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:

1. **Comments on the Appraisal Consultation Document from** Recordati Rare Diseases/Helsinn Healthcare SA
   a. **Appendix**

2. **Consultee and commentator comments on the Appraisal Consultation Document** from:
   a. British Association of Dermatologists (BAD)
   b. Lymphoma Action
   c. UK Cutaneous Lymphoma Group
   The Royal College of Physicians endorse the response from BAD

3. **Comments on the Appraisal Consultation Document from experts:**
   a. Sean Whittaker, Professor of Skin Oncology – clinical expert, nominated by Recordati Rare Diseases and
   Julia Scarisbrick, Consultant Dermatologist – clinical expert, nominated by British Association of Dermatologists & Recordati Rare Diseases

4. **Comments on the Appraisal Consultation Document received through the NICE website**

5. **Evidence Review Group critique of company comments on the ACD**

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

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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):	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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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 – Overestimation of phototherapy efficacy	The studies evaluating phototherapy that have been referenced in the appraisal to date, such as those used to inform the naïve comparison presented as part of the Company Submission, and those included in Phan *et al.* (2019), are of low quality.[1] Notably these studies are frequently retrospective in nature and associated with the inherent limitation that the reported response rates are not determined using an objective measure such as Composite Assessment of Index Lesion Severity (CAILS) or Modified Severity-Weighted Assessment Tool (mSWAT), but instead relied on clinical experts making subjective decisions about whether patients have responded to treatment or not.[1] This is acknowledged in the Appraisal Consultation Document: *'The clinical experts said that the reason the response rates in Study 201 appeared lower than the phototherapy trials is that Study 201 used clear criteria for assessing response (CAILS and mSWAT), whereas most of the phototherapy trials were based on less reliable assessments by clinicians.'.* The randomised controlled trial of phototherapy (Whittaker *et al.*), is a prospective, controlled trial that used an objective scoring system to capture response and is therefore less subject to bias.[2] The response rates reported for phototherapy were considerably lower than reported by Phan *et al.* This suggests that the Phan *et al.* studies may overestimate phototherapy efficacy, and this notion is also supported by discussions at the Committee meeting, where it became apparent that the sources available to inform phototherapy efficacy may not necessarily provide a comparable assessment of response rates to that utilised for chlormethine gel in Study 201 (as phototherapy is often subjectively, rather than objectively measured), and may therefore overestimate the effectiveness for phototherapy compared to what would be expected in real-world practice.[1, 3] As described in the Company Submission (Section B.2.8), [redacted] • [redacted] • [redacted] [redacted] In contrast, the retrospective studies informing the Phan *et al.* estimate of phototherapy efficacy are from settings outside of the UK and hence may be less generalisable to the real-world efficacy of phototherapy in the National Health Service, and are based on less reliable assessment measures, as discussed above.[1]

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	[redacted] The Company acknowledges that there are limitations with all sources of evidence for phototherapy efficacy and hence there is inevitable uncertainty associated with this estimate. Therefore, the Company has maintained the use of complete response, partial response and progressed disease response rates from Phan *et al.* (2019) in the base case for the updated cost-effectiveness model (see the accompanying appendix to this response).[1] However, a scenario analysis has also been conducted using complete response and partial response rates from PROCLIPI, as this source represents real-world practice in the UK and provides objective estimates of phototherapy efficacy that would appear to have more clinical plausibility (particularly in terms of rate of complete response).[5]
2 – Cost-effectiveness evidence	The following limitations of the cost-effectiveness model are outlined in the Appraisal Consultation Document: Page 3: '*The evidence used to estimate cost effectiveness is uncertain because it oversimplifies the treatment pathway for people with MF-CTCL and does not reflect clinical practice. Other things that are not certain include:* • *Time to skin symptom progression after response to treatment* • *The length of time people have systemic treatment once skin symptoms progress'* Page 7: *'Many people have more than one course of treatment, although the number of courses of phototherapy is limited by the cumulative UV dose. Repeated courses of chlormethine gel would also be offered, and in practice phototherapy could be followed by chlormethine gel or vice versa. The committee understood that people are likely to have multiple rounds of treatment (which may include phototherapy or chlormethine gel) until the symptoms no longer respond. Then the person may be offered systemic therapies such as oral bexarotene or peginterferon alfa. The clinical experts explained that treatment decisions are based on the extent and severity of the skin disease, rather than the overall stage of disease. In practice, people with advanced MF-CTCL (stage 2B to 4) who have disease at sites other than the skin, and may be having chemotherapy, could still have skin lesions that could be treated with chlormethine gel. The committee concluded that people with MF-CTCL have multiple treatments in different sequences until symptoms no longer respond.'* Page 10: *'The company's model structure does not reflect the treatment pathway for people with MF-CTCL in clinical practice. In the company's model, people were assumed to have only one round of either chlormethine gel or phototherapy.'*

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	Page 11: *'In both arms of the model, people who had a complete response in skin symptoms were assumed to progress to bexarotene or peginterferon alfa earlier than people who had a partial response in skin symptoms.'* and *'The clinical experts stated that if someone has a complete skin symptom response, their condition may then deteriorate but they may still only have very limited disease. It may be appropriate to 'watch and wait' rather than immediately progress to bexarotene or peginterferon alfa.'* Page 13: *'The committee concluded that the base case cost-effectiveness estimates were highly uncertain and depended on the time horizon affecting the duration of subsequent treatment.'* As part of the response to the Appraisal Consultation Document, the Company has revisited the cost-effectiveness model in order to attempt to address the uncertainties outlined by the Evidence Review Group, and the National Institute for Health and Care Excellence Committee. As requested by the National Institute for Health and Care Excellence, this updated model is described in a separate document accompanying this response, where results and key scenario analyses are also presented.
3 – Dosing sources	Throughout the Appraisal Consultation Document, the mean dose of chlormethine gel proposed by the Company ([redacted] g; [redacted] g for Low Skin Burden and [redacted] g for High Skin Burden) is repeatedly described as uncertain. However, the Company have provided the Evidence Review Group and the National Institute for Health and Care Excellence Committee with the individual patient data from Study 201, in addition to transparent calculations to explain how these values have been derived from these data. Further, the Company have also not been able to reproduce the mean dose specified in the Valchor® summary of product characteristics (2.8 g) that is used in the Evidence Review Group's preferred base case, despite this also being supposedly derived from patients in Study 201.[6] Specifically, the Company disagree with the wording of the following statement, and consider it misleading and unjustified, *'The ERG was concerned that the company may have underestimated how much chlormethine gel would be used and therefore the cost. For example, the company's model did not account for people keeping unfinished tubes, or not attending follow-up appointments. The committee noted that the company and the ERG both sourced their dose estimates from Study 201 but there was no direct evidence that the ERG estimate was incorrect.'* Firstly, the Company disagree with, *'the company's model did not account for people keeping unfinished tubes, or not attending follow-up appointments.'* This is a speculative statement that assumes poor trial practice, and is not based on evidence. The Study 201 Clinical Study Report clearly outlines that patients received their assigned supplies at the Baseline visit and each subsequent visit from the site pharmacist or other designated unblinded personnel. The dates and quantity of containers dispensed, the Subject Number and initials, the assigned Randomization Number, batch number, and the dates and quantity of containers returned, were recorded on the Dispensing and Inventory Record Form maintained by the pharmacist or other unblinded study personnel. All patients were reminded to return all empty containers and any unused study drug at their next scheduled visit. Such containers (both used and unused) were to be returned to the site pharmacist or other designated

	unblinded study personnel at each clinic visit. In addition, only [redacted] patients ([redacted]) in the chlormethine gel arm were lost to follow-up in Study 201, suggesting that the vast majority of patients are accounted for and thus would not have discontinued without returning tubes at subsequent visits.[7] Secondly, the Company are unclear of the foundation for the statement '*but there was no direct evidence that the ERG estimate was incorrect'*, which appears to imply that the value of 2.8 g should be considered to be the appropriate estimate unless it can be proven to be incorrect. The relevant question that requires resolution is "what is an appropriate estimate of the mean dose of chlormethine gel used in Study 201?". From first principles, the Company considers that the most appropriate answer to that question (i.e. the most appropriate estimate of the mean dose of chlormethine gel used in Study 201) is the mean value that results from a reproducible calculation applied to the raw trial individual patient data, using an analysis methodology that is considered appropriate for deriving a mean estimate. The Company has performed this calculation, provided the trial individual patient data to the Evidence Review Group for verification, and had it confirmed by the Evidence Review Group that the calculation performed was accurate (based on the Evidence Review Group's critique to the Company's Technical Engagement response). Conducting such a calculation produces a value of [redacted] g, not 2.8 g. Beyond demonstrating that the calculated mean of the individual patient data is not 2.8 g, it is not clear how the value of 2.8 g in the Valchor® summary of product characteristics could be proven to be "incorrect". More fundamentally, the full origins and derivation of the value of 2.8 g in the Valchor® summary of product characteristics value are not known, and it is therefore not possible to know what this value truly represents; therefore, it is not clear that demonstration of its correctness or incorrectness is of any relevance compared to the availability of the trial individual patient data that allows calculation of the desired value from first principles.[6] Thirdly, the Company note that in their use of the value of 2.8 g from the Valchor® summary of product characteristics, the ERG has taken the approach of assuming that the consumption for Low and High Skin Burden is [redacted] g and [redacted] g, which replicates the method utilised by the Company to derive skin burden/disease stage-specific dose estimates from a single overall mean. However, the Company wish to highlight that data on dosing by disease stage are available directly from the Valchor® summary of product characteristics: these are reported as a mean daily dose of 1.77 g and 4.28 g for Low and High Skin Burden, respectively. Whilst the Company fundamentally do not agree with the use of the Valchor® summary of product characteristics estimates over the mean dose derived directly from the individual patient data, we consider that any scenarios exploring the use of the Valchor® summary of product characteristics estimates should utilise these directly reported stage-specific values (1.77 g, 4.28 g) as opposed to the 1.14 g and 5.10 g used by the Evidence Review Group currently.[6] Additionally, and as acknowledged in the Appraisal Consultation Document, clinical experts have indicated that *'in stage 1B most people have limited skin disease, and that people with advanced disease do not necessarily need more gel. They estimated that people would use 1 tube every 1 to 2 months, which is 6 to 12 tubes a year with a mean daily dose of approximately 1 g to 2 g and lower than what was estimated by both the company and the ERG.'* Thus, the individual patient data analysis from the Company may even be conservative with regards to chlormethine gel usage in clinical practice when considering this expert opinion. This is further supported by individual patient data from the PROVe trial, which the Company

	has sought to provide evidence for the consumption of chlormethine gel in the real-world setting. An Excel spreadsheet containing these data has been provided as part of this response. These data are associated with limitations, as patients were permitted to receive concomitant medication (in contrast to in Study 201 where concomitant medication was not permitted, apart from to treat non- mycosis fungoides-type cutaneous T-cell lymphoma lesions/other medical conditions), and the fact that data for body surface area were not available for all patients for which the number of tubes dispensed over the treatment interval and the duration of the treatment interval were available.[7, 8] As such, a small proportion of the overall PROVe study are able to contribute to the dosing calculations. Nevertheless, these data indicate that use of chlormethine gel in real-world clinical practice may be lower than that indicated in the clinical trial setting, with a calculated mean daily dose per treatment interval of [redacted] g for Low Skin Burden patients and [redacted] g for High Skin Burden patients.[8]
4 – Acknowledgement of MF-CTCL as a rare disease	As described in Document B of the Company Submission (Section B.1.3), the fact that mycosis fungoides-type cutaneous T-cell lymphoma is a rare disease was recognised by the granting of an orphan designation for chlormethine gel (Ledaga®) by the Committee for Orphan Medicinal Products on 22nd May 2012.[9] Further, epidemiological data on cutaneous T-cell lymphoma (and mycosis fungoides-type cutaneous T-cell lymphoma) for England specifically is available from a Public Health England National Cancer Registration and Analysis Services Short Report on registration of cutaneous T-cell lymphoma in England between 2009 and 2013. In this audit of cases of newly diagnosed cutaneous T-cell lymphoma, a total of 1,659 cases were reported across the time period studied, corresponding to an average number of annual diagnosed cases of cutaneous T-cell lymphoma in England of 332. In the same audit, it was stated that 920 cases of mycosis fungoides-type cutaneous T-cell lymphoma diagnosis were recorded between 2009 and 2013, thereby indicating that approximately 55% of cutaneous T-cell lymphoma cases diagnosed over this period were mycosis fungoides-type cutaneous T-cell lymphoma. This would therefore correspond to an estimate of 182 new diagnoses of mycosis fungoides-type cutaneous T-cell lymphoma on average in England each year.[10] Mycosis fungoides-type cutaneous T-cell lymphoma is therefore a rare disease. There is a lack of acknowledgement of mycosis fungoides-type cutaneous T-cell lymphoma as a rare disease throughout the Appraisal Consultation Document. Such context is important to include, as rare diseases may have limited, licensed treatment options due to lack of research investment, and therapies used to treat them are often associated with sparse (and often low-quality) evidence bases, not least as a result of small patient pools from which to conduct clinical trials. These two key issues together can give rise to considerable unmet need for available treatment options that are associated with good quality evidence for their efficacy and safety. The lack of evidence available in rare diseases also leads to inherent challenges in determining the relative efficacy of treatments. Despite a general sparsity of high quality evidence in mycosis fungoides-type cutaneous T-cell lymphoma, the British Association of Dermatologists guidelines rate the evidence available for chlormethine gel that is provided by Study 201 as at a low risk of bias, and that the study was 'well-conducted' (overall rating of 1+), supporting that chlormethine gel has the potential to provide a treatment option with a more robust evidence base for its efficacy and safety in this rare disease.[11] Further,

	chlormethine gel was the only topical therapy in the British Association of Dermatologists guidelines with this high evidence rating. This is not acknowledged in the Appraisal Consultation Document. These issues are discussed in more detail below in the context of this appraisal and the Appraisal Consultation Document specifically. **Lack of licensed therapies for mycosis fungoides-type cutaneous T-cell lymphoma** As described in Section B.1.3 of the Company Submission, there is a considerable unmet need for licensed treatments that are supported by robust evidence and that specifically target the skin patches and plaques associated with mycosis fungoides-type cutaneous T-cell lymphoma. Despite reference to many treatment options in the British Association of Dermatologists guidelines, there are few therapies that have proven clinical efficacy through randomised controlled trials and widespread use in UK clinical practice.[12] The Company considers it important to understand the clinical need not only for a treatment that effectively treats the skin symptoms of mycosis fungoides-type cutaneous T-cell lymphoma and is convenient for home use, but also for options that are licensed and supported by a more robust evidence base for its efficacy and safety (as chlormethine gel is) for patients with this rare condition.[3, 13] Further, whilst the Appraisal Consultation Document states that '*The committee concluded that chlormethine gel is not a disease-modifying treatment, but it relieves skin symptoms and improves quality of life*', the Company believe that it is important to highlight that, unlike treatments such as topical steroids, chlormethine gel can be considered 'anti- cutaneous T-cell lymphoma', as it is a cytotoxic, bifunctional deoxyribonucleic acid alkylating agent which inhibits rapidly proliferating (i.e. malignant cancer) cells, rather than simply reducing the pain and irritation associated with patches and plaques.[14, 15] **Relative efficacy versus phototherapy** Whilst Study 201 was a randomised controlled trial (with level 1+ evidence as per the British Association of Dermatologists guidelines), for phototherapy, the majority of studies from the British Association of Dermatologists guidelines and/or clinical systematic literature review were judged to be of poor quality, particularly in relation to the factors such as their historical nature, small sample size, study design (e.g. retrospective studies) and limited reporting of patient characteristics; this conclusion is coherent with the overall rating of evidence for phototherapy in the British Association of Dermatologists guidelines (ranging from 2- to 2+). Further, there were notable issues of comparability with Study 201, in particular around response outcome definition. Therefore, there were very limited options when attempting to compare the relative efficacy of chlormethine gel versus phototherapy.[3, 12] Even the Phan *et al.* (2019) systematic review that was identified by the ERG during the appraisal process for this submission included only retrospective observational studies with subjective clinician assessment of response.[1]

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	Given that the Appraisal Consultation Document does not reflect these considerations, it is not clear that the rarity of the condition and the consequences of this outlined above have been taken into account in the decision-making, in particular with respect to acknowledgement of the quality of the evidence available for efficacy and safety of chlormethine gel compared to phototherapy.
5 – Acknowledgement of real-world evidence sources supporting the use of chlormethine gel in advanced stage patients	On page 9 of the Appraisal Consultation Document, the Committee highlight *'that there could be people with advanced disease who might benefit from chlormethine gel, however, no such people were included in Study 201.'* Although the Company fully agree that advanced stage patients were not included in Study 201, it is important to report here that real-world evidence is available from the French ATU and PROVe studies, and was presented in the Company Submission, to support the use of chlormethine gel in advanced mycosis fungoides-type cutaneous T-cell lymphoma.[16-18]
6 – Minor wording amendment	On pages 6–7 of the Appraisal Consultation Document, it states, *'The first choice for early stage MF-CTCL (stage 1A to 2A) includes topical treatments, phototherapy or localised radiotherapy. If these become unsuitable, or the condition progresses to an advanced stage, systemic therapies such as oral bexarotene and peginterferon alfa are options. Although it is a systemic treatment, oral bexarotene aims to treat the skin symptoms of MF-CTCL.'* However, both pegylated interferon and bexarotene are systemic treatments that also aim to treat the skin symptoms of mycosis fungoides-type cutaneous T-cell lymphoma. The Company would suggest amending to the following: *'The first choice for early stage MF-CTCL (stage 1A to 2A) includes topical treatments, phototherapy or localised radiotherapy. If these become unsuitable, or the condition progresses to an advanced stage, systemic therapies such as oral bexarotene and peginterferon alfa are options. Although they are ~~it is a~~ systemic treatments, oral bexarotene and peginterferon alfa aim~~s~~ to treat the skin symptoms of MF-CTCL.'*
7 – Minor wording amendment	On page 14 of the Appraisal Consultation Document, it states, *'Comparison of symptom response rates from Study 201 and the phototherapy trials used in the model suggest that chlormethine gel is less effective than phototherapy for treating skin symptoms. But the company's model predicted that chlormethine gel is more effective than phototherapy.'* However, the Company do not consider the latter part of this to be accurate. The Company would suggest amending to the following: *'Comparison of symptom response rates from Study 201 and the phototherapy trials used in the model suggest that chlormethine gel is less effective than phototherapy for treating skin symptoms. However, when considering the entire treatment pathway experienced by patients for either chlormethine gel or phototherapy within the cost-effectiveness model, the results indicate that chlormethine gel is associated with increased QALYs versus phototherapy ~~But the company's model predicted that chlormethine gel is more effective than phototherapy~~.'*

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Checklist for submitting comments

- Use this comment form and submit it as a Word document (not a PDF).
- Complete the disclosure about links with, or funding from, the tobacco industry.
- Combine all comments from your organisation into 1 response. We cannot accept more than 1 set of comments from each organisation.
- Do not paste other tables into this table – type directly into the table.
- Please underline all confidential information, and separately highlight information that is submitted under [redacted] and all information submitted under [redacted]. If confidential information is submitted, please also send a 2nd version of your comment with that information replaced with the following text: 'academic / commercial in confidence information removed'. See the Guide to the processes of technology appraisal (section 3.1.23 to 3.1.29) for more information.
- Do not include medical information about yourself or another person from which you or the person could be identified.
- Do not use abbreviations
- Do not include attachments such as research articles, letters or leaflets. For copyright reasons, we will have to return comments forms that have attachments without reading them. You can resubmit your comments form without attachments, it must send it by the deadline.
- If you have received agreement from NICE to submit additional evidence with your comments on the appraisal consultation document, please submit these separately.

Note: We reserve the right to summarise and edit comments received during consultations, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during our consultations 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 comments we received, and are not endorsed by NICE, its officers or advisory committees.

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Appendix to the Stakeholder Comments Form – Recordati Rare Diseases and Helsinn Healthcare SA

Introduction

As described in the main body of the stakeholder comments form from Recordati Rare Diseases and Helsinn Healthcare SA (the Company), the cost-effectiveness model for Ledaga® in the treatment of mycosis fungoides-type cutaneous T-cell lymphoma has been revisited in order to attempt to address the uncertainties outlined by the Evidence Review Group and the National Institute for Health and Care Excellence Committee, as summarised below:

Page 3: '*The evidence used to estimate cost effectiveness is uncertain because it oversimplifies the treatment pathway for people with MF-CTCL and does not reflect clinical practice. Other things that are not certain include:*

- *Time to skin symptom progression after response to treatment*
- *The length of time people have systemic treatment once skin symptoms progress'*

Page 7: *'Many people have more than one course of treatment, although the number of courses of phototherapy is limited by the cumulative UV dose. Repeated courses of chlormethine gel would also be offered, and in practice phototherapy could be followed by chlormethine gel or vice versa. The committee understood that people are likely to have multiple rounds of treatment (which may include phototherapy or chlormethine gel) until the symptoms no longer respond. Then the person may be offered systemic therapies such as oral bexarotene or peginterferon alfa. The clinical experts explained that treatment decisions are based on the extent and severity of the skin disease, rather than the overall stage of disease. In practice, people with advanced MF-CTCL (stage 2B to 4) who have disease at sites other than the skin, and may be having chemotherapy, could still have skin lesions that could be treated with chlormethine gel. The committee concluded that people with MF-CTCL have multiple treatments in different sequences until symptoms no longer respond.'*

Page 10: *'The company's model structure does not reflect the treatment pathway for people with MF-CTCL in clinical practice. In the company's model, people were assumed to have only one round of either chlormethine gel or phototherapy.'*

Page 11: *'In both arms of the model, people who had a complete response in skin symptoms were assumed to progress to bexarotene or peginterferon alfa earlier than people who had a partial response in skin symptoms.'* and *'The clinical experts stated that if someone has a complete skin symptom response, their condition may then deteriorate but they may still only have very limited disease. It may be appropriate to 'watch and wait' rather than immediately progress to bexarotene or peginterferon alfa.'*

Page 13: *'The committee concluded that the base case cost-effectiveness estimates were highly uncertain and depended on the time horizon affecting the duration of subsequent treatment.'*

As requested by the National Institute for Health and Care Excellence, this updated model is described below, in addition to the associated results and key scenario analyses relevant to decision making.

Model Structure

An updated model structure is presented in Figure 1 below. This structure is based on the model submitted as part of the original Company Submission and response to Technical Engagement, but has some key changes in order to address the key uncertainties highlighted by the National Institute for Health and Care Excellence Committee outlined in the Appraisal Consultation Document. New transitions are indicated by orange arrows and original transitions are indicated by blue arrows.

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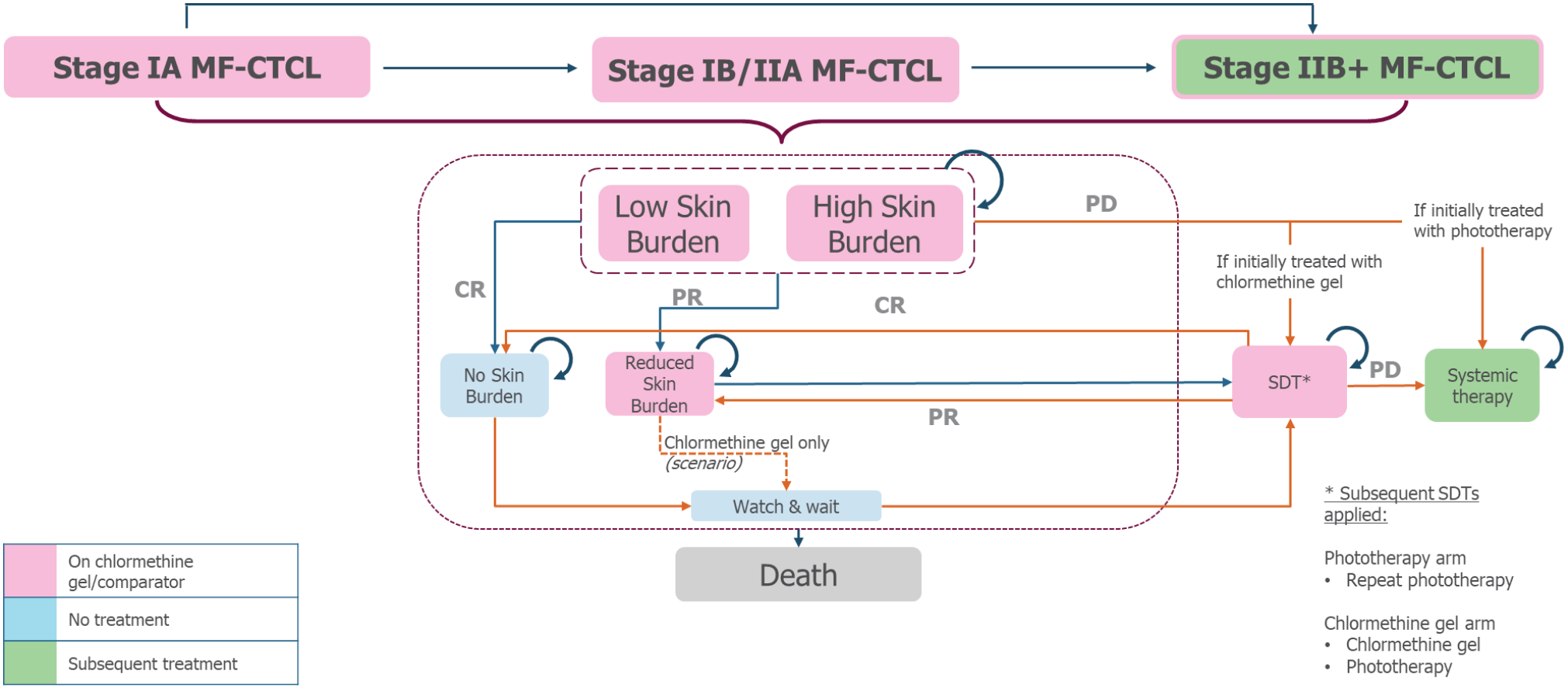
Figure 1: Updated cost-effectiveness model structure



Abbreviations: CR: complete response; MF-CTCL: mycosis fungoides cutaneous T-cell lymphoma; PD: progressive disease; PR: partial response; SDT: skin-directed therapy.

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As per the model submitted as part of the Company Submission and that provided in response to Technical Engagement, there are three defined staging 'categories' based on clinically accepted definitions of early (Stage IA–IIA) and late (Stage IIB–IV) stage disease, as well as further separation into categories within which patient treatments, monitoring and prognosis would be expected to be similar:

- Stage IA
- Stage IB/IIA
- Stage IIB+

Patients in Stage IA or Stage IB/IIA (early stage disease) are assumed to receive active treatment for skin lesions only (i.e. chlormethine gel or phototherapy), whilst patients in Stage IIB+ (advanced stage disease) are assumed to receive active treatment for disseminated cancer i.e. systemic therapies, in addition to their treatment for skin lesions. Following feedback provided by the Evidence Review Group during Technical Engagement, advanced disease treatment baskets are varied based on the treatment a patient is receiving and the health state in which they reside (see the Company's Technical Engagement response for more detail).

Upon entering the model, patients are defined as either Low or High Skin Burden within each disease stage category. The Low/High distinction was based on the percentage body surface area affected: Low = <10% body surface area; High = 10–80% body surface area. Patients with >80% body surface area would be classed as erythrodermic and are excluded from the model based on clinical feedback which indicates that erythrodermic patients would not be considered for treatment with chlormethine gel. Stage IA patients are assumed to have Low Skin Burden at model entry and Stage IB/IIA patients are assumed to have High Skin Burden at model entry. Patients in Stage IIB–IV are assumed to consist of a combination of patients with Low Skin Burden and patients with High Skin Burden.

Patients in the Low or High Skin Burden health states within each disease stage category were modelled to experience degrees of response to treatment, including remission, relapse of skin lesions or no change (see Figure 1). Responses of complete response (CR), partial response (CR), stable disease (SD) and progressed disease (PD) are aligned to the response categories from Study 201 based on the modified Severity Weighted Assessment Tool (mSWAT) index.[1]

Whilst the possible transitions relating to patients experiencing an initial remission (either complete response, resulting in transition to No Skin Burden, or partial response, resulting in transition to Reduced Skin Burden) or no change (i.e. stable disease, resulting in patients remaining in Low/High Skin Burden) remain the same as the original model submitted as part of the Company Submission, transitions relating to a relapse of skin lesions have been modified as part of this most recent model:

- Patients receiving chlormethine gel who experience progressed disease in the Low/High Skin Burden health states transition to a new 'SDT' health state to reflect that they may receive phototherapy in clinical practice. Patients may also transition into the SDT health state if they achieve a partial response after initial treatment or from the 'Watch and Wait' health state (see below and Figure 1), with chlormethine gel patients receiving either chlormethine gel or phototherapy and phototherapy patients receiving repeat phototherapy. This state has been included to align with clinical practice, where patients may switch between skin-directed therapies or receive the same skin-directed therapy more than once. This health state also ensures that patients do not progress into the systemic treatment health state too quickly, which was a concern of the Evidence Review Group/National Institute for Health and Care Excellence Committee with regards to the previous versions of the model, where patients were in the Progressed from 1L health state for a long duration
    - In the SDT health state, patients have the opportunity to achieve either a complete response (and transition to No Skin Burden), partial response (and transition to Reduced Skin Burden), progressed disease (progressing to the 'Systemic Therapy' health state; see below) or stable disease (remaining in the SDT state). The efficacy of treatments in the SDT state are assumed to be the same as for patients first entering the model (given that there are no data available to inform efficacy for repeat treatment) and patient quality of life is assumed to be the same as that in their original Skin Burden health state
- Patients receiving phototherapy, who experience progressed disease in the Low/High Skin Burden health states, transition to the Systemic Therapy health state (see below). This is based on clinical expert feedback that patients who progress (or remain stable) when receiving phototherapy for the first

time would not receive phototherapy for a second time and would instead receive either bexarotene or pegylated interferon-α

- In the Systemic Therapy health state (which replaced the Progressed from 1L health state present in earlier versions of the model), patients receive either bexarotene or pegylated interferon-α in a 50:50 split. Once patients enter the Systemic Therapy health state, they remain there until death and their quality of life is assumed to be as per the previous Progressed from 1L health state
- Patients who achieve stable disease in the Low/High Skin Burden health states are assumed to receive bexarotene or pegylated interferon-α, but are assumed to not move into the systemic therapy health state as this would result in a decrease in their quality of life, which would not be reflective of clinical practice

For patients who achieve an initial complete response (transitioning to No Skin Burden), a new Watch and Wait health state has also been added into the model to address the concerns from the Evidence Review Group and the National Institute for Health and Care Excellence Committee that patients achieving complete response were, counterintuitively, progressing to systemic therapies faster than those achieving a partial response. Based on clinical expert opinion and data for the duration of Watch and Wait from the PROCLIPI registry, following a complete response, patients remain in the Watch and Wait health state for 8 months, before entering the SDT health state described above. In Watch and Wait, patients are assumed to have the same quality of life as a partial response patient.

Patients could transition to the Death health state from any other health state and from any disease stage.

Timepoint for Assessing Response

In both previous versions of the cost-effectiveness model, patients were assumed to be assessed for progression of skin symptoms at 6 months. This was based on the fact that in Study 201, patients were only categorised as having progressed disease at the end of the trial period (or last known follow-up); the time frame of 6 months was based on clinical expert opinion that a patient experiencing a sufficient worsening of skin symptoms would not be classed as having progressed, and therefore moved onto a new treatment, until this timepoint after initiating treatment.[1] However, in this latest version of the model, whilst patients are assessed for progression on chlormethine gel at 6 months, patients receiving phototherapy are assessed at 3 months, to reflect that response would be assessed after a course of phototherapy was complete i.e. at 13 weeks (2.99 months).

Phototherapy Efficacy

As per the Technical Engagement response, in the base case for the updated cost-effectiveness model, response rates for phototherapy (complete response, partial response and progressed disease) are derived from Phan *et al.* (2019).[2] However, as described in the stakeholder comment form, the Company believe that the response rates from Phan *et al.* overestimate the efficacy of phototherapy that would be seen in clinical practice in the UK and are objective in nature. Therefore, as part of the cost-effectiveness model updates, the Company have included the option to utilise complete response and partial response rates for phototherapy from the PROCLIPI registry.[3] These are explored in a scenario analysis below and have the benefits of being specific to UK clinical practice [redacted] The Company acknowledges that utilising complete response and partial response rates from PROCLIPI has a large effect on the cost-effectiveness results; given the uncertainty in the estimates for phototherapy efficacy, the results of this scenario are useful to demonstrate that the efficacy source for phototherapy is a key driver of the model results and the effects of lowering the complete response and partial response rates for phototherapy to those measured objectively (with the Modified Severity-Weighted Assessment Tool) and in UK clinical practice (i.e. a potentially more reliable and realistic source).

In the base case, the source for relapse post-complete response and post-partial response is maintained as Whittaker *et al.* (2012) and assumed equal to initial progressed disease, respectively, again as per the Technical Engagement response.[4] A scenario is also presented where Phan *et al.* (2019) is used to inform these transitions, with the duration of response downgraded for both post-complete response and post-partial response (see 'Downgrading of Phototherapy Duration of Response' below). However, and as mentioned in the Technical

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Engagement response, Recordati/Helsinn is concerned that the use of Phan *et al.* (2019) to inform these transitions is inappropriate for the following reasons:[2]

- The Company has been unable to replicate the median time to relapse post-complete response cited in Phan *et al.* (2019) from the original sources[2]
- Phan *et al.* (2019) cites the median and range of the time to relapse estimates from across the source studies, which highlights a very large range of reported time to relapse data.[2] Whilst taking the median of the estimates (as opposed to the mean) is less subject to skew by outlier data, the Company is concerned that the wide reported range indicates that the studies are not measuring like-for-like and are subject to considerable sources of heterogeneity between studies. As such, adopting the median of the reported values is a simplification that doesn't account for the uncertainty associated with this estimate
- It should also be noted that whilst Phan *et al.* (2019) took the median of the reported time to relapse estimates, the individual study estimates were a mix of median and mean time to relapse[2]
- Finally, and most importantly, there are reasons to consider that some of the studies informing the median estimate from Phan *et al.* (2019) are not appropriate.[2] Multiple studies used maintenance phototherapy, which would likely help to prolong time to relapse post-complete response but is not representative of UK clinical practice where maintenance phototherapy is not used due to the risk of associated malignancies. In addition, some studies use considerably more phototherapy sessions than the 12.5 weeks at two sessions/week (i.e. total of approximately 25 sessions) recommended in the UK, as per the British Association of Dermatologists guidelines[5]

Stopping Rule for Chlormethine Gel

In response to discussions at the first Committee meeting, the Company have incorporated functionality within the updated cost-effectiveness model that allows a stopping rule at 12 months to be introduced for chlormethine gel. Please note that this stopping rule is only applied to patients on their first round of chlormethine gel treatment given the constraints of applying the stopping rule within the Markov model structure.

There are two options when applying the stopping rule in terms of the efficacy assumed for patients when they discontinue chlormethine gel. Firstly, patients can maintain the efficacy from Study 201 (i.e. no change in terms of efficacy from the base case) or secondly, patients can assume the efficacy associated with the Watch and Wait health state, based on data from the PROCLIPI registry.[1, 3] The Company considers using Study 201 data to be more appropriate, as it is expected that relapse rates are treatment-specific, even once the patient has discontinued, and it is not known what treatments patients received prior to Watch and Wait in PROCLIPI. In contrast, efficacy from Study 201 is specific to chlormethine gel.

The stopping rule is not included within the base case (as there is no stopping rule specified in the summary of product characteristics for chlormethine gel) but has been explored in scenario analyses.[6]

Time Horizon

A time horizon of 20 years is used in the base case for the updated cost-effectiveness model (a lifetime horizon was initially used in the Company Submission model and that supporting the Technical Engagement response). Whilst mycosis fungoides-type cutaneous T-cell lymphoma is a lifelong condition, and therefore a lifetime horizon may be the most appropriate approach for modelling this disease, there is a lot of uncertainty in terms of the treatment pathway, efficacy and therefore cost-effectiveness estimates for chlormethine gel in the long-term. A shorter time horizon of 10 years would not be appropriate as there is a substantial proportion of patients still receiving benefit from a skin-directed therapy (i.e. not in Systemic Therapy) and therefore realising the benefits of treatment at this timepoint. Specifically, at 10 years, only 9% of patients are on systemic therapy in the chlormethine gel arm, and 46% of patients are in the No/Reduced Skin Burden health states. Therefore, a shorter time horizon (e.g. 10 years) would be too short to capture the full treatment benefit of chlormethine gel. Whilst the Company acknowledges that the time horizon does influence the cost-effectiveness model results, 20 years has been selected as a compromise between shorter durations and a lifetime horizon.

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Downgrading of Phototherapy Duration of Response

When Phan *et al.* (2019) is selected as a source for relapse post-complete response and relapse post-partial response the duration of response has been adjusted to account for the fact that several trials in Phan *et al.* incorporated maintenance therapy, which is not reflective of clinical practice in the UK, or how phototherapy has been modelled. Specifically, the duration of response post-complete response and post-partial response has been adjusted, based on the relative duration for patients who did and did not receive maintenance phototherapy.[2] This is aligned with the Evidence Review Group critique of company response to Technical Engagement (page 11); however, the Evidence Review Group only applied this downgrading for post-complete response; this was deemed appropriate as patients with a partial response immediately received systemic therapy after their course of phototherapy, considered by the Evidence Review Group as similar to maintenance phototherapy. However, in this updated Company model, this downgrading has also been applied to post-partial response, as the model now assumes that partial response patients who finish their course of phototherapy would discontinue treatment, and would not commence treatment again until relapse (the same as complete response patients). Therefore, similar to the appropriateness of applying the downgrading post-complete response, this has also now been applied for post-partial response.

Dosing from Valchor® Summary of Product Characteristics

As mentioned in the stakeholder comments form, the company note that in their use of the value of 2.8 g from the Valchor® summary of product characteristics, the Evidence Review Group has taken the approach of assuming that the consumption for Low and High Skin Burden is 1.14 g and 5.10 g, which replicates the method utilised by the company to derive skin burden/disease stage-specific dose estimates from a single overall mean. However, the company wish to highlight that data on dosing by disease stage are available directly from the Valchor® summary of product characteristics: these are reported as a mean daily dose of 1.77 g and 4.28 g for Low and High Skin Burden, respectively. Whilst the company fundamentally do not agree with the use of the Valchor® summary of product characteristics estimates over the mean dose derived directly from the individual patient data (the Study 201 individual patient data are utilised in the base case results presented below), we consider that any scenarios exploring the use of the Valchor® summary of product characteristics estimates should utilise these directly reported stage-specific values (1.77 g, 4.28 g) as opposed to the 1.14 g and 5.10 g used by the Evidence Review Group currently.[7]

Therefore, these stage-specific values (1.77 g and 4.28 g) have been added in as dosing options in the updated cost-effectiveness model, and their use is explored in scenario analyses presented below.

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Updated Cost-Effectiveness Model Results

Base Case Results

	Total costs	Total LYs	Total QALYs	Incremental costs	Incremental LYs	Incremental QALYs	Chlormethine gel ICER (£/QALY)	NMB
Chlormethine gel	£156,177	10.50	8.21	-	-	-	-	-
Phototherapy (PUVA/UVB)	£150,645	10.50	7.88	£5,532	0.00	0.33	£16,956	£4,256

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

Scenario Analyses

Various scenario analyses were conducted to explore the impact of assumptions and sources of parameter or structural uncertainty.

[redacted]

Justification for conducting the scenario analyses is as follows.

Discount for bexarotene

Bexarotene is associated with a PAS; however, this discount is unknown to the Company. Therefore, scenarios where 20% and 30% discounts have been included for bexarotene are presented below.

Evidence Review Group preferred source for relapse post-complete response and relapse post-partial response

In the base case, the source for relapse post-complete response is Whittaker *et al.* (2012) and relapse post-partial response is assumed to be the same as initial progressed disease.[4] Whilst the Company believes that this is the most appropriate source for these transitions and that the use of the Phan *et al.* (2019) source is associated with serious limitations (see 'Phototherapy Efficacy' above), a scenario has been conducted utilising Phan *et al.* (2019), in order to demonstrate the influence of this on the cost-effectiveness model results.[2]

Early population only

The population of interest in the base case analysis considers all stages of mycosis fungoides-type cutaneous T-cell lymphoma and this aligns with the full licensed population for chlormethine gel in the UK and the expected use of chlormethine gel for the treatment of skin lesions as discussed in Section B.3.2.1 of Document B of the

Company Submission.[6] However, given that the patient population of Study 201 included only patients with early stage disease (Stage IA–IIA), a subgroup analysis for the early stage population specifically has been conducted.

PROCLIPI for complete response and partial response rates

As described in detail in the stakeholder comments form, the studies included in the Phan *et al.* systematic review may overestimate phototherapy efficacy, and this notion is also supported by discussions at the Committee meeting, where it became apparent that the sources available to inform phototherapy efficacy may not necessarily provide a comparable assessment of response rates to that utilised for chlormethine gel in Study 201 (as phototherapy is often subjectively, rather than objectively measured), and may therefore overestimate the effectiveness for phototherapy compared to what would be expected in real-world practice.[2, 8] Therefore, a scenario has been conducted using the complete response and partial response rates for phototherapy from the PROCLIPI registry, which may represent a more realistic and accurate estimate of phototherapy efficacy in UK clinical practice given that PROCLIPI is a UK-based registry, and [redacted] when assessing chlormethine gel.

No adverse events for chlormethine gel

In the base case analysis, adverse events at Grade 3 or greater that occurred in ≥5% of patients for chlormethine gel or the comparator (phototherapy) were included, as it was considered that these adverse events would be the ones associated with a substantial cost and/or quality of life burden. However, safety data from the PROVe real-world evidence study suggest that there were [redacted] serious adverse events that occurred in ≥5% patients receiving chlormethine gel (even when given in combination with concomitant therapies), reflecting that perhaps in clinical practice (where concomitant administration of corticosteroids to manage adverse events would be permitted) adverse events with chlormethine gel may be lower than observed in Study 201 (where concomitant steroid use was not permitted).[9] Therefore, a scenario analysis in which the chlormethine gel adverse event rates are set to 0% was conducted.

Stopping rule

A scenario analysis has been conducted exploring the effect of patients receiving chlormethine gel discontinuing treatment after 12 months, as this is the duration for which patients were treated in Study 201. Whilst the summary of product characteristics for chlormethine gel does not specify that a stopping rule should be implemented, this scenario has been conducted to demonstrate the effects of such a stopping rule on the cost-effectiveness of chlormethine gel versus phototherapy.[6] Two scenarios are presented below: one where the efficacy of patients who have discontinued is based on Study 201 (i.e. no change from when they were on treatment) and one where Watch and Wait efficacy from PROCLIPI is applied.[1, 3] As described in 'Stopping Rule for Chlormethine Gel' above, the Company believe that Study 201 efficacy is more appropriate, as it is expected that relapse rates are treatment-specific, even once the patient has discontinued, and it is not known what treatments patients received prior to Watch and Wait in PROCLIPI. In contrast, efficacy from Study 201 is specific to chlormethine gel.

Proportion patients receiving chlormethine gel in SDT health state

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In the base case, 80% patients in the SDT health state are assumed to receive chlormethine gel, based on the fact that approximately 20% patients progressed from chlormethine gel in Study 201, and therefore these patients would receive an alternative SDT (phototherapy) in clinical practice.[8] However, given the uncertainty in this parameter, two extreme scenarios have been conducted to demonstrate the effect of varying the proportion of patients receiving treatment with chlormethine gel as their second SDT within the cost-effectiveness model: 0% or 100% receiving chlormethine gel.

Valchlor® summary of product characteristics by disease stage dosing

Whilst the Company strongly believes that the use of the individual patient data from Study 201 to inform chlormethine gel dosing is the most appropriate approach (as is used in the base case), a scenario has been conducted investigating the effects of utilising the by-stage dosing from the Valchor® summary of product characteristics as this source was previously preferred by the Evidence Review Group.[7]

	Incremental costs	Incremental LYs	Incremental QALYs	Chlormethine gel ICER (£/QALY)	NMB	Chlormethine gel ICER (£/QALY) with [redacted] discount for chlormethine gel
Base case	£5,532	0.00	0.33	£16,956	£4,256	[redacted]
1) 20% discount for bexarotene	£15,179	0.00	0.33	£46,526	-£5,392	[redacted]
2) 30% discount for bexarotene	£20,003	0.00	0.33	£61,311	-£10,215	[redacted]
3) Evidence Review Group preferred source for relapse post-complete response and relapse post-partial response	£19,876	0.00	0.14	£138,963	-£15,585	[redacted]
3) Early population only	£1,898	0.00	0.35	£5,391	£8,663	[redacted]
4) PROCLIPI for complete response and partial response rates	-£11,404	0.00	0.43	Phototherapy dominated	£24,218	[redacted]
5) No adverse events for chlormethine gel	£5,384	0.00	0.36	£14,751	£5,565	[redacted]
6) Stopping rule (with Study 201 efficacy after 12 months)	-£24,160	0.00	0.34	Phototherapy dominated	£34,390	[redacted]
7) Stopping rule (with Study 201 efficacy after 12 months) + early population only	-£28,905	0.00	0.37	Phototherapy dominated	£39,949	[redacted]
8) Stopping rule (with Study 201 efficacy after 12 months) + early population only + Evidence Review Group preferred source for relapse post-complete response and relapse post-partial response + 20% discount for bexarotene	-£4,342	0.00	0.19	Phototherapy dominated	£10,077	[redacted]

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9) Stopping rule (with Study 201 efficacy after 12 months) + early population only + Evidence Review Group preferred source for relapse post-complete response and relapse post-partial response + 30% discount for bexarotene	£71	0.00	0.19	£370	£5,664	[redacted]
10) Stopping rule (with Watch and Wait efficacy after 12 months)	£118	0.00	0.28	£428	£8,172	[redacted]
11) Proportion patients receiving chlormethine gel in SDT health state: 100%	£16,582	0.00	0.28	£59,230	-£8,183	[redacted]
12) Proportion patients receiving chlormethine gel in SDT health state: 0%	-£10,885	0.00	0.38	Phototherapy dominated	£22,333	[redacted]
13) Valchlor® summary of product characteristics by disease stage dosing	£27,008	0.00	0.33	£82,782	-£17,220	[redacted]

Abbreviations: ICER: incremental cost effectiveness ratio; LY: life year; NMB: net monetary benefit; QALY: quality adjusted life year; SDT: skin-directed therapy.

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Probabilistic Sensitivity Analysis

The results of the probabilistic sensitivity analysis (2,000 iterations) are presented below. The incremental probabilistic results and incremental cost-effectiveness ratio (that take into account the combined uncertainty across model parameters) are similar to those estimated in the base case analysis, confirming the robustness of the base case analysis.

	Total costs	Total QALYs	Incremental costs	Incremental QALYs	Chlormethine gel ICER (£/QALY)
Chlormethine gel	£158,070	8.19	-	-	-
Phototherapy (PUVA/UVB)	£151,430	7.89	£6,640	0.29	£22,515

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

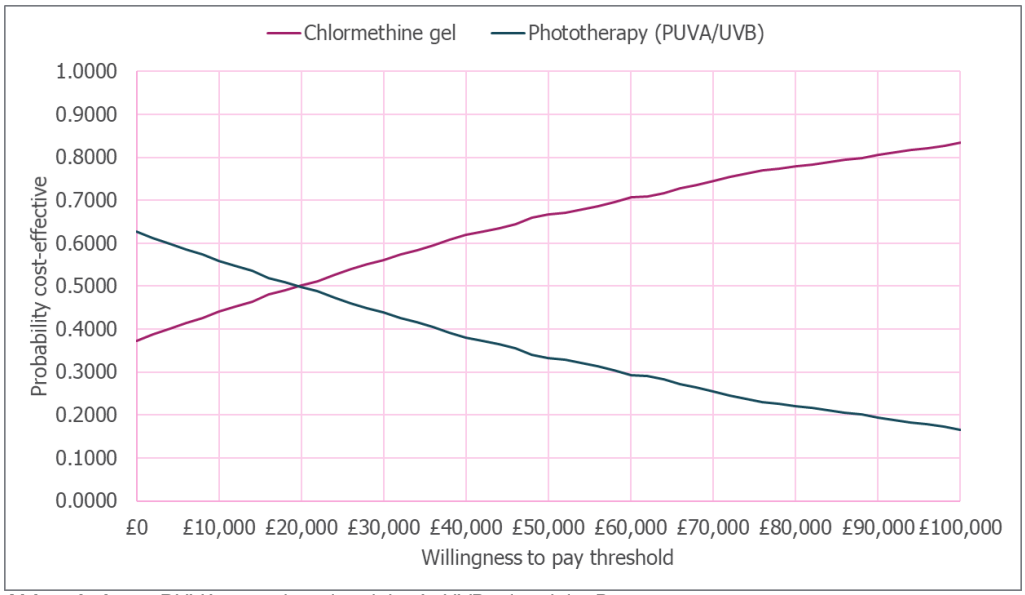
A scatter plot showing the incremental costs and QALYs for chlormethine gel versus phototherapy (PUVA/UVB) is presented in Figure 2 below. Assuming a willingness-to-pay threshold of £30,000 per QALY gained, the probability of chlormethine gel being the most cost-effective treatment option is 56.05%.

Figure 2: PSA scatterplot for chlormethine gel versus phototherapy (PUVA/UVB)

Abbreviations: PSA: probabilistic sensitivity analysis; QALYs: quality-adjusted life years; WTP: willingness-to-pay.

Cost-effectiveness acceptability curves for chlormethine gel versus phototherapy (PUVA/UVB) are presented in Figure 3 below.

Figure 3: Cost-effectiveness acceptability curve for chlormethine gel versus phototherapy (PUVA/UVB)



Abbreviations: PUVA: psoralen-ultraviolet A; UVB: ultraviolet B.

Deterministic Sensitivity Analysis

Deterministic sensitivity analysis was conducted by varying all parameters for which there were single input values in the model. Health state utility values within the model were varied using the standard deviation obtained directly from the vignettes which informed the mean values, with the upper and lower values of each adjacent utility value bound by one another in order to maintain appropriate ordering. In the absence of data on the variability around a particular value, all other model inputs were varied by ±20% in the DSA. Finally, transition probabilities were not included within the DSA given that they are dependent variables.

Tornado diagrams showing the top ten drivers of the cost-effectiveness in the comparison of chlormethine gel versus phototherapy (PUVA/UVB) are presented in Figure 4 to

Figure 7 below. Across these tornado plots, the most influential parameters were the treatment cost per month for chlormethine gel (High Skin Burden), mean body surface area and the proportion of patients receiving second line treatment with chlormethine gel in the SDT health state.

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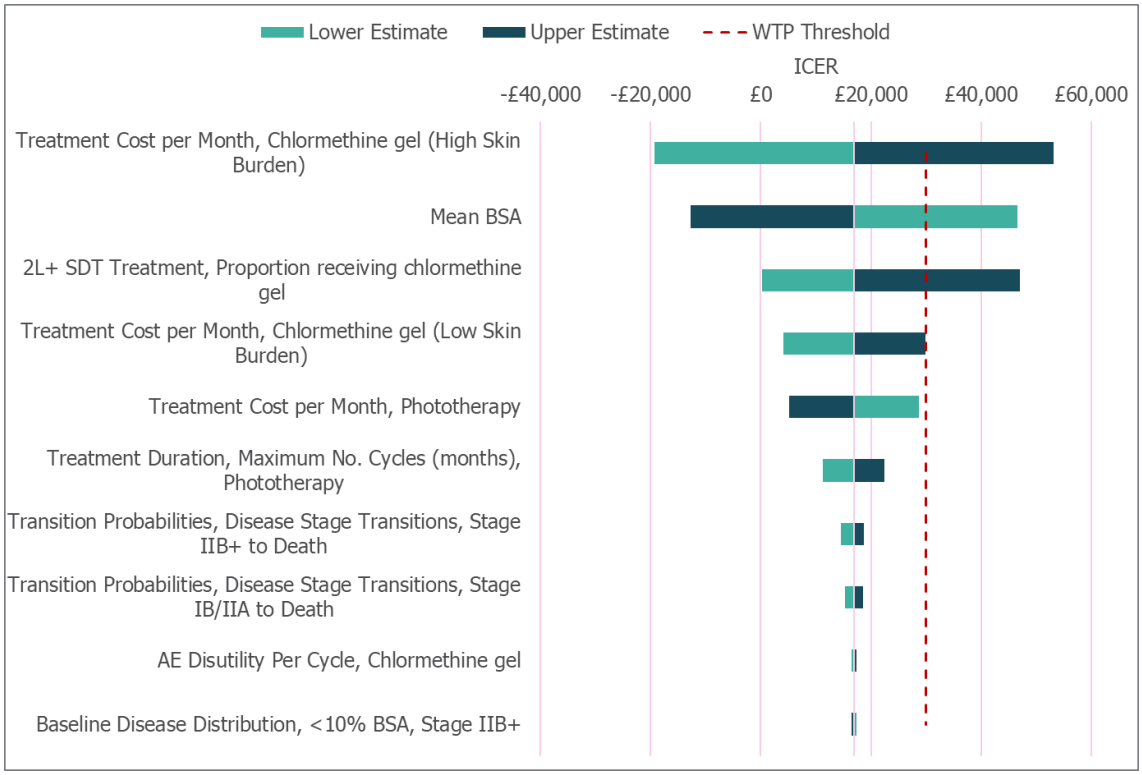
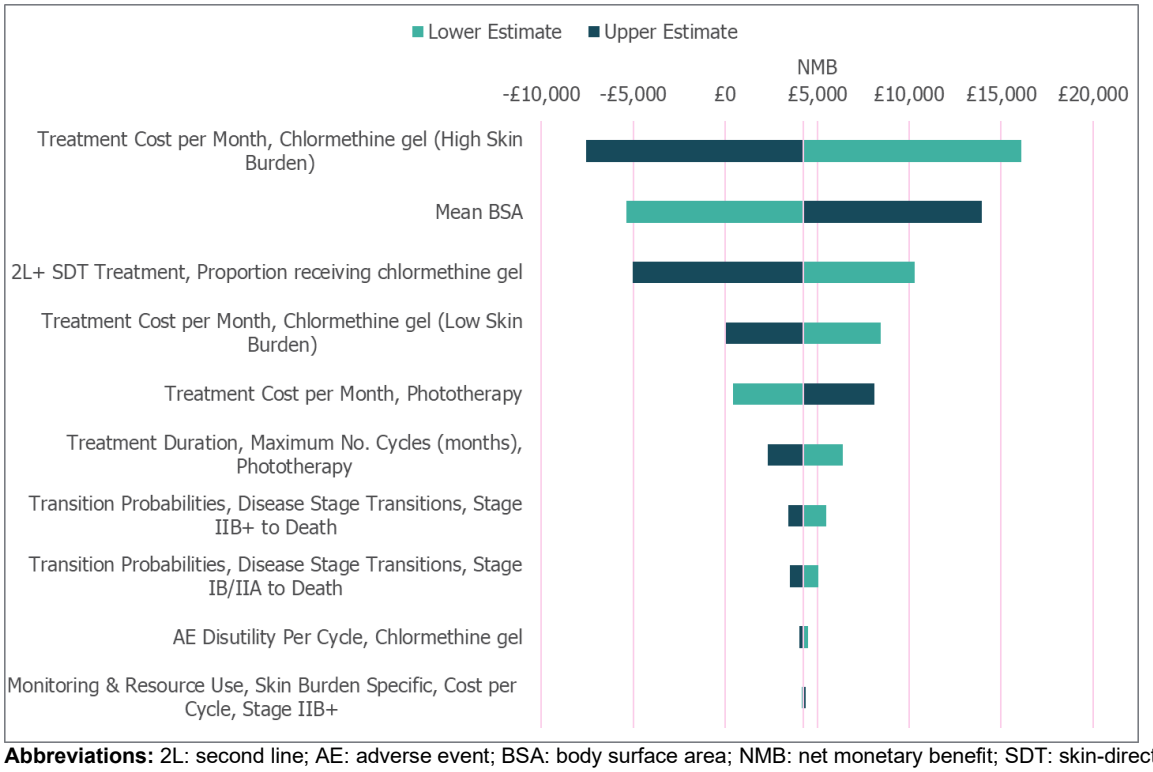
Figure 4: Deterministic sensitivity analysis – incremental cost-effectiveness ratio tornado plot of the top ten most influential parameters



Abbreviations: 2L: second line; AE: adverse event; BSA: body surface area; ICER: incremental cost-effectiveness ratio; SDT: skin-directed therapy; WTP: willingness-to-pay.

Figure 5: Deterministic sensitivity analysis – net monetary benefit tornado plot of the top ten most influential parameters



Abbreviations: 2L: second line; AE: adverse event; BSA: body surface area; NMB: net monetary benefit; SDT: skin-directed therapy.

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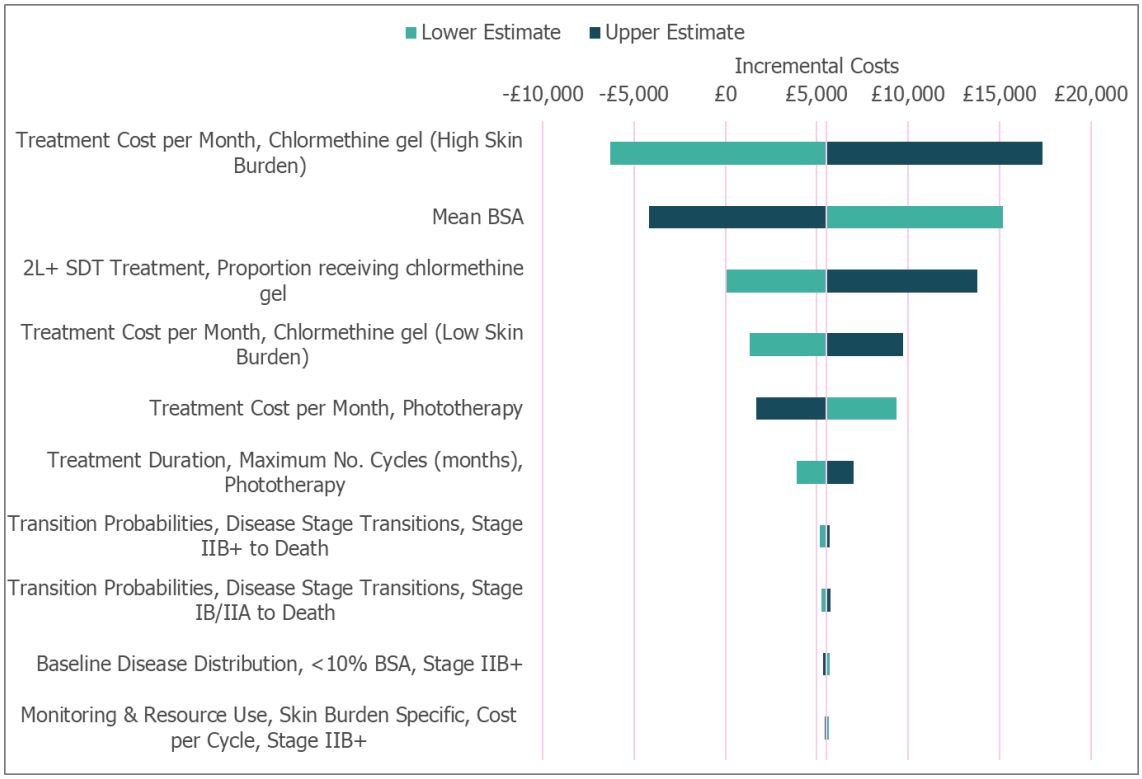
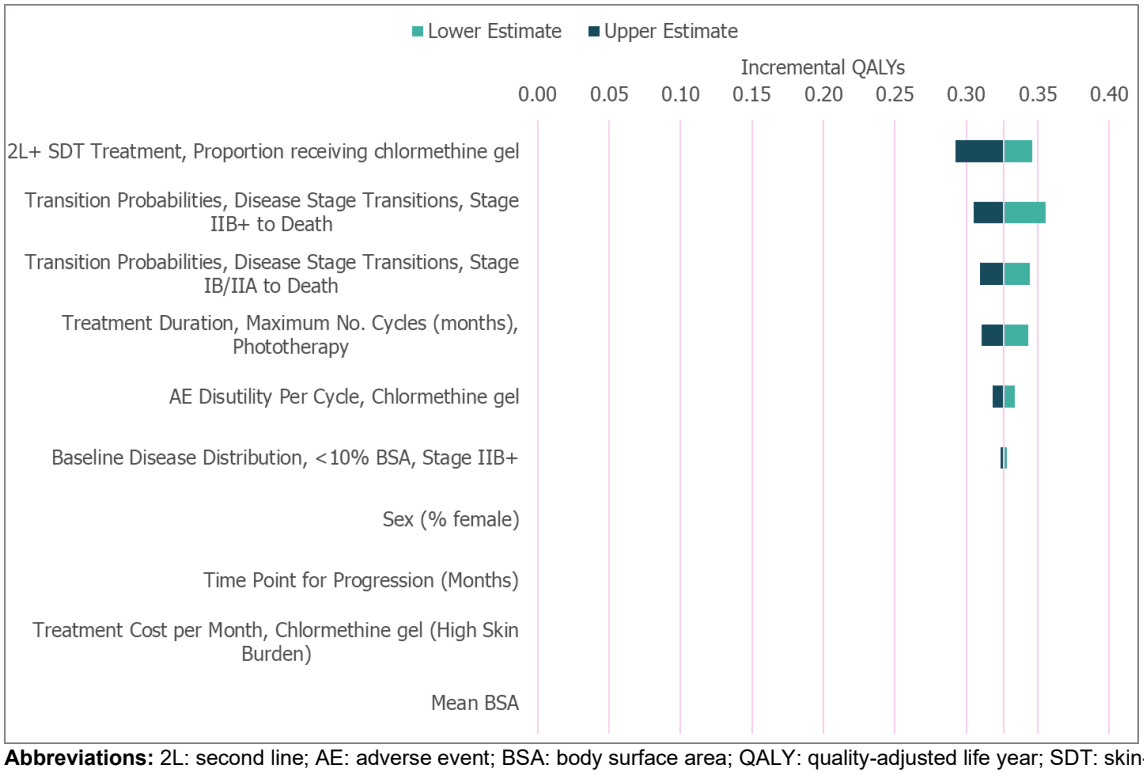
Figure 6: Deterministic sensitivity analysis – incremental cost tornado plot of the top ten most influential parameters



Abbreviations: 2L: second line; BSA: body surface area; SDT: skin-directed therapy.

Figure 7: Deterministic sensitivity analysis – incremental quality-adjusted life years tornado plot of the top ten most influential parameters



Abbreviations: 2L: second line; AE: adverse event; BSA: body surface area; QALY: quality-adjusted life year; SDT: skin-directed therapy.

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

Consultation on the appraisal consultation document – deadline for comments 5pm on Wednesday 26 August 2020 **email:** NICE DOCS XXXX

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Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	British Association of Dermatologists (the BAD)
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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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	NICE have evidence that chlormethine gel is effective in treating symptoms of mycosis fungoides (MF) but have rejected its use on the lack of cost efficacy data by comparison with phototherapy. MF is a rare and heterogeneous disease. We consider that this is withholding an important therapy against expert advice.
2	Chlormethine gel is a simpler treatment for patients with stage 1A disease than a course of phototherapy. In those living in rural areas, regular phototherapy may not be practical due to the time and travel involved.
3	Phototherapy requires travel to hospital three times weekly for a duration of 6-10 weeks. This is a burden due to the inconvenience and expense of travel, parking, disruption to work and everyday activities. The costs of providing the service in hospitals which requires space and specialised equipment and staff to run it. Repeated UV eventually increases the likelihood of skin cancers. MF is a lifelong disease, so even if effective UV treatment cannot be safely continued in early stage patients during their entire disease course. chlormethine has not been shown to have this risk. Chlormethine gel applied at home has economic benefits beyond the NHS costs of providing phototherapy used in the cost analyses. During the COVID-19 pandemic many phototherapy departments were shut down as 'non-essential' work. Effective topical therapies which can be applied at home such as chlormethine gel reduce pressure on hospital departments and reduce the risk of hospital visits in vulnerable patients.
4	Topical corticosteroids are cheap and may improve symptoms of MF so should be offered prior to chlormethine. Patients with early stage mycosis fungoides experience diagnostic delay. During this time, they often use topical steroids. MF is a lifelong disease, so topical steroids often need to be used off-licence and may cause atrophy, telangiectasia and striae with long term use. Chlormethine gel does not cause skin damage with atrophy with long term use. It can lead to complete remission in a cohort of patients with stage IA disease, where phototherapy may not be considered a suitable option.
5	Topical chlormethine gel can be used long term – up to 12 months in the 201 study, and longer in clinical practice where it has been found to be effective. During this same time patients may receive two or more courses of phototherapy the costs of which to the patient and hospital have not been taken into account.
6	Trial 201 was at the time of publication the largest RCT reported in patients with mycosis fungoides. Prior to the publication of this work nitrogen mustard was the standard of care for patients in Stanford, USA where the trial was reported; this centre had a well characterised cohort of >700 patients with CTCL. This centre reported its data of 688 patients with CTCL in Kim et al 2003. The response rates in these historical data are comparable to studies of reported response to phototherapy used in the comparison by NICE and which is also largely based on retrospective cohort analysis
7	The 201 trial of the novel chlormethine gel reported on a cohort of 260 patients who were

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	not treatment naive; all had received at least 1 prior therapy. Based on historical data it might be expected that they would have lower response rates as they had already relapsed or had incomplete response to prior therapy. The overall RR of 58.5% (CAILS) or 46.9% (mSWAT) is therefore not necessarily comparable to RR to phototherapy as used by NICE, particularly from European studies where phototherapy is typically given as first line treatment.
8	The ERG has based cost effectiveness on estimates of how much gel a patient would use (2.8g) which is higher than the real-world data of clinical experts and the clinical trial 201 (1.8g). However, in the 201 trial many patients would have used the gel to the whole skin surface. This would mean that reported 1.8g daily usage is still an overestimate compared to likely usage in the UK, where whole body application has never been advocated.
9	Experience of usage of nitrogen mustard in the UK is limited, with centres in London and Manchester being the main advocates for this therapy. The BAD has been informed that when supply of nitrogen mustard became unavailable in Manchester there was a 'waiting list' of 10 patients who wished to restart therapy should it be sourced again, suggesting patient acceptance or preference for this treatment over other therapies. We understand that the patients who provided evidence to NICE had not used this treatment.
10	The formulation of nitrogen mustard as a novel chlormethine gel offers considerable advantages over traditional nitrogen mustard preparations for hospital departments and patients. Traditional nitrogen mustard requires compounding in specialised units with risks to pharmacy staff due to the toxicity and teratogenicity of the raw powder product. The compounded ointment was expensive to produce and had limited stability data. It was made in a greasy ointment vehicle rendering it cosmetically unacceptable and difficult to use with clothing and bedding. The novel gel does not require specialised compounding in hospital departments and is cosmetically acceptable to use by patients. We understand that these factors were not taken into account by NICE.
11	Due to the rarity of mycosis fungoides there is only a small patient cohort who can advocate for different treatment options – unlike common cancers such as breast, lung or colon cancer. Conducting clinical trials is a challenge requiring international collaboration to achieve sufficient patient numbers. Patients with MF in the UK are disadvantaged by not having access to treatments available in USA or Europe e.g. Bexarotene gel for early stage disease, HDAC inhibitors and Denileukin Diftitox for advanced disease. These treatments are approved by the FDA and EMA for use elsewhere. In a world with social media and online support groups, we have been told that UK patients are now aware of these treatment differences and may find it difficult to understand why the NHS does not provide treatments available in some comparator nations.
12	Failure to approve chlormethine gel for use in the UK will limit patient and clinician choice. The alternative options of topical steroids, phototherapy or radiotherapy are either less effective, more expensive to deliver or less convenient for patients and carers.
	References: 1. Phan K, Ramachandran V, Fassihi H, Sebaratnam DF. Comparison of Narrowband UV-B With Psoralen–UV-A Phototherapy for Patients With Early-Stage Mycosis Fungoides: A Systematic Review and Meta-analysis. *JAMA*

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- Complete the disclosure about links with, or funding from, the tobacco industry.
- Combine all comments from your organisation into 1 response. We cannot accept more than 1 set of comments from each organisation.
- Do not paste other tables into this table – type directly into the table.
- Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise and all information submitted under 'academic in confidence' in yellow. If confidential information is submitted, please also send a 2nd version of your comment with that information replaced with the following text: 'academic / commercial in confidence information removed'. See the Guide to the processes of technology appraisal (section 3.1.23 to 3.1.29) for more information.
- Do not include medical information about yourself or another person from which you or the person could be identified.
- Do not use abbreviations
- Do not include attachments such as research articles, letters or leaflets. For copyright reasons, we will have to return comments forms that have attachments without reading them. You can resubmit your comments form without attachments, it must send it by the deadline.
- If you have received agreement from NICE to submit additional evidence with your comments on the appraisal consultation document, please submit these separately.

Note: We reserve the right to summarise and edit comments received during consultations, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during our consultations are published in the interests of openness and

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transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

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Consultation on the appraisal consultation document – deadline for comments 5pm on Tuesday 25 August 2020 **email:** NICE DOCS XXXX

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Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	Lymphoma Action
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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	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	We are concerned that clinical trial data and real-world experience supporting the use of chlormethine for mycosis fungoides (MF) has been unreasonably dismissed. Formulations of chlormethine have been used to treat skin lymphoma for over 50 years. Chlormethine ointment, the comparator in the main trial of chlormethine gel, was accepted as an effective treatment for MF in the UK from the 1980s and 1990s but its availability was limited nationally due to the need to prepare it for each patient in specialised pharmacy departments, causing an unacceptable health risk due to chemotherapy spillage. It has continued to be used in Manchester, UK, until recently [DR Eileen Parry, Christie Hospital, Manchester]. It is unfair to dismiss the clinical evidence supporting chlormethine gel on the basis that the comparator is no longer available in the UK. Chlormethine gel has been shown to be as effective as a previously accepted treatment but is far more convenient to prescribe and administer. It has been widely used internationally.
2	We feel that the recommendation does not adequately address unmet needs for people with MF. It is baffling that the committee specifically acknowledges that there is a clinical need for chlormethine gel as an alternative treatment for people with MF but fails to recommend it for NHS funding. Notably in light of the COVID pandemic, where hospital footprints are being reduced and services such as phototherapy halted, an effective home treatment is highly desirable. As stated in the committee report, patients with early stage MF often have multiple courses of topical treatments, phototherapy or localised radiotherapy. If symptoms fail to respond to these treatments, systemic therapy becomes necessary. Having an additional effective, well tolerated and convenient topical treatment therefore has the potential to delay the need for systemic treatments – an option that would be welcomed by patients and would also reduce the burden on the NHS.
3	We feel that too much emphasis has been placed on the fact that chlormethine gel is not curative. No early stage MF treatments are curative and all are given to reduce symptom burden and improve quality of life for symptoms, functions and emotions. The recommendation acknowledges that treatments for MF aim to relieve symptoms rather than cure the disease. Indeed, this is the case for the specified comparator agents. The committee also acknowledges in a statement that chlormethine gel is effective at relieving symptoms but does not seem to give this due consideration. Symptoms have a considerable impact on the day-to-day lives of patients and effective symptom control has the potential to significantly improve the quality of life of people affected by CTCL.
4	We do not consider that the indirect benefits of an effective topical therapy have been adequately considered. Chlormethine gel is administered by the patient (or caregiver) in their own home without the need to travel for appointments. Obviously this relieves pressures on outpatient departments and treatment centres but it also reduces travel time and costs for patients and their carers – which can be significant when travelling to specialised centres that provide phototherapy – and reduces the need for people who are employed to take time off work. As well as improving quality of life, this has indirect economic benefits. In addition, unlike systemic therapies, chlormethine gel does not

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	require patients to undergo blood test monitoring during treatment.
5	We are concerned that the committee seems to have based cost-effectiveness on the ERG estimate of how much gel a "typical patient" would use per month rather than the lower estimates provided by clinical experts and the submitting company (based on real-world clinical experience and clinical trial data, respectively). There is no recognition that a topical at-home therapy reduces treatment times and sick leave from work that thrice weekly phototherapy visits to hospitals incur. The committee report states, 'The resulting incremental cost-effectiveness ratio (ICER) was above what NICE considers a cost-effective use of NHS resources' but there is no justification provided for using the ERG estimate in preference to other estimates. The committee states that there was 'no direct evidence that the ERG estimate was incorrect', but it does not provide direct evidence that the ERG estimate is correct. Neither does it provide direct evidence that the company or clinician estimates are incorrect, so it is difficult to comprehend why the committee has chosen ERG estimates above the others.
6	

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Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	**UK Cutaneous Lymphoma Group**
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], **consultant dermatologist, on behalf of UKCLG**

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	Do not paste other tables into this table, because your comments could get lost – type directly into this table.
	NICE agree that Chlormethine gel is effective in treating symptoms of mycosis fungoides but have unfairly dismissed it on the 'grounds that there is "no robust evidence of its effectiveness compared to phototherapy', "concerns regarding its cost-effectiveness due to the patient pathway being oversimplified" and "uncertainty regarding dose per application of gel". We believe this is an unreasonable decision by NICE and the following~~These~~ and have detailed our rebuttal below.
1	In the clinical studies early stage mycosis fungoides includes patients with stage IA to IIA disease. This is a very heterogeneous group as the current ISCL/EORTC staging system does not take into account skin tumour burden (as defined by mSWAT) but uses an arbitrary threshold of less or more than 10% basal surface area (BSA). This group could include a patient with 1% BSA – with 1 or 2 patches (mSWAT 1, stage 1A) and a patient with more than 50% BSA with patches and plaques (mSWAT > 50, stage IB). These patients will have different symptoms and treatment needs and UK specialists are likely to make different recommendations for them. While most specialists are currently likely to recommend phototherapy for the stage IB patient; the risk/benefit ratio of phototherapy for the stage IA patient is less clear. There is therefore a differential unmet need for effective topical therapies for stage IA patients (other than topical steroids) which Chlormethine gel could provide; in this group of stage IA chlormethigine is a safer more practical therapy (less travel time/time off work, no increase risk of skin cancer from UV light and terageted not whole body treatment so unaffected skin is being spared treatment.
2	Three of the studies of phototherapy preferred by the ERG (Phan et al) did not use comparable definitions for complete response (CR) using 'clearance' of between 80-95% instead which negates the comparability of CR with Chlormethine gel in the 201 trial. In addition, many of these retrospective and non-RCTs will have allowed the use of topical corticosteroids for symptom control in addition to phototherapy whereas the 201 trial Lessin trial of chlormethine did not allow concomitant use of topical corticosteroids.
3	Phototherapy requires travel to a specialised treatment unit and repeated visits three times weekly for a duration of 6-10 weeks. This is a burden for patients and carers due to the inconvenience and expense of travel, parking, disruption to work and everyday activities, before taking into account the costs of providing the service for hospitals which requires specialised equipment and staff to run it. Furthermore repeated treatments increase the likelihood of other skin cancers and limits the life time use of phototherapy. So even if effective the treatment can not be continued in early stage patients during their entire disease course. Chlormethine has not been shown to have this risk. The use of Chlormethine gel as a treatment applied at home therefore has economic benefits beyond the NHS costs of providing phototherapy used in the cost analyses. In addition, during the Covid pandemic many UK dermatology phototherapy departments were shut down as 'non-essential' work and are only just being reinstated. Many have long waiting times for treatment due to this delay and the need for social distancing requirements for Covid which allow fewer treatments to be provided in a session. Effective topical therapies which can be applied at home such as Chlormethine gel are therefore needed to reduce pressure on hospital departments in addition to reduce risk of hospital visits in vulnerable patients.

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4	The ERG agreed that topical steroids were not a reliable treatment comparator for patients with mycosis fungoides. Topical corticosteroids are cheap and may improve symptoms of MF so it is not unreasonable to assume all patients will have had corticosteroid treatment prior to chlormethine but clearly we agree it is not a comparator. Patients with early stage mycosis fungoides experience diagnostic delay; median 36 months from the PROCLIPI registry. During this time, they frequently use topical steroids without overall benefit, so by the time the correct diagnosis is made many have lost faith in this treatment modality. There is limited evidence for the effectiveness of topical steroids; however, this requires the use very potent topical steroids. These have the potential for skin damage with atrophy, telangiectasia and striae with long term use. Patients dislike topical steroids, and many are phobic regarding their use. The use of Chlormethine gel provides an advantage over topical corticosteroids as it does not cause skin damage with atrophy with long term use. It can lead to complete remission in a cohort of patients and is especially beneficial in patients with stage IA disease, where phototherapy may not be considered a suitable option.
5	The reality of treatment for patients with mycosis fungoides is that they may receive multiple courses of skin directed therapy to control symptoms, reduce skin disease burden and improve quality of life. This approach may continue until disease progression occurs or they become refractory to skin directed therapy and require moving to systemic options. While the company model provided may have been oversimplified, this does not refute the need for a new topical therapy for patients with early stage disease. Topical Chlormethine gel can be used long term – up to 12 months in the 201 study, and longer in clinical practice where it has been found to be effective. During this same time patients may receive 2 or more courses of phototherapy; and often switch from UVB to PUVA if the former is ineffective or not tolerated. The costs of repeated courses of phototherapy have not been taken into account or the indirect costs to patients of having a hospital-based therapy vs a home treatment.
6	Trial 201 was at the time of publication the largest RCT reported in patients with mycosis fungoides. The Committee dismiss the trial as Chlormethine gel is compared to a treatment no longer available (Nitrogen mustard ointment – specifically compounded). However, the committee has failed to take into account historical data. Prior to the publication of this work nitrogen mustard was the standard of care for patients in Stanford, USA where the trial was reported; this centre had a well characterised cohort of >700 patients with CTCL. This centre reported its data of 688 patients with CTCL in Kim et al 2003. 203 patients had nitrogen mustard as initial primary therapy: first as an aqueous solution but after 1980 as a compounded nitrogen mustard ointment. Response rates for T1 patients, n=107 (stage IA) were CR 65%, PR 28%, and for T2 patients, n=88 (stage IB) were CR 34%, PR 38%. The median time to CR was 12 months (range 1-106). Of 100 patients who achieved CR, freedom from relapse (FFR) at 5 years was greater for T1 than T2 as expected; 52% vs. 19%, with median time to relapse 6 years for T1 and 4.5 years for T2. Although many patients were given maintenance treatments, the rate of relapse was the same after treatment was stopped regardless of maintenance duration. Nitrogen mustard was shown to be a good salvage treatment for patients who relapsed after initial nitrogen mustard therapy (n=46, CR 67%) and in patients who had received different modalities of initial therapy (n= 81, CR 41%). This study confirmed the effectiveness of nitrogen mustard as first line therapy with a significant proportion of patients with T1 disease relapse free at 5 years. The response rates in this historical data is comparable to studies of reported response to phototherapy used in the comparison by NICE and which is also largely based on

	retrospective cohort analysis
7	The 201 trial of the novel Chlormethine gel reported on a cohort of 260 patients who were not treatment naive; all had received at least 1 prior therapy. Based on historical data it might be expected that they would have lower response rates as they had already relapsed or had incomplete response to prior therapy. The overall RR of 58.5% (CAILS) or 46.9% (mSWAT) is therefore not necessarily comparable to RR to phototherapy as used by NICE, particularly from European studies where phototherapy is typically given as first line treatment.
8	The ERG has based cost effectiveness on estimates of how much gel a patient would use (2.8g) which is higher than the real world data of clinical experts and the clinical trial 201 (1.8g). However, in the 201 trial many patients would have used the gel to the whole skin surface, as was typical when using nitrogen mustard at Stanford, particularly for T2 patients, compared to T1 patients who were more likely to apply gel only to skin lesions. This would mean that reported 1.8g daily usage is still an overestimate compared to likely usage in the UK, where whole body application has never been advocated. There is no justification for NICE to assume the higher amount of 2.8g is correct and ignore evidence from the trial which is still likely to be an overestimate on UK usage.
9	Experience of usage of nitrogen mustard in the UK is limited, with centres in London and Manchester being the main advocates for this therapy. It is no surprise that clinicians at these sites spent time in the USA at regional centres where nitrogen mustard was a standard of care. The only published data from the UK by Monk et al in 1983 reported on 29 patients who achieved a CR of 86%. Unpublished data from Manchester from 22 patients showed ORR of 68% (CR 14%, PR 55%), although only 7 used it as initial therapy. When supply of nitrogen mustard became unavailable in Manchester there was a 'waiting list' of 10 patients who wished to restart therapy should it be sourced again: highlighting the patient preference for this treatment over other therapies. It is a notable that none of the patient's who provided evidence to NICE had first-hand experience of using nitrogen mustard and therefore were unable to provide accurate knowledge of its use.
10	The formulation of nitrogen mustard as a novel Chlormethine gel offers considerable advantages for treating departments and patients. One of the reasons uptake was poor in the UK was the need for compounding in specialised units with inherent risks to pharmacy staff due to the toxicity and teratogenicity of the raw powder product. The compounded ointment was expensive to produce and had limited stability data. It was made in an ointment vehicle rendering it cosmetically unacceptable due to the greasy feel and transfer of product to clothes and bedding. The novel gel does not require specialised compounding in hospital departments and is cosmetically acceptable to use by patients. These factors were not taken into account by NICE.
11	Due to the rarity of mycosis fungoides there is only a small patient cohort who can advocate for different treatment options – unlike common cancers such as breast, lung or colon cancer. Conducting clinical trials is a challenge in this rare disease – most requiring international collaboration to achieve sufficient patient numbers and power to show differences in response or long term outcome. Patients in the UK are already disadvantaged by not having access to treatments available in USA or Europe e.g. Bexarotene gel for early

	stage disease, HDAC inhibitors and Denileukin Diftitox for advanced disease. Yet these treatments are approved by the FDA and EMA for use elsewhere. Within the global community of social media and online support groups UK patients are aware of these treatment differences and fail to understand why they are disadvantaged.
12	As treatment for mycosis fungoides is not considered curative effective topical therapies may delay the need for more aggressive and expensive systemic agents. There is also a small cohort who achieve longstanding remission with nitrogen mustard, particularly with IA disease. Failure to approve Chlormethine gel for use in the UK will limit patient and clinician choice in what is already a limited treatment armamentarium. The alternative options of topical steroids, phototherapy or radiotherapy are either less effective, more expensive to deliver and less convenient for patients and carers.
	References: 1. Phan K, Ramachandran V, Fassihi H, Sebaratnam DF. 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(3):335–341. doi:10.1001/jamadermatol.2018.5204 2. 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*. 2019;181(2):350-357. doi:10.1111/bjd.17258 3. Lessin SR, Duvic M, Guitart J, et al. Topical chemotherapy in cutaneous T-cell lymphoma: positive results of a randomized, controlled, multicenter trial testing the efficacy and safety of a novel mechlorethamine, 0.02%, gel in mycosis fungoides. *JAMA Dermatol*. 2013;149(1):25-32. doi:10.1001/2013.jamadermatol.541 4. Kim YH, Martinez G, Varghese A, Hoppe RT. Topical nitrogen mustard in the management of mycosis fungoides: update of the Stanford experience. *Arch Dermatol*. 2003;139(2):165-173. doi:10.1001/archderm.139.2.165 5. Monk BEVollum DIdu Vivier AW Combination topical nitrogen mustard and photochemotherapy for mycosis fungoides. *Clin Exp Dermatol.* 1984;9243- 247 6. E Parry; data unpublished; presented to Genopharm sponsored nitrogen mustard workshop, London

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Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	[**British Association Dermatology**]
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	[**Consultancy Recordati. Helsinn J Scarisbrick**]
Name of commentator person completing form:	[Prof Julia Scarisbrick, Prof Sean Whittaker]

Comment number	**Comments** Insert each comment in a new row.

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Example 1	We are concerned that this recommendation may imply that ……..
1	As experts representing the British Association of Dermatology we are unsure why the clinical trial data and real-world experience supporting the benefit from use of chlormethine in MF has been dismissed. Formulations of chlormethine [nitrogen mustard] have been used to treat skin lymphoma for >50 years. Chlormethine, was accepted as an effective treatment for MF in UK from 1980's-1990's but it's availability was limited nationally due to preparation in pharmacy which was later deemed as an unacceptable health risk due to chemotherapy spillage. Usage in Manchester, UK continued until recently [Dr Eileen Parry, Christie Hospital, Manchester]. It is unfair to dismiss clinical evidence supporting chlormethine gel on the basis that the comparator is no longer available in the UK. The Lessin trial [1] showed chlormethine gel to be as effective as the ointment but in a more convenient vehicle to prescribe and administer. It is already being widely used internationally. Particularly in COVID times reducing hospital footprint and making available an effective home treatment to protect this vulnerable group from hospital attendances and helping reduce the hospital footfall [2]. There are no available curative treatments for early MF so it is unfair and unreasonable to exclude this on the basis of a 20% complete response and 50-60% partial response which compares favourably to other anti CTCL therapy [3]. Patients with MF have a poor quality of life from symptoms (pruritus, pain, burning) emotional distress from a visible disfiguring condition and poor function due to cutaneous lesions preventing daily activity. Improving skin tumour burden using chlormethine gel will improve the quality of life in these areas [4,5]. 1 Lessin et al. Topical chemotherapy in cutaneous T-cell lymphoma: positive results of a randomized, controlled, multicenter trial testing the efficacy and safety of a novel mechlorethamine, 0.02%, gel in mycosis fungoides. JAMA Dermatol. 2013 Jan;149(1):25-32. 2 Papadavid et al . Management of primary cutaneous lymphoma patients during COVID-19 pandemic: EORTC CLTF guidelines. J Eur Acad Dermatol Venereol. . 2020 Aug;34(8):1633-1636. 3 Gilson et al British Association of Dermatologists and UK Cutaneous Lymphoma Group Guidelines for the Management of Primary Cutaneous Lymphomas. Br J Dermatol. 2019 Mar;180(3):496-526 4 Jonak et al Health-related quality of life in cutaneous lymphomas: past, present and prospective. *Acta Derm* 1;99(7):640-646, 2019 5 Wright et al. Prevalence and Severity of Pruritus and Quality of Life in Patients With Cutaneous T-Cell Lymphoma. *J Pain Symptom Manage.* 2013; 45:114-9

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Name	[redacted]
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Notes	
Comments on the ACD:	

I'm really disappointed with the Nice response. Phototherapy is not always available especially during lockdown.
Missed treatment can push back treatment timings. It is also time consuming.
Not all mycosis fungoides patients can have phototherapy due to issues and risks re skin cancer.
There cannot be blanket treatment for mycosis fungoides as each patient is unique and responds uniquely making data gathering problematic.
Therefore I suggest that as this is a long term and often debilitating condition priority should be given to consideration of the quality of life for patients

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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 Appraisal Consultation Document

Produced by Aberdeen HTA Group

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Overview

This document provides the ERG's critique of the revised model structure and economic analysis received by the ERG on 26/08/2020. This critique should be read in conjunction with the company ACD response document and additional appendix describing revisions to the company's economic model structure and the ERG report (for a critique of the original model). This document provides the ERG's critique of the revised cost-effectiveness evidence, focusing on three issues: 1) revised economic model structure, 2) phototherapy effectiveness parameters used in the model, namely complete response (CR), partial response (PR) and duration of response and 3) treatment acquisition costs for chlormethine gel. The report also reproduces all of the company base case and scenario analysis ICERs using the agreed PAS price for chlormethine gel.

Issue 1: Revised economic model structure and time horizon

The company have provided a revised economic model structure in response to concerns that the original model structure presented by the company was too simplistic, and did not fully reflect UK clinical practice. The revised model (See Figure 1) includes several new health states, specifically 'watch and wait' and 'skin directed therapy', which more accurately reflect the clinical pathway, and in particular the management of patients achieving complete response (CR) or partial response (PR) following treatment with chlormethine gel or phototherapy. The previously named 'Progressed from 1L' health state has been renamed as 'Systemic therapy' to make clear that the state relates to progressed skin disease, rather than progression of the underlying cancer. Initial transitions from low / high skin burden to "no skin burden" (CR), "reduced skin burden" (PR) and remaining in the "low / high" skin burden state (SD) remain unchanged from the model submitted in response to technical engagement and are not discussed further.

One concern raised in the ACD was that the original life time horizon model increased uncertainty in cost-effectiveness by extending the time period in the 'Systemic therapy' state. The company have amended their model time horizon, reducing it to 20 years. The ERG consider that the shorter (than lifetime) time horizon is appropriate to capture all the relevant costs and QALY implications of a decision to treat with chlormethine gel or phototherapy. Implications for the ICER of varying the time horizon are explored in scenario analyses.

The following modifications have been implemented in the company's revised economic model:

Structural modification 1: transitions for initial progressed disease (PD)

The original model structure assumed that patients with initial PD (i.e. those that do not achieve a CR, PR or have SD) move directly to 2nd line systemic treatment with bexarotene (50%) or interferon-alpha (50%), without the possibility of having more than one course of treatment with chlormethine gel or phototherapy. The company's revised model structure maintains this assumption for the phototherapy treated cohort. However, in the chlormethine gel arm of the model, those with progressive skin disease (PD) enter a new "skin directed therapy - SDT" state, where 80% receive a second round of chlormethine gel and 20% receive a course of phototherapy treatment with efficacy equal that of first line chlormethine

gel/phototherapy skin treatment respectively. As outlined in Figure 1, this new 'SDT' state includes both patients who achieve an initial response to chlormethine gel, but subsequently relapse and those who do not achieve a CR or PR and have progressive skin disease.

The ERG are concerned that the revised model structure provides an unfair advantage for chlormethine gel by removing the direct transition to the systemic therapy state whilst retaining it for phototherapy. The ERG therefore propose an alternative approach, where the proportion of the cohort with initial PD in both arms are allowed to transition directly to the 'Systemic therapy' health state. The ERG's approach then allows for treatment with bexarotene or IFN-a for the phototherapy arm (as per the original submission), but now includes a 13-week course of phototherapy applied for those progressing from the chlormethine gel arm of the model. Instead of the original 50:50 split between bexarotene and IFN-a, the inclusion of phototherapy in the treatment basket for progressed skin burden in the chlormethine gel arm results in a treatment distribution of bexarotene (44.65%), IFN-a (44.65%) and phototherapy (10.71%). The proportion on phototherapy was calculated by assuming everyone in the systemic therapy health state receives one course of phototherapy lasting 2.99 months and dividing those months by the total time spent in the 'Systemic therapy' health state.

The ERG's modification continues to allow those with PD following chlormethine gel to receive phototherapy, but has the advantage of retaining a similar model structure for both treatment arms. The ERG's modification also has the advantage of ensuring that the company's new "SDT" state includes only patients who have previously responded to therapy, as opposed to a mix of patients who have previously responded and those with PD *(discussed further under structural modification 2 below)*. The ERG's clinical expert opinion is that those with PD have more treatment resistant disease and cannot be considered equal to previous responders who subsequently relapse following a response. Therefore, the ERG consider it better to distinguish between those that had a response and relapse into the SDT state and those with progressed disease that transition into the 'Systemic therapy' health state.

Structural modification 2: Allow repeat courses of treatment for patients who achieve an initial response to treatment

The company have included two additional health states in the model, a "watch and wait" health state, where patients who initially achieve a CR to either chlormethine gel or phototherapy would be monitored before initiation of another round of treatment in a new "skin directed therapy – SDT" health state if their symptoms relapsed and required re-treatment. The utility of the 'watch and wait' health state is assumed to be equal to the utility value in the 'reduced skin burden' state. The utility in the 'SDT' state is assumed to be equal to the utility in the 'initial skin burden' health states. In the absence of any robust data to suggest otherwise, the ERG consider these to be reasonable assumptions.

The new model 'SDT' state allows for repeat courses of chlormethine gel or phototherapy in the proportion of the cohort who have a relapse following an initial response to treatment. The company's submitted model assumes that phototherapy treated patients would receive a repeat course of phototherapy, while chlormethine gel treated patients could receive a second round of chlormethine gel treatment (80%) or switch to phototherapy (20%) for subsequent lines of treatment. The health state costs and efficacy of treatment applied in the SDT state for the chlormethine gel arm of the model are therefore dependent on the proportion of patients treated with chlormethine gel / phototherapy. The phototherapy cohort cannot be re-treated with chlormethine gel in the model. The ERG considers this to be an appropriate assumption for decision making, by excluding the intervention under investigation from the comparator arm of the model. The ERG accept however, that in real world clinical practice, if chlormethine gel was available on the NHS, clinicians might consider switching skin direct therapy treatments in the phototherapy arm as well.

For the chlormethine gel arm of the model, the ERG's understanding from the company's documentation is that the 80/20 split for 2nd and subsequent rounds of skin directed therapy is informed by the proportion of chlormethine gel patients in Study 201 who develop progressive disease and need re-treatment from the initial skin burden health state. As has been described under *modification 1* above, the ERG have adapted the company model structure to re-route those with progressive disease into the 'Systemic therapy' state, in which case it is likely more reasonable to assume that chlormethine gel patients in the 'SDT' state would be re-treated with chlormethine gel if they had an initial favourable response to the

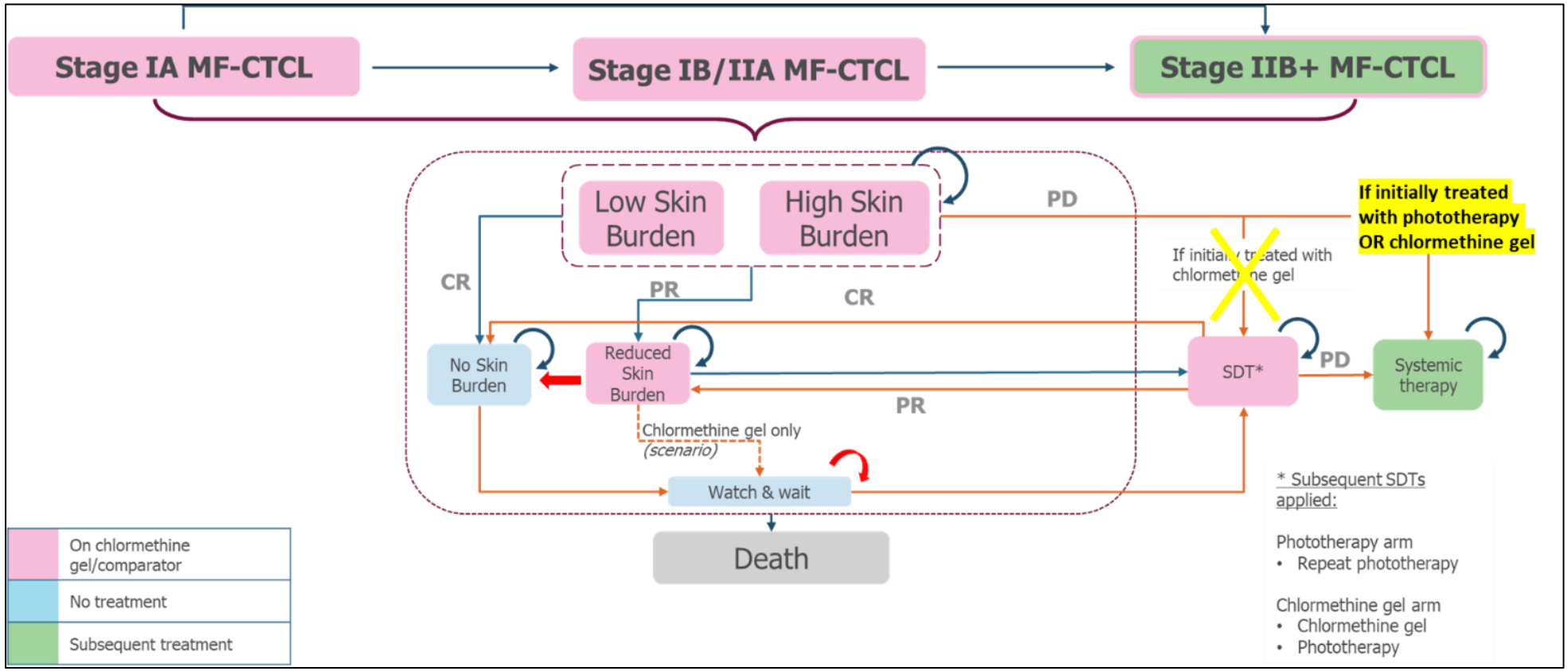
treatment. The ERG therefore prefers an assumption that 100% of chlormethine gel patients who have a response following initial treatment would receive re-treatment with the gel.

The ERG note that the company's model assumes that effectiveness of second line treatments (i.e. CR / PR from the 'SDT' state) is equal to initial treatment in terms of CR / PR and the duration of that response. The ERG's clinical expert view is that this is not plausible because additional rounds of treatment used in clinical practice are observed to have decreasing effectiveness. In the absence of published data to inform the magnitude of reduction in treatment effectiveness estimates for 2nd and subsequent treatment lines, the ERG preferred approach is based on our own clinical expert opinion that a plausible modification would be to assume that CR and PR for both chlormethine gel and phototherapy treatments used as 2nd and subsequent line SDTs would be 75% of those used in first line. Similarly the duration of response could also plausibly be reduced by 50%. To implement these scenarios, the ERG have created an additional model health state ("no skin burden 2+") to allow for differential effectiveness parameters to be applied to both model arms for first and subsequent lines of SDT treatment. As these effectiveness parameters for 2nd and subsequent lines of treatment are highly uncertain, the ERG adapted model includes functionality to apply a range of percentage reductions in scenario analyses.

The ERG agree that the new model structure submitted by the company is a more realistic representation of the treatment pathway, and is more in line with clinical practice by allowing patients to receive repeat skin directed therapy treatments if they achieve an initial response to chlormethine gel or phototherapy. The implication of the revised model is that the cohort are delayed from entry to the semi-absorbing "Systemic therapy" health state where they receive systemic bexarotene or interferon-alpha therapy for the remaining life years. The ERG believes that the company's modification, in addition to the ERGs further modification to allow differential treatment effectiveness for subsequent lines of SDTs and to apply a similar structure for progressed disease in both model arms leads to a more accurate representation of the treatment pathway and facilitates exploration of uncertainty around the effectiveness of multiple lines of SDT.

The company's revised model structure is presented in Figure 1 below, with ERG modifications highlighted in yellow.

Figure 1: State transition diagram, with ERG modifications (Source: Adapted from Figure 1 of the appendix to the company submitted response to the appraisal consultation document)



*State transition diagram obtained from the appendix of the company's ACD response document, amended to reflect ERG modifications (in yellow). Red arrows indicate transitions that were configured within the company's submitted model, but were not depicted on the diagram.

Issue 2: Phototherapy effectiveness sources

The ERG reiterate the point made in the initial ERG report and critique of response to technical engagement. The evidence base for phototherapy is limited and heterogeneous, and the true effect of chlormethine gel versus phototherapy in the modelled population remains highly uncertain. There is insufficient evidence to support any form of robust indirect comparison. The implication is that estimates of the ICER are highly sensitive to decisions about the source of phototherapy effectiveness data for use in the model. All sources considered, both by the company and the ERG are open to criticism and these have been discussed extensively in the company and previous ERG documentation.

Response data (CR / PR)

The company suggest an alternative scenario analysis using response data collected retrospectively from the UK PROCLIPI registry because it has the benefit of using the mSWAT score as a measure of response, maintaining consistency of response measure with that used in Study 201.[1,2] The ERG accepts that the use of consistent measures of outcome across the different arms helps to minimise uncertainty. However, the company have not provided any data on duration of response using the PROCLIPI registry data, which means that, given the data currently available, it is not possible to use the PROCLIPI registry information to derive all phototherapy effectiveness parameters used in the model. Furthermore, the ERG are unconvinced by the company's argument that using Phan et al. generates inappropriate response estimates for use in the model[3]. The ERG note that the RCT data from the NCT01686594 study[4] (CR=70% and PR=30%) measured CR and PR using mSWAT (consistent with Study 201) and found similar response rates for phototherapy to those reported in Phan et al (CR: Stage IA-IIA: 70.24%, Stage IB: 61.79%, and PR: Stage IA-IIA: 22.56%, Stage IB: 19.83%)[3]. This would suggest that the use of data from Phan et al are not unreasonable or inconsistent with Study 201[2]. The seven studies originally identified by the company from the BAD guidelines also found similar response data[5].

Duration of response (CR / PR)

The company prefer the use of data from Whittaker et al. to populate the phototherapy arm of the model with regards to duration of CR and PR[6]. The ERG prefer the use of data from Phan et al. because it enables a consistent application of source for response rate and

duration, with a granular level of detail by type of phototherapy and stage of disease not available from other studies[3]. The ERG accept that the company raises concerns about the use of data from Phan et al. for duration of response and they make valid points of concern about the inconsistency of response definition in Phan et al. compared to Study 201[2]. However, the ERG note that whilst Whittaker et al. use an objective response measure, even this is a different response measurement tool to that used in Study 201[2,6]. Furthermore, the use of Whittaker et al. to populate duration of phototherapy response is open to criticism because of the small sample size and the exclusion of Stage 1A disease. A tabulated comparison of the company and ERG preferred sources has been provided in the ERG's critique of the company's response to technical engagement for reference.

The ERG note that in scenarios where the company use Phan et al. for duration of phototherapy response, the duration post CR and post PR are both adjusted downwards to account for the use of maintenance phototherapy in several studies in the Phan et al. review[3]. The original ERG base case only adjusted duration post CR because the company had included bexarotene and IFN-a for PR in the phototherapy arm. The revised company model removes the costs of bexarotene and IFN-a, and applies an adjustment to downgrade the duration of phototherapy response post PR. The ERG consider the company's approach to downgrading the duration (in months) from 28.86 (PUVA) and 12.87 (UVB) to 17.40 (PUVA) and 7.76 (UVB) post CR and from 35.98 (PUVA) and 16.05 (UVB) to 21.70 (PUVA) and 9.68 (UVB) post PR to be appropriate given the revisions to the treatments included in the model for phototherapy partial responders. The ERG reiterate that not all studies in Phan et al. included maintenance phototherapy and therefore the adjustment likely provides a conservative estimate of response duration[3].

In summary, the company's preferred approach uses different data sources for different phototherapy effectiveness parameters. This introduces substantial decision making uncertainty that could bias the ICER in favour or against chlormethine gel, depending on the sources chosen. The ERG maintain our original preference to use data from Phan et al. [3] because 1) it applies a consistent source to all phototherapy effectiveness parameters, 2) the quoted response rates are not dissimilar to those from the NCT01686594 study which uses mSWAT as the measure of response [4] and 3) data are provide at a granular level by stage of disease and type of phototherapy. ERG and company preferred phototherapy effectiveness parameters are provided in Table 1.

Table 1 Comparison of ERG and company preferred phototherapy effectiveness parameters

	ERG						Company					
	Chlormethine gel			Phototherapy			Chlormethine gel			Phototherapy		
	Value		Source	Value		Source	Value		Source	Value		Source
	Stage IA[B] (low skin burden)	Stage IB/IIA[B] (high skin burden)		Stage IA[B] (low skin burden)	Stage IB/IIA[B] (high skin burden)		Stage IA[B] (low skin burden)	Stage IB/IIA[B] (high skin burden)		Stage IA[B] (low skin burden)	Stage IB/IIA[B] (high skin burden)	
CR	[redacted]	[redacted]	Study 201[2]	PUVA: 82.10% UVB: 62.10% Weighted: 70.24%	PUVA: 67.60% UVB: 57.80% Weighted: 61.79%	Phan et al. 2019 [3]	[redacted]	[redacted]	Study 201[2]	PUVA: 82.10% UVB: 62.10% Weighted: 70.24%	PUVA: 67.60% UVB: 57.80% Weighted: 61.79%	Phan et al. 2019 [3]
PR	[redacted]	[redacted]	Study 201[2]	PUVA: 12.90% UVB: 29.20% Weighted: 22.56%	PUVA: 27.60% UVB: 14.50% Weighted: 19.83%	Phan et al. 2019 [3]	[redacted]	[redacted]	Study 201[2]	PUVA: 12.90% UVB: 29.20% Weighted: 22.56%	PUVA: 27.60% UVB: 14.50% Weighted: 19.83%	Phan et al. 2019 [3]

	ERG						**Company**					
	Chlormethine gel			**Phototherapy**			**Chlormethine gel**			**Phototherapy**		
	Value		**Source**	**Value**		**Source**	**Value**		**Source**	**Value**		**Source**
	Stage IA[B] (low skin burden)	**Stage IB/IIA[B] (high skin burden)**		**Stage IA[B] (low skin burden)**	**Stage IB/IIA[B] (high skin burden)**		**Stage IA[B] (low skin burden)**	**Stage IB/IIA[B] (high skin burden)**		**Stage IA[B] (low skin burden)**	**Stage IB/IIA[B] (high skin burden)**	
PD / failed response	[redacted]	[redacted]	PD from Study 201[2]	PUVA: 9.63% UVB: 25.00% Weighted: 18.74%	PUVA: 15.98% UVB: 32.22% Weighted: 25.61%	Failed response from Phan et al. 2019 [3]	[redacted]	[redacted]	PD from Study 201[2]	PUVA: 9.63% UVB: 25.00% Weighted: 18.74%	PUVA: 15.98% UVB: 32.22% Weighted: 25.61%	Failed response from Phan et al. 2019 [3]
Duration of CR (months)[C]	17.31		Kim et al. 2003[7]	PUVA: 17.40 UVB: 7.76		Phan et al. 2019 [3]	17.31		Kim et al. 2003[7]	6.48		Whittaker et al. 2012 [6]
Duration of PR (months)[C]	[redacted]		Study 201 [2]	PUVA: 21.70 UVB: 9.68		Phan et al. 2019 [3]	[redacted]		Study 201 [2]	N/A[A]		Phan et al. 2019 [3]

[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. For people with Stage IIA-IV, their skin burden was based on the %BSA affected from the PROCLIPI registry. The registry data showed that the majority of people with Stage IIA had >10% BSA affected. Therefore, it was assumed in the model that 100% of Stage IIA patients had high skin burden. For people with Stage IIB+, [redacted] had low skin burden and [redacted] had high skin burden, according to the PROCLIPI registry. Due to lack of data, it was assumed that for people in Stage IIB+, the Stage IA and Stage IB/IIA efficacy data in Table 1 were applied to those with low and high skin burden, respectively.

[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.

Issue 3: Chlormethine Gel treatment acquisition costs

The company have used a mean daily gel dosage of [redacted] ([redacted] and [redacted] for low and high skin burden respectively to calculate treatment acquisition costs of chlormethine gel[8]. The ERG critique in response to technical engagement noted that this is inconsistent with the mean daily gel usage reported in the Valchlor® summary of product characteristics (2.81g), and a subsequent dosing clarification sent to the FDA by the manufacturer of Valchlor®. An excerpt from that letter was provided by the company and shared with the ERG after the first appraisal committee meeting[9].

The ERG acknowledge that the company have provided IPD data from Study 201 outlining the number of returned tubes at each study follow up visit. This data relates to N=[redacted] patients (including N=128 of whom are also in the safety set (i.e. any patient who received one or more tubes)). The ERG have reproduced the company's calculation of [redacted] using the formula:

Average daily dose per patient = (total number of returned tubes*25g / 365.25)/[redacted]

However, the ERG believes that this calculation approach underestimates the mean daily dose of chlormethine gel, whilst on treatment. The estimate of daily gel usage includes the gel usage for all patients, regardless of treatment response, apportioned equally across each day in a full year. However, this calculation approach is inconsistent with how the gel was used in Study 201, how it would be used in clinical practice, or how treatment costs were applied in the economic model (i.e. patients would be removed from treatment if they had a complete response). The company's approach essentially assumes that patients who achieved a CR would continue on the gel, thereby underestimating the average daily gel usage. As those achieving a CR correctly do not incur the treatment acquisition costs of chlormethine gel in the model, the implication is that including complete responders in the calculation of daily gel usage underestimates the daily usage of gel for patients who are on treatment.

The ERG has reviewed the additional evidence provided in the FDA dosing clarification letter and believes that the estimate of 2.81g per patient is correct and appropriate for use in the economic model as it represents the mean daily dosage for patients whilst on treatment. The ERG accepts that these data are obtained from the safety set, as opposed to the full analysis set, however the difference between these analysis sets is only one patient who did not receive any treatment, hence the impact on calculated mean gel dosage would be minimal

(approximately 0.05g). The evidence provided by the company from the FDA documentation specifically states that: [redacted]. The data provided in the company's IPD analysis does not include information at the patient level for the number of days on study drug, but the ERG believes that if these data were available, it would likely be possible to replicate the estimate of 2.81g from the Valchlor® summary of product characteristics [9]. Data included in the company submission support this. For example, Table 27 of the original company submission notes that the mean (SD) duration of exposure to study drug was [redacted] weeks. For this reason, the ERG therefore reiterates the concern that the company's approach to calculating mean daily gel dosage may underestimate the total gel usage and hence the treatment acquisition costs for chlormethine gel.

Furthermore, the ERG believes that the estimate of 2.81g is likely to be a conservative estimate of gel usage and hence treatment acquisition costs because:

1) Treatment costs would more accurately be reflected by the number of dispensed, rather than returned tubes. The ERG's clinical expert notes that the point at which a tube is dispensed is the point at which the cost is incurred (i.e. if a patient returned an unopened tube, it would not be re-used, even if the seal remained in place). Whilst the company disagree that the number of dispensed and returned tubes are likely to be different, evidence to the contrary exists from the additional FDA documentation provided by the company, aligned to the VALCHLOR® summary of product characteristics, where the footnote to table 6 describes [redacted] patients who were dispensed [redacted] and [redacted] containers respectively, none of which were returned). The ERG is unaware of whether the number of dispensed tubes = the number of returned tubes for the remainder of the trial participants, but it is feasible to assume that there may be at least some discrepancy;

2) The Company note in their response to the ACD that "only [redacted] patients [redacted] in the chlormethine gel arm were lost to follow-up in Study 201, suggesting that the vast majority of patients are accounted for and thus would not have discontinued without returning tubes at subsequent visits". The ERG accept that the proportion is small, but note that any bias, even small in magnitude caused due to loss to follow up would increase the treatment acquisition costs of chlormethine gel. The ERG maintain that our

original critique is both accurate, and justified, and can be considered a conservative estimate.

3) In addition to the points raised in the original ERG critique, the ERG also note that it may not necessarily be possible to fully compensate high gel dose in some patients with low gel dose in others. Therefore, for example, if patients were on continual treatment for a full year, each individual patient in the IPD dataset would consume a minimum of 0.99g / day due to the shelf life of the drug, regardless of %BSA affected. However, as the duration of study treatment is not provided for each individual patient in the IPD dataset, it is not possible to identify which, if any patients would need to have their dosage adjusted to account for the minimum required dose. Any bias would serve to increase the treatment acquisition costs of chlormethine gel further, but the magnitude of that bias is unclear, without access to additional data.

The ERG note two further points raised by the company in their ACD response. The first is that the company have highlighted that daily gel usage reported in the Valchor® summary of product characteristics is available as a mean daily dose of [redacted] and [redacted] for Low and High Skin Burden, respectively. The ERG agree with the company that any use of these data should utilise the reported data by degree of skin burden. For all the reasons outlined in this section, the ERG therefore prefers the use of a mean daily dose of [redacted] and [redacted] for low and high skin burden respectively and have applied these values in our preferred base case analysis.

The second point is that the company refer to further evidence from clinical experts and from the PROVe study[10] showing that real world usage of the gel may be less than that used in Study 201, and clinical experts indicated at the first AC meeting that this may be particularly true for Stage IIB+ patients. Whilst the ERG accept that there may be some heterogeneity in the use of the gel in clinical practice, it is essential for decision making that the treatment acquisition costs are obtained from the same data used to derive effectiveness parameters. It is unclear how any changes to gel dosage from that used in Study 201 might modify the effectiveness parameters used in the model. The ERG therefore agree with the company that the use of data from Study 201 is appropriate for informing treatment acquisition costs of chlormethine gel in the model[2].

Results of company analyses

Table 2 and figures 2-5 re-produce the company analyses using the agreed simple discount ([redacted]) PAS price for chlormethine gel.

Table 2: Scenario analyses on the company base case with chlormethine gel PAS (reproduced table from the company's response to ACD - Appendix to the Stakeholder Comments Form)

	Incremental costs	Incremental QALYs	Chlormethine gel ICER (£/QALY)
Base case	[redacted]	0.33	[redacted]
1) 20% discount for bexarotene	[redacted]	0.33	[redacted]
2) 30% discount for bexarotene	[redacted]	0.33	[redacted]
3) Evidence Review Group preferred source for relapse post-complete response and relapse post-partial response	[redacted]	0.14	[redacted]
3) Early population only	[redacted]	0.35	[redacted]
4) PROCLIPI for complete response and partial response rates	[redacted]	0.43	[redacted]
5) No adverse events for chlormethine gel	[redacted]	0.36	[redacted]
6) Stopping rule (with Study 201 efficacy after 12 months)	[redacted]	0.34	[redacted]
7) Stopping rule (with Study 201 efficacy after 12 months) + early population only	[redacted]	0.37	[redacted]
8) Stopping rule (with Study 201 efficacy after 12 months) + early population only + Evidence Review Group preferred source for relapse post-complete response and relapse post-partial response + 20% discount for bexarotene	[redacted]	0.19	[redacted]

	Incremental costs	**Incremental QALYs**	**Chlormethine gel ICER (£/QALY)**
9) Stopping rule (with Study 201 efficacy after 12 months) + early population only + Evidence Review Group preferred source for relapse post-complete response and relapse post-partial response + 30% discount for bexarotene	[redacted]	0.19	[redacted]
10) Stopping rule (with Watch and Wait efficacy after 12 months)	[redacted]	0.28	[redacted]
11) Proportion patients receiving chlormethine gel in SDT health state: 100%	[redacted]	0.28	[redacted]
12) Proportion patients receiving chlormethine gel in SDT health state: 0%	[redacted]	0.38	[redacted]
13) Valchlor® summary of product characteristics by disease stage dosing	[redacted]	0.33	[redacted]

Figure 2: Tornado diagram (ICER) – with chlormethine gel PAS

*The tornado diagram was reproduced for the company base case with the chlormethine gel PAS. It was obtained from the company's Appendix to the Stakeholder Comments Form (Figure 4) and reproduced.

Figure 3: Tornado diagram (net monetary benefit) – with chlormethine gel PAS

[redacted]

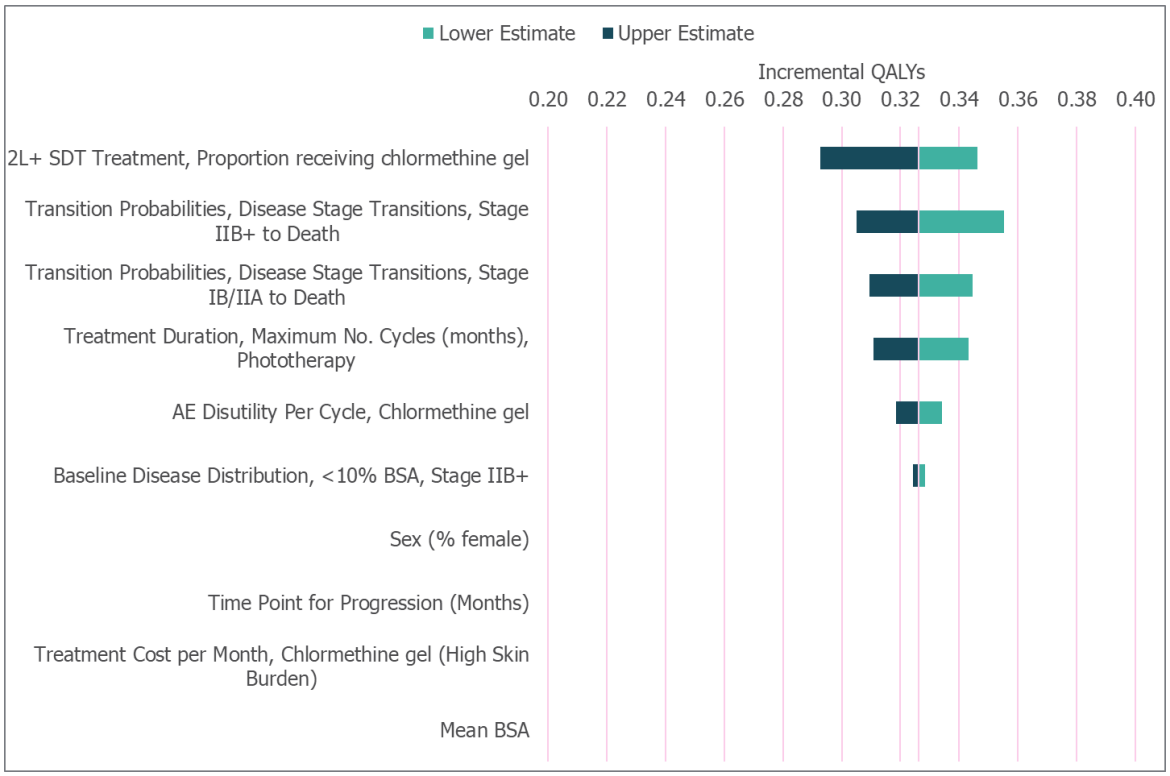
*The tornado diagram was reproduced for the company base case with the chlormethine gel PAS. It was obtained from the company's Appendix to the Stakeholder Comments Form (Figure 5) and reproduced.

Figure 4: Tornado diagram (incremental costs) – with chlormethine gel PAS

[redacted]

*The tornado diagram was reproduced for the company base case with the chlormethine gel PAS. It was obtained from the company's Appendix to the Stakeholder Comments Form (Figure 6) and reproduced.

Figure 5: Tornado diagram (incremental QALYs) – with chlormethine gel PAS



*The tornado diagram was reproduced for the company base case with the chlormethine gel PAS. It was obtained from the company's Appendix to the Stakeholder Comments Form (Figure 7) and reproduced.

Results of additional ERG analyses

Table 3 reports the cumulative impact of applying the ERG's preferred base case assumptions around model structure, phototherapy effectiveness and chlormethine gel treatment acquisition costs identified under issues 1-3 above. Table 4 illustrates the impact of several scenario analyses conducted around subgroups of disease severity, model time horizon, phototherapy effectiveness source and chlormethine gel stopping rules. Each scenario in Table 4 is applied as a single change to the ERG preferred base case analysis. All analyses in Tables 3 and 4 apply a simple discount ([redacted]) PAS to the list price for chlormethine gel.

Table 3: Cumulative impact of ERG preferred assumptions on the ICER

	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER
Company base case					
Chlormethine gel	[redacted]	8.21			
Phototherapy (PUVA/UVB)	£150,645	7.88	[redacted]	0.33	[redacted]
Source of phototherapy effectiveness data for duration of CR and PR (Phan et al. 2019)[3] [A]					
Chlormethine gel	[redacted]	8.21			
Phototherapy (PUVA/UVB)	£136,301	8.07	[redacted]	0.14	[redacted]
ERG modifications to model structure for initial progressed disease [B]					
Chlormethine gel	[redacted]	8.13			
Phototherapy (PUVA/UVB)	£136,301	8.07	[redacted]	0.07	[redacted]
Apply reduced effectiveness for 2nd and subsequent rounds of skin directed therapy for patients who initially respond but subsequently relapse [C]					
Chlormethine gel	[redacted]	8.09			
Phototherapy (PUVA/UVB)	£154,967	7.87	[redacted]	0.22	[redacted]

	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER
Apply reduced phototherapy effectiveness for chlormethine patients with initial progressed disease in the Systemic therapy health state [C]					
Chlormethine gel	[redacted]	8.09			
Phototherapy (PUVA/UVB)	£154,967	7.87	[redacted]	0.21	[redacted]
Apply the mean daily chlormethine gel dose from Valchlor® SmPC by disease stage (Stage IA: [redacted], Stage IB/IIA: [redacted]) (ERG preferred base case) [9]					
Chlormethine gel	[redacted]	8.09			
Phototherapy (PUVA/UVB)	£154,967	7.87	[redacted]	0.21	[redacted]

Abbreviations: CR: Complete Response; ERG: Evidence Review Group; ICER: Incremental Cost-Effectiveness Ratio; PAS: Patient Access Scheme; PR: Partial Response; QALY: Quality Adjusted Life Years; SmPC: Summary of Product Characteristics

[A] This analysis ensures that the same data source is used to populate all phototherapy effectiveness parameters, including CR, PR, failed response and duration of CR and PR. Duration of CR and PR applied by stage and type of phototherapy (PUVA / UVB).

[B] ERGs preferred modifications to the model structure include 1) Assume those with a failed initial response on chlormethine gel transition directly to the "Systemic Therapy" state; 2) Assume that the proportion of the cohort entering the "Systemic Therapy" state all receive a single course of phototherapy and 3) assume that all responders will have the same treatment in the subsequent rounds of skin directed therapy.

[C] Second or subsequent round of skin directed therapy, applied in either the SDT state (chlormethine gel or phototherapy) or in the systemic therapy state (phototherapy following chlormethine gel PD) all assume that CR and PR = 75% of 1st line; and duration of response = 50% of first line, based on ERG clinical expert opinion.

Table 4: Further exploratory analyses conducted by the ERG (Applied individually to the ERG's preferred base case analysis)

	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER
ERG preferred base case					
Chlormethine gel	[redacted]	8.09			
Phototherapy (PUVA/UVB)	£154,967	7.87	[redacted]	0.21	[redacted]
Model population: early stage MF-CTCL (Stage IA, IB & IIA)					
Chlormethine gel	[redacted]	9.42			
Phototherapy (PUVA/UVB)	£140,631	9.18	[redacted]	0.24	[redacted]
Model population: later stage MF-CTCL (Stage IIB+ only)					
Chlormethine gel	[redacted]	2.92			
Phototherapy (PUVA/UVB)	£210,732	2.82	[redacted]	0.10	[redacted]
10-year time horizon [A]					
Chlormethine gel	[redacted]	5.50			
Phototherapy (PUVA/UVB)	£97,044	5.44	[redacted]	0.06	[redacted]

	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER
Lifetime horizon [A]					
Chlormethine gel	[redacted]	9.51			
Phototherapy (PUVA/UVB)	£193,699	9.22	[redacted]	0.29	[redacted]
Use Whittaker et al. 2012 data for phototherapy response rates and duration of response (consistency of source)[6] [B]					
Chlormethine gel	[redacted]	8.08			
Phototherapy (PUVA/UVB)	£157,776	7.96	[redacted]	0.13	[redacted]
Stopping rule for chlormethine gel: apply watch and wait efficacy after 12 months					
Chlormethine gel	[redacted]	8.01			
Phototherapy (PUVA/UVB)	£154,967	7.87	[redacted]	0.13	[redacted]

Abbreviations: CR: Complete Response; EORTC: European platform of Cancer Research; ERG: Evidence Review Group; ICER: Incremental Cost-Effectiveness Ratio; PAS: Patient Access Scheme; PD: Progressed Disease; PR: Partial Response; QALY: Quality Adjusted Life Years; SD: Stable Disease

[A] Note that the base case time horizon was 20 years

[B] This scenario analysis uses data from Whittaker et al. (EORTC study) as an alternative consistent data source to populate both phototherapy response and duration of response in the model[6]. For this scenario, data on CR (25/78) and PR (44/78) (i.e. transitions to the 'no skin burden' and 'reduced skin burden' states respectively) are obtained from Whittaker et al. 2012. It is assumed that the remainder (i.e. those that do not achieve the definition of CR or PR are divided equally between SD and PD, based on data from the EORTC study[6]. Relapse post a CR is also obtained from Whittaker (company preferred source), with median months to relapse =6.48. Relapse post a PR was assumed to be equal to initial PD due to a lack of data from Whittaker et al. [6]

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Appendix

This appendix provides additional model output information that may be of interest to the committee. Table 5 shows the breakdown of life years accrued in each of the health states in the revised economic model under company and ERG preferred assumptions. It should be noted that under both the ERG and company preferred assumptions that the proportion of life years spent in the systemic therapy (previously 'progressed from 1L') health state has reduced substantially as a result of the model modifications and shortened time horizon (20 years).

Table 5 Breakdown of the life years spent in each health state

Company base case – Chlormethine gel							
	Low SB	**High SB**	**No SB**	**Reduced SB**	**Watch & Wait**	**SDT**	**Systemic Therapy**
LY	0.42	0.26	3.12	4.24	0.77	0.67	1.04
%	3.99%	2.45%	29.66%	40.34%	7.29%	6.39%	9.87%
Company base case - Phototherapy							
LY	0.07	0.09	2.06	0.90	2.10	0.65	4.62
%	0.63%	0.87%	19.68%	8.58%	20.01%	6.24%	43.99%
ERG base case - Chlormethine gel							
LY	0.42	0.26	2.19	4.45	0.55	1.21	1.43
%	3.99%	2.45%	20.80%	42.41%	5.25%	11.50%	13.60%
ERG base case - Phototherapy							
LY	0.07	0.09	2.14	0.53	1.74	0.78	5.15
%	0.63%	0.86%	20.43%	5.04%	16.55%	7.43%	49.06%

Abbreviations: LY: Life years; SB: Skin burden; SDT: Skin directed therapy

Tables 6 and 7 illustrate the output of the Markov traces showing the proportion of the cohort in each state at 1,2,5 and 10 years for each arm of the model under ERG and company preferred assumptions respectively.

Table 6 Markov trace – ERG base case

	Chlormethine gel							
Year	**Initial health state (low skin burden)**	**Initial health state (high skin burden)**	**No skin burden (CR)**	**Reduced skin burden (PR)**	**Watch and Wait**	**SDT**	**Systemic Therapy**	**Dead**
1	0.170	0.074	0.086	0.555	0.009	0.023	0.040	0.044
2	0.060	0.008	0.167	0.540	0.029	0.053	0.055	0.088
5	0.003	0.000	0.207	0.355	0.054	0.106	0.077	0.198
10	0.000	0.000	0.157	0.251	0.043	0.101	0.112	0.335
	Phototherapy							
Year	**Initial health state (low skin burden)**	**Initial health state (high skin burden)**	**No skin burden (CR)**	**Reduced skin burden (PR)**	**Watch and Wait**	**SDT**	**Systemic Therapy**	**Dead**
1	0.001	0.001	0.444	0.105	0.205	0.081	0.119	0.044
2	0.000	0.000	0.310	0.073	0.240	0.105	0.184	0.088
5	0.000	0.000	0.161	0.042	0.175	0.080	0.344	0.198
10	0.000	0.000	0.080	0.021	0.089	0.042	0.433	0.335

Table 7 Markov trace – Company base case

	Chlormethine gel							
Year	**Initial health state (low skin burden)**	**Initial health state (high skin burden)**	**No skin burden (CR)**	**Reduced skin burden (PR)**	**Watch and Wait**	**SDT**	**Systemic Therapy**	**Dead**
1	0.170	0.074	0.097	0.566	0.009	0.036	0.004	0.044
2	0.060	0.008	0.200	0.556	0.034	0.040	0.012	0.088
5	0.003	0.000	0.283	0.345	0.070	0.058	0.043	0.198
10	0.000	0.000	0.240	0.222	0.064	0.052	0.089	0.335
	Phototherapy							
Year	**Initial health state (low skin burden)**	**Initial health state (high skin burden)**	**No skin burden (CR)**	**Reduced skin burden (PR)**	**Watch and Wait**	**SDT**	**Systemic Therapy**	**Dead**
1	0.001	0.001	0.322	0.111	0.305	0.090	0.126	0.044
2	0.000	0.000	0.246	0.100	0.285	0.090	0.191	0.088
5	0.000	0.000	0.164	0.078	0.188	0.060	0.313	0.198
10	0.000	0.000	0.096	0.050	0.108	0.034	0.377	0.335

The model trace now shows that the proportion of the Markov model cohort in the "Systemic Therapy" state at each time point is substantially reduced from previous versions of the model. That is primarily because the revised economic model allows the option of retreatment with chlormethine gel or phototherapy in patients who have achieved a response but subsequently relapse. The ERG's change to the model structure slightly increased the time spent in the systemic therapy state for chlormethine gel relative to the company's structure. That is because the ERG's adaption to allow the proportion of the cohort with initial progressive disease to transition directly from the initial skin burden state into the systemic therapy state in the chlormethine gel arm of the model. This modification ensures consistency of structure for both phototherapy and chlormethine gel. Overall, the phototherapy arm progresses more quickly into 'Systemic Therapy' state because CR is higher on phototherapy compared to chlormethine gel and progression time post CR is shorter than progression time post PR.