging that the assumptions used in these models are flawed. However, due to the rarity of MF-CTCL the **overall costs to the NHS** from recommending this therapy will be low compared to the costs of providing therapy for other common cancers.
5	Lastly, the committee should not underestimate the effect of the Covid pandemic on the

	treatment choices for patient with MF-CTCL. During the first wave there was a disproportionate shutting down of dermatology services compared to other specialities. The effect of staff redeployment/shielding and self-isolation led to many phototherapy units to shut completely. In some regions there are exceptionally long waiting times for UVB or PUVA treatment, some units are still not open or have shut again during the third wave of the pandemic. It will likely take several years for the effect of the Covid pandemic on phototherapy services to resolve. Chlormethine gel provides patients with a therapy which can be applied at home, reducing travel and footfall within hospitals. By not recommending Chlormethine gel for use in the NHS currently means that many patients with early stage disease have very limited access to specific therapy.
6	**References** 1. PHE. Cutaneous T-cell lymphoma short report NB241016, 2016. 2. Breast Cancer Statistic UK -World Cancer Research Fund. 3. The PROCLIPI international registry of early stage mycosis fungoides identifies substantial diagnostic delay in most patients. Scarisbrick J, Quaglino P, Prince HM et al. *Brit J Dermatol* 2019; **181**: 350-357. 4. Topical chemotherapy in cutaneous T-cell lymphoma: positive results of a randomised, controlled, multicentre trial testing the efficacy and safety of a novel mechlorethamine 0.02% gel in mycosis fungoides. Lessin SR, Duvic M, Guitart J et al. *JAMA Dermatol* 2013; 149: 25-32. 5. Topical nitrogen mustard in the management of mycosis fungoides: Update of the Stanford experience. Kim Y, Martinez G, Varghese A et al. *Arch Dermatol* 2003**; 39**: 165-173. 6. Long term efficacy, curative potential and carcinogenicity of topical mechlorethamine chemotherapy in cutaneous T-cell lymphoma. Vonderheid E, Tan E, Kantor A et al. *J Am Acad Dermatol* 1989; **20**: 416-428 7. Topical mechlorethamine therapy for early stage mycosis fungoides. Ramsay D, Halperin P, Zelenich-Jacquotte A. *J Am Acad Dermatol*. 1988; **19**: 684-691. 8. Recent clinical evidence for topical mechlorethamine in mycosis fungoides. Sahu J, Sepassi M, Nagato M et al. Clinical Investigation. *Clin Invest* 2014; **4**: 745–761.

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- Combine all comments from your organisation into 1 response. We cannot accept more than 1 set of comments from each organisation.

NICE National Institute for Health and Care Excellence

Chlormethine gel for treating mycosis fungoides-type cutaneous T-cell lymphoma [ID1589]

Consultation on the appraisal consultation document – deadline for comments 5pm on Thursday 11 February 2021 **email:** NICE DOCS

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Chlormethine gel for treating mycosis fungoides-type cutaneous T-cell lymphoma [ID1589]

ERG critique of the revised economic model and analysis submitted by the company in response to the 2nd Appraisal Consultation Document

Produced by Aberdeen HTA Group

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Overview

This document provides the ERG's critique of the company's revised analyses following the 2nd appraisal committee (AC) meeting for this topic. The company provide a revised base case analysis configured to the committee's preferred assumptions from the 2nd AC meeting and apply a new PAS price agreed between the company and NHS England, received by the ERG on 22/03/2021. This critique should be read in conjunction with the company ACD response documents, the ERG's critique of the company's previous ACD response document (following the first AC meeting), and the ERG report (for a critique of the original model) for a full discussion of the relevant issues. This document focuses on the ERG's critique of the company's application of the new PAS prices for chlormethine gel. This is version 2.0 of the document which incorporates further points of clarification provided by the company in advance of the 3rd AC meeting.

Issues raised in company response to the 2nd ACD

The company's response to ACD2 raises a concern that the committee preferred base-case modelling assumptions represent a worst-case estimate of the ICER for chlormethine gel. The company specifically raise concerns about: 1) the use of Phan et al. for phototherapy efficacy[1], 2) the use of dosing information from Valchor® summary of product characteristics[2] and 3) the model structural assumption that patients refractory to treatment with chlormethine gel only receive one course of phototherapy before receiving systemic therapy for their skin symptoms. The ERG notes the company's concerns and accept that there are several key issues of uncertainty. However, the ERG has presented the case to support its preferred assumptions in detail in previous documentation.

The ERG notes that NICE's preferred base case assumptions were applied in the company's revised analyses in response to the 2nd ACD. As such, the ERG now considers these issues to be resolved as fully as they can be given the limited evidence base. The variation in the ICER between the ERG and company preferred modelling assumptions is illustrated in the company's response to ACD2.

ERG critique of revised PAS

The company has provided details of a new patient access scheme (PAS) agreement with NHS England. The company's response to ACD indicates that two new PAS prices have been agreed, with a different discount depending on the subgroup of the population considered. The company response states that:

"*It should be noted that the [redacted] PAS would apply to a population defined as "early-stage" or a population defined as "Low Skin Burden" (either within early stage, or irrespective of stage).*"

The ERG interprets this as meaning that the company are willing to supply chlormethine gel at the [redacted] discounted price for either a population of early disease patients (i.e. stages IA, IB and IIA only) or a population defined as "Low Skin Burden" (i.e. <10% body surface area (BSA) affected, irrespective of stage), depending on the decision reached by NICE. However, the company state that only a [redacted] discount could be offered if the recommendation was for Stage IA patients only.

The company have supplied two economic model files describing the impact of the different PAS discounts on cost-effectiveness (defined by stage of disease as opposed to skin burden). A discount of [redacted] applied to a cohort of patients with stage IA disease only (revised price per 60g tube of [redacted]), but with a [redacted] discount for all early stage disease (i.e. stages IA, IB and IIA), leading to a revised price per 60g tube of [redacted]).

The ERG considers it important at this stage to reiterate the relationship between disease stages (IA, IB, IIA) and skin burden definition (low: <10% BSA affected; high: ≥10% BSA affected). All stage IA patients have low skin burden, whereas all stage IB patients have high skin burden. Stage IIA patients may have high or low skin burden. Data provided by the company from the PROCLIPI registry[3] indicate that [redacted] % of stage IIA patients would have low skin burden. However, in the economic model, the combined state of stage IB / IIA are assumed to all have high skin burden. The ERG notes that the [redacted] % proportion of stage IIA patients with low skin burden reported in the company response is identical to the proportion of stage IIB+ patients assumed to have low skin burden in the original economic model. As the ERG do not have direct access to the PROCLIPI registry data[3], it is not possible to verify what stages of disease these proportions apply to.

In relation to stage IIB+ disease, the ERG note that the revised economic models submitted by the company no longer include an assessment of cost-effectiveness for later (stage IIB+) disease. If chlormethine gel were to be recommended in stage IIB+ disease, the ERG is unclear as to what price / discount would apply and whether it would be restricted to 'low skin burden' only. However, the company has subsequently clarified that, although chlormethine gel is licensed for all disease stages, they are no longer seeking approval for the use of chlormethine gel in advanced (stage IIB+) disease. The company has re-distributed the starting proportions of the model cohort to only include Stage IA or the full early stage population (Stage IA – IIA) depending on the subgroup considered. The ERG considers the company decision to be in line with the 2nd NICE ACD and is consistent with Study 201 which did not provide any evidence on the use of chlormethine gel in advanced stage disease.

The company acknowledge that the current configuration of the economic model precludes an assessment of the cost-effectiveness of chlormethine gel for subgroups defined as "low" or "high" skin burden separately across the disease stages. That is because the model is built around disease stage, rather than skin burden health states. The ERG agrees with the

company that determining cost-effectiveness specifically in a population with "low skin burden" would require a substantial re-build of the economic model and would likely encounter substantial issues regarding data parameterisation.

The ERG is satisfied that the application of the [redacted] PAS discount for stage IA is consistent with applying a discount to the proportion of low-skin burden patients that have stage IA disease. However, as noted by the company, this would exclude patients with low-skin burden in stage IIA disease. Furthermore, applying the [redacted] PAS to all early stage disease in the economic model generates cost-effectiveness estimates based on the assumption that the discount would apply to both low- and high-skin burden patients within those stages. The company suggest this is a conservative estimate of cost-effectiveness because high-skin burden patients are included in the analysis. The ERG considers this to be a reasonable assumption in so far as restricting the population to low-skin burden would lead to lower treatment acquisition costs than high-skin burden. However, it is less clear what impact restricting the use of chlormethine gel to stage IB / IIA patients with 'low skin burden' would have on treatment effectiveness and hence cost-effectiveness. The company has subsequently clarified that their preference is to seek a recommendation for chlormethine gel for the full early-stage disease population, including both low and high skin burden patients. The ERG agrees that the company's preference is consistent with the results produce from the model configured to provide early stage disease results.

To conclude, the ERG considers an assessment of cost-effectiveness defined according to disease staging to be more robust than one based on definitions of skin burden, as the latter cannot be demonstrated within the restriction of the current economic model structure. The ERG is concerned that assessments of cost-effectiveness based on definitions of skin burden (low or high) would be based on assumptions that cannot necessarily be verified using the company's economic model. Furthermore, the ERG considers that restrictions of treatment on the basis of %BSA may be difficult to implement in clinical practice.

ERG replication of committee preferred base case assumptions

The ERG has inspected the company's revised economic model file for "early stage" disease and attempted to generate the company's reported results (configured to the committee preferred assumptions from ACD 2). To do this, the ERG used the version of the model

dated 15.10.20 to attempt the calibration. Setting all assumptions and parameters in that model to the committee preferred assumptions lead to different incremental costs and incremental QALYs, compared to those reported in the company response to ACD2.

Further inspection of the company's submitted economic model identified an additional undocumented change to the transition probabilities for underlying disease. The source for disease stage progression transition probabilities used in both the ERG and the company preferred analyses is Agar et al[4]. However, for the company's current model, transition probabilities have been revised to assume that the full cohort remain in the initial disease stage for the duration of the model time horizon (i.e. no transition into stage IIB+ for the early stage model and no transition out of stage IA for the stage IA only model), though the transition between stages IA and IB/IIA is retained. This essentially means that the model cohort remain within the underlying disease stages for which chlormethine gel treatment is modelled.

Subsequent to version 1 of this critique, the company further clarified the justification for the removal of underlying disease transitions. This was a simplification of the model to avoid the need for substantial model adaptions, including to transition probabilities into the SDT health state, to accurately reflect treatment options in stage IIB+ when chlormethine gel was not available. The ERG note it would have been more clinically intuitive to allow for underlying disease progression within the model, as this would more accurately account for mortality within the model. The approach taken by the company could risk mis-representing the proportion of the cohort entering the death state over time and therefore the proportion of the cohort on treatment. However, the ERG accepts the company's justification as reasonable on the grounds that the probability of disease progression is low, progression is retained within the model for the subgroups in which chlormethine gel approval is being sought (i.e. progression from Stage IA to IB/IIA is retained for the early disease population, and finally, disease progression is appropriately modelled independently for chlormethine gel and phototherapy. The magnitude of any biases, should they exist, are likely to be small. Table 1 details the transition probabilities used in the current version of the "early stage" model compared with those from Agar et al for the committee's information.[4]

Table 1: Transition probabilities used to populate underlying disease progression

Transition	Calculated from Agar et al.	Applied in company "early stage" model	Applied in company "Stage IA" model
Stage 1A – IB/IIA	0.0010	0.0010	0.0000
Stage 1A – IIB+	0.0000	0.0000	0.0000
Stage IB/IIA – IIB+	0.0016	0.0000	0.0000

The ERG acknowledge that underlying disease progression is not a primary driver of cost-effectiveness results and do not consider this issue to be a major source of uncertainty. The ERG confirms that re-setting these transition probabilities to the data from Agar et al.[4] allows replication of earlier versions of the model. The ERG is therefore satisfied that the company's model revisions appropriately reflect the committee preferred assumptions from the 2nd AC meeting.

Cost-effectiveness results

The company has provided multiple scenario analyses in their response to the ACD. Table 2 provides the company implementation of the committee preferred assumptions on the ICER. The ERG agrees that the company has implemented the committee's preferred set of assumptions. Results are presented for stage IA only (with a [redacted] chlormethine gel PAS) and for all early stage disease (Stage IA, IB, IIA, with a [redacted] chlormethine gel PAS). The ERG has provided a full set of analyses in a confidential appendix to this document, detailing all ICERs from the company response to ACD 2 applying the agreed confidential PAS discount for bexarotene in the economic model.

Table 2: Summary of committee preferred base case cost-effectiveness results

	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER	NMB
Company implementation of committee base case assumptions; Early stage (IA, IB, IIA); PAS chlormethine gel: [redacted]; PAS bexarotene: none						
Chlormethine gel	[redacted]	[redacted]				
Phototherapy (PUVA/UVB)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Company implementation of committee base case assumptions; Stage IA only; PAS chlormethine gel: [redacted]; PAS bexarotene: none						
Chlormethine gel	[redacted]	[redacted]				
Phototherapy (PUVA/UVB)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

ICER: incremental cost-effectiveness ratio; NMB: Net monetary benefit; PAS: patient access scheme; QALY: quality adjusted life year

[A] Note that ICERs generating cost savings and QALY losses are located in the south-west quadrant of the cost-effectiveness plane, hence a negative INB for an ICER <£20,000 per QALY.

The ERG further notes that incremental QALYs for chlormethine gel vs. phototherapy are negative for the stage IA only population but are positive for the overall early disease population (stage IA, IB, IIA). The positive incremental QALYs in early stage disease overall were expected and are consistent with previous analyses considered by the committee at the 2nd AC meeting. However, the ERG is concerned that the change in directional effect on incremental QALYs in the stage IA only subgroup has not been acknowledged or adequately explained in the company's initial response to the 2nd ACD. Cost-effectiveness results for stage IA only have not been presented in any of the previous company analyses and the assumptions required to generate the analysis were not documented.

To understand the reasons for differing results by subgroup, the ERG has compared the key effectiveness parameters that drive QALYs in the economic model. Table 3 reports sources of data for CR, PR, failed response, duration of CR and duration of PR for the committee's information. The ERG also reports the transition matrices between health states separately for stage IA and stage IB/IIA for chlormethine gel and phototherapy respectively in appendix 1 of this document.

Table 3: Comparison of key effectiveness parameters included in the economic model.

	Chlormethine gel			**Phototherapy**				
	Value		**Source**	**Value**				**Source**
	Stage IA (low skin burden)	**Stage IB/IIA (high skin burden)**		**Stage IA (low skin burden)**		**Stage IB/IIA (high skin burden)**		
CR	[redacted]	[redacted]	Study 201[5]	PUVA: 82.10% Weighted: 70.24%	UVB: 62.10%	PUVA: 67.60% Weighted: 61.79%	UVB: 57.80%	Phan et al. 2019[1]
PR	[redacted]	[redacted]	Study 201[5]	PUVA: 12.90% Weighted: 22.56%	UVB: 29.20%	PUVA: 27.60% Weighted: 19.83%	UVB: 14.50%	Phan et al. 2019[1]
PD / failed response	[redacted]	[redacted]	PD from Study 201[5]	PUVA: 9.63% Weighted: 18.74%	UVB: 25.00%	PUVA: 15.98% Weighted: 25.61%	UVB: 32.22%	Failed response from Phan et al. 2019[1]
Duration of CR (months)[C]	17.31		Kim et al. 2003[6]	PUVA: 17.40		UVB: 7.76		Phan et al. 2019[1]
Duration of PR (months)[C]	[redacted]		Study 201[5]	PUVA: 21.70		UVB: 9.68		Phan et al. 2019[1]

CR: Complete response; PD: Progressed disease; PR: Partial response

[A] Note that the transition probability in the model for failure following a PR in the company's preferred base case is assumed to be equal to the probability of initial progressive disease (obtained as failed response from Phan et al.), and as such is not derived from any direct information on duration of PR.

[B] According to the TNMB classification system, people with Stage IA and Stage IB have <10% and >10% of their BSA affected, respectively. People with <10% BSA affected are assumed to have low skin burden and people with >10-80% BSA affected are assumed to have high skin burden.

[C] Due to lack of data, the sourced values for the duration of CR and PR were applied across all disease stages. Phan et al. also reported the duration of response by type of phototherapy, and therefore, a weighted average based on the proportion having PUVA and UVB in the model was applied.

The ERG suspects that one of the main drivers of QALY differences between the subgroups is the greater difference in partial response between chlormethine gel and phototherapy in stage IB/IIA ([redacted] vs. 19.83%) as opposed to in stage IA alone ([redacted] vs. 22.56%).

The company has subsequently provided further clarification explaining that the main reason for negative QALYs in stage IA is due to differential phototherapy effectiveness estimates by disease stage (sourced from Phan et al.). The company clarify that phototherapy response rates (both CR and PR) and transition probabilities to the "no skin burden" and "reduced skin burden" health states (sourced from Phan et al.) are higher for stage IA than Stage IB/IIA. Whilst PD is lower for chlormethine gel than phototherapy in Stage IA, this benefit is not sufficient to offset the poorer response rates, contributing to negative incremental QALYs.

Furthermore, the ERG note that when comparing phototherapy and chlormethine's probabilities of achieving a response (i.e. transitioning from initial skin burden to 'no' or 'reduced' skin burden states), chlormethine gel achieves better transition probabilities (combination of response and time to response) in stage IB/IIA than IA, whereas phototherapy achieves better transition probabilities in Stage IA than in IB/IIA. This also contributes to the negative QALYs for chlormethine gel in the Stage IA subgroup.

Finally, in relation to phototherapy PD (i.e. transitioning into the 'Systemic Therapy' state), there is a lower probability of having PD in Stage IA than IB/IIA, which improves the case for phototherapy relative to chlormethine gel in the Stage IA subgroup, also contributing to the negative incremental QALYs.

Overall, for the combination of reasons outlined above, phototherapy performs better (taking into account probabilities of achieving a response, duration of response, and probability of having PD) in the Stage IA subgroup analysis than chlormethine gel, resulting in the reported negative QALY difference in the Stage IA subgroup.

The ERG accepts that the company explanation provides reassurance about the validity of the model outputs. The ERG is satisfied that the combination of company and ERG provided explanations covers the reasoning for negative QALYs in this subgroup. The company reiterate their concerns about the use of Phan et al as a source of clinical effectiveness parameters for phototherapy. As stated in the ERG's previous documentation, and as accepted by the company, the evidence base is highly uncertain, with significant heterogeneity across chlormethine gel and phototherapy studies. This means that the true

incremental effectiveness of chlormethine gel compared to phototherapy is highly uncertain and different potential data sources lead to substantial variation in the ICER, with some scenarios generating positive incremental QALYs and others generating negative incremental QALYs for chlormethine gel in the stage IA population.

Appendix 1: Transition probabilities by disease stage

The purpose of providing the detailed transition matrices by stage and treatment arm is to illustrate potential reasons for differences in directional effect of incremental QALYs for chlormethine gel vs. phototherapy between the stage IA and IB/IIA subgroups of the population. The transition matrices are reported for the economic model version configured to the committee preferred assumptions from ACD2. As noted above, these data are provided for information, and the ERG would welcome further explanation from the company regarding the reasons for differences in incremental QALYs between subgroups.

Table 4: Transition matrices for stage IA compared to stage IB/IIA for chlormethine gel

Stage IA							**Stage IB/IIA**						
	End Health State:							**End Health State**					
Start Health State:	**Low Skin Burden**	**No Skin Burden**	**Reduced Skin Burden**	**Watch & Wait**	**SDT**	**Systemic Therapy**	**Start Health State**	**High Skin Burden**	**No Skin Burden**	**Reduced Skin Burden**	**Watch & Wait**	**SDT**	**Systemic Therapy**
Low Skin Burden	[redacted]	[redacted]	[redacted]		[redacted]	[redacted]	**High Skin Burden**	[redacted]	[redacted]	[redacted]		[redacted]	[redacted]
No Skin Burden		[redacted]		[redacted]			**No Skin Burden**		[redacted]		[redacted]		
Reduced Skin Burden		[redacted]	[redacted]		[redacted]		**Reduced Skin Burden**		[redacted]	[redacted]		[redacted]	
Watch & Wait				[redacted]	[redacted]		**Watch & Wait**				[redacted]	[redacted]	
SDT		[redacted]	[redacted]		[redacted]	[redacted]	**SDT**		[redacted]	[redacted]		[redacted]	[redacted]

SDT: skin directed therapy state; Grey shading indicates impossible transitions in the model.

Table 5: Transition matrices for stage IA compared to stage IB/IIA for phototherapy

Stage IA							**Stage IB/IIA**						
	End Health State							**End Health State**					
Start Health State	**Low Skin Burden**	**No Skin Burden**	**Reduced Skin Burden**	**Watch & Wait**	**SDT**	**Systemic Therapy**	**Start Health State**	**High Skin Burden**	**No Skin Burden**	**Reduced Skin Burden**	**Watch & Wait**	**SDT**	**Systemic Therapy**
Low Skin Burden	0.5523	0.3333	0.0820			0.0324	**High Skin Burden**	0.5594	0.2752	0.0713			0.0942
No Skin Burden		0.9335		0.0665			**No Skin Burden**		0.9335		0.0665		
Reduced Skin Burden		0.0168	0.9294		0.0538		**Reduced Skin Burden**		0.0196	0.9267		0.0538	
Watch & Wait				0.8825	0.1175		**Watch & Wait**				0.8825	0.1175	
SDT		0.3333	0.0820		0.5523	0.0324	**SDT**		0.2752	0.0713		0.5594	0.0942

SDT: skin directed therapy state; Grey shading indicates impossible transitions in the model.

References

1. Phan K, Ramachandran V, Fassihi H, et al. Comparison of Narrowband UV-B With Psoralen–UV-A Phototherapy for Patients With Early-Stage Mycosis Fungoides: A Systematic Review and Meta-analysis. JAMA Dermatology 2019;155:335-341.
2. Food and Drug Administration (FDA). Valchor Summary of Product Characteristics (SmPC). August 2013. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2013/202317lbl.pdf [Last Accessed 31 March 2021].
3. PROCLIPI Registry Data. 2019.
4. Agar NS, Wedgeworth E, Crichton S, et al. Survival outcomes and prognostic factors in mycosis fungoides/Sezary syndrome: validation of the revised International Society for Cutaneous Lymphomas/European Organisation for Research and Treatment of Cancer staging proposal. Journal of Clinical Oncology 2010; 28(31), 4730-9.
5. Yaupon Therapeutics Inc. Data on File. Study 201 Clinical Study Report (CSR). July 2011.
6. Kim YH. Management with topical nitrogen mustard in mycosis fungoides. Dermatol Ther 2003; 16(4), 288-98.