**National Institute for Health and Care Excellence**

**Single Technology Appraisal (STA)**
**Chlormethine gel for treating mycosis fungoides-type cutaneous T-cell lymphoma [ID1589]**
**Response to consultee and commentator comments on the draft remit and draft scope (pre-referral)**

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

**Comment 1: the draft remit**

| Section | Consultee/ Commentator | Comments [sic] | Action |
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| Wording | NCRI Lymphoma Clinical Study Group and Royal College of Physicians | yes | Thank you for your comment. No action needed. |
| | Recordati Rare Diseases/Helsinn Healthcare SA | No changes are required to the wording of the remit.<br>It is not anticipated that this wording would:<br>• Exclude from full consideration any people protected by the equality legislation who fall within the patient population for which the treatment is licensed;<br>• Lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the technology;<br>• Have any adverse impact on people with a particular disability or disabilities. | Thank you for your comments. No action needed. |
| Timing Issues | NCRI Lymphoma Clinical Study Group and Royal | Medium urgency | Thank you for your comment. No action needed. |

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| | College of Physicians | | |
| | Recordati Rare Diseases/Helsinn Healthcare SA | There is a considerable unmet need for licensed treatments that specifically target the skin patches and plaques associated with mycosis fungoides type cutaneous T-cell lymphoma (MF-CTCL) and that have an evidence base supporting their efficacy and safety in this regard. There are currently no guidelines from NICE informing treatment decisions for this condition.<br>Current treatments often require patients to make regular trips to hospital, which can be highly disruptive to their career and family life; they are also associated with adverse events that negatively impact upon those affected. Moreover, patients often feel embarrassed by the patches and plaques on their skin, which can negatively affect quality of life, and also diminish their ability to work and socialise.<br>Chlormethine gel (Ledaga®) can be self-applied at home and is the only topical therapy rated 1+ for evidence according to the British Association of Dermatologists (BAD) guidelines, based on the results of the randomised controlled trial, Study 201.[1, 2] In contrast, efficacy and safety has not been adequately demonstrated for most other skin directed therapies (SDTs). In addition, different formulations of chlormethine (also referred to as mechlorethamine [MCH]) have been used previously in clinical practice in the UK, and chlormethine therefore has a well-characterised and manageable safety profile, with some clinicians highly experienced in prescribing this compound. However, chlormethine is currently not accessible for UK clinicians, due to issues associated with previous formulations such as compound stability and inconvenience. These issues are addressed with the new formulation.<br>Therefore, a positive recommendation from NICE would allow patients to access a treatment option for the skin patches and plaques related to MF-CTCL that is supported by an evidence base for its efficacy and is associated with a distinct safety profile *versus* relevant comparators. This option would also be expected to decrease the need for patients to spend time travelling to and from hospital, alleviating burden on individual patients and on NHS resources.<br>This appraisal is therefore highly relevant to the NHS and should be treated accordingly as a matter of urgency by NICE. | Thank you for your comments. No action needed. |

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| Additional comments on the draft remit | Recordati Rare Diseases/Helsinn Healthcare SA | No additional comments on the draft remit. | - |

**Comment 2: the draft scope**

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| Background information | NCRI Lymphoma Clinical Study Group and Royal College of Physicians | This is a clear and accurate description | Thank you for your comment. No action needed. |
| | Lymphoma Action | The background information does not include information on the impact of MF symptoms on quality of life, sleep or psychological factors. These are key concerns of people with MF.<br>Radiotherapy is occasionally used to treat plaques or tumours. | Thank you for your comments. The quality of life of people with MF will be discussed during the appraisal. No action needed. |
| | Recordati Rare Diseases/Helsinn Healthcare SA | The background information section states that *"Between 2009 and 2013, 1,659 people were newly diagnosed with cutaneous T-cell lymphomas of which around 55% were mycosis fungoides.[3]"* However, it does not specify the geographical region that is being considered in this statistic. Therefore, Recordati/Helsinn suggest that this is amended to read, *"In England, between 2009 and 2013, 1,659 people were newly diagnosed with cutaneous T-cell lymphomas of which around 55% were mycosis fungoides.[3]"*<br>The draft scope document also includes the following wording, *"Skin directed therapies are the main treatment for Stage IA, IB or IIA disease and include photo therapy (such as psoralen and ultraviolet A treatment [PUVA] and narrow band ultraviolet B treatment [UVB]), total skin electron beam therapy, topical chemotherapy agents, and topical corticosteroids."* | Thank you for your comments. The background section was updated considering all comments received on the background section of the scope. |

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| | | Firstly, based on clinical expert opinion, and treatment guidelines from the European Society of Medical Oncology (ESMO), Recordati/Helsinn Healthcare SA understands that SDT can be used in patients with MF-CTCL of all disease stages for the treatment of the skin symptoms of their disease.[4] Therefore, Recordati/Helsinn Healthcare SA suggests that the above wording be updated to, *"Skin directed therapies are the main treatment for Stage IA, IB or IIA disease, but can also be used to treat the skin symptoms of MF-CTCL in advanced disease stages, where they are used in combination with systemic treatments."* Please also refer to Recordati/Helsinn Healthcare SA's later comments on scope comparators and consider updating the list of "main treatments" in this background section accordingly.<br><br>In addition, the following wording is included in the draft scope: *"Systemic therapies are aimed at treating late stage disease, and include chemotherapy (such as methotrexate, gemcitabine, liposomal doxorubicin or multi-agent chemotherapy–cyclophosphamide, doxorubicin, vincristine, and prednisolone), immunotherapy (interferon alpha) or retinoids (bexarotene)."* Based on expert clinical input and the ESMO guidelines for CTCL, some systemic therapies, notably interferon (IFN) and systemic bexarotene, may be used in the treatment of patients with early stage MF-CTCL. Specifically, the ESMO guidelines recommend retinoids (systemic bexarotene) and IFN alone or in combination with SDTs at Stage IA–IIA disease, for patients with more extensive infiltrated plaques and tumours, or those refractory to SDTs; their use is not restricted solely for the delay or prevention of progression to advanced stage disease. As such, the categorisation in the draft scope of SDTs being for early stages and systemic therapies for later stages is not entirely accurate. In addition, based on feedback from clinical experts, it is anticipated that IFN will not be available in clinical practice from October 2019, and that pegylated IFN may be used as an alternative. Therefore, Recordati/Helsinn suggests that this wording be updated to: *"Systemic therapies are aimed at treating late stage disease, and include chemotherapy (such as methotrexate, gemcitabine, liposomal doxorubicin or multi-agent chemotherapy–cyclophosphamide, doxorubicin, vincristine, and prednisolone), immunotherapy (interferon alpha) or retinoids (bexarotene). Some systemic therapies (e.g. systemic bexarotene and pegylated interferon) may also be used at early disease stages in some patients.* | |
| | British Association of Dermatologists | See amendments below under "any additional comments" | Thank you for your comments. The background section was updated considering all comments received on |

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| | | | the background section of the scope. |
| The technology/ intervention | NCRI Lymphoma Clinical Study Group and Royal College of Physicians | yes | Thank you for your comment. No action needed. |
| | Lymphoma Action | There is no mention that chlormethine in solution or ointment formulations has been used to treat skin lymphomas for over 50 years. It is not currently available in the UK pending the decision on chlormethine gel. | Thank you for your comment. No action needed. |
| | Recordati Rare Diseases/Helsinn Healthcare SA | The description of chlormethine gel is accurate. | Thank you for your comment. No action needed. |
| Population | NCRI Lymphoma Clinical Study Group and Royal College of Physicians | Yes.<br>Within this population, there are patients who may conventionally be referred for photo therapy. However, they may not tolerate this treatment due to photo sensitivity. In addition, photo therapy units are not uniformly situated around the UK and some patients find the distance to travel for photo therapy is too great to make this a feasible option. In association with this restricted provision of photo therapy, some units have waiting lists of many months and so patients are suffering while waiting for treatment. In these situations, Chlormethine gel plays an vital role as a very satisfactory substitute to photo therapy | Thank you for your comments. No action needed. |

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| | Recordati Rare Diseases/Helsinn Healthcare SA | Recordati/Helsinn Healthcare SA agrees with the proposed population as per the draft scope, as this is in line with the marketing authorisation of chlormethine gel.<br><br>However, Recordati Rare Diseases/Helsinn Healthcare SA wish to be transparent in highlighting that data from Study 201, which investigated the efficacy and safety of chlormethine gel *versus* the ointment formulation of chlormethine, and forms the primary evidence base for the planned submission, is for patients with early stage (Stage IA–IIA) MF-CTCL only.[1] Therefore, the economic analyses presented in the submission may explore subgroups for patients with early and advanced stage disease separately, in order to account for uncertainty that may be associated with the use of chlormethine gel in later stage disease. However, clinical expert opinion, and experience in using other formulations of chlormethine in UK clinical practice, suggests that clinicians would support the option to prescribe chlormethine gel in patients with all stages of MF-CTCL for the treatment of the skin symptoms associated with their disease, in line with the wording of the licensed indication from the European Medicines Agency (EMA). | Thank you for your comments. No action needed. |
| | British Association of Dermatologists | Not as likely to be useful for early stage patients, this is a rare cancer | Thank you for your comments. No action needed. |
| Comparators | NCRI Lymphoma Clinical Study Group and Royal College of Physicians | Yes, the comparators are correct.<br><br>Photo therapy would be considered as the “best standard care” for patients for whom topical steroids are not suitable (usually too extensive or refractory to steroids) | Thank you for your comments. The section was updated considering all comments received on comparators in the scope. |
| | Recordati Rare Diseases/Helsinn Healthcare SA | Recordati Rare Diseases/Helsinn Healthcare SA acknowledge the lack of NICE guidance available for the treatment of patients with MF-CTCL. However, expert clinical input sought to inform this response, in addition to information derived from the BAD guidelines, indicates that of the comparators defined in the draft scope (“*Other skin directed therapies such as photo therapy (PUVA, UVB), total skin electron beam therapy, topical chemotherapy, and topical corticosteroids.”*), the only relevant comparator to chlormethine gel is phototherapy; namely, PUVA and UVB. | Thank you for your comments. The section was updated considering all comments received on |

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| | | Total skin electron beam therapy (TSEB) is not considered to be a relevant comparator to chlormethine gel. Whilst both treatments are used to target the skin symptoms of MF-CTCL, these therapies would be used to treat patients with notably different degrees of skin involvement in MF-CTCL. Chlormethine gel is anticipated to be used on specific thin patches and plaques, whilst TSEB, as a treatment for the whole body, would be considered for patients with very widespread plaques covering most of the body. Therefore, chlormethine gel and TSEB would be considered for distinct patients and hence the introduction of chlormethine gel would not displace the use of TSEB. Therefore, Recordati Rare Diseases/Helsinn Healthcare SA consider that this intervention should not be a comparator in the final scope.<br><br>Topical chemotherapy may include topical bexarotene, topical carmustine, topical imiquimod and alternative formulations (other than chlormethine gel) of topical chlormethine (e.g. chlormethine ointment). However, none of these treatments are licensed for use in clinical practice in the UK and clinician feedback to Recordati Rare Diseases/Helsinn Healthcare SA indicates that their use off-label is sporadic at most and that they do not form part of routine clinical practice in the UK. Therefore, topical chemotherapy is not considered to be a relevant comparator and should be removed from the list of comparators in the final scope.<br><br>Topical corticosteroids are also not considered to be a relevant comparator. Clinical expert opinion indicates that in UK clinical practice it would be expected that all patients would have already received topical corticosteroids prior to being prescribed chlormethine gel; in other words, chlormethine gel and topical corticosteroids would not be used at the same point in the treatment pathway. Patients would often be prescribed topical corticosteroids prior to an MF-CTCL diagnosis in order to control undiagnosed skin symptoms or in response to patient mis-diagnosis with a benign skin condition. In addition, topical corticosteroids are not 'anti-MF-CTCL', as they do not specifically treat the skin symptoms of MF-CTCL; rather, they are used to reduce symptoms of inflammation and irritation, aligned with their use across a wide range of non-oncological skin conditions.[5]<br>In summary, Recordati Rare Diseases/Helsinn Healthcare SA consider that, of the comparators defined in the draft scope, only phototherapy (PUVA and UVB) represents a relevant comparator, based on clinical expert opinion. Relevant comparators to chlormethine gel are those treatment approaches that:<br>• are currently used in UK clinical practice; and | comparators in the scope. |

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| | | • are used to treat the patches and plaques (skin symptoms) associated with MF-CTCL (i.e. are not used with the specific intention of delaying or preventing progression of the underlying cancer); and<br>• would be used for patients who present with a similar degree of skin involvement (i.e. similar level of plaque skin coverage) to that for which chlormethine gel would be considered as an appropriate treatment option<br>The other listed therapies in the draft scope are either not used in UK clinical practice or are used at a different point in the treatment pathway, and for a different purpose, to that of chlormethine gel.<br>Based on the above, Recordati/Helsinn Healthcare SA therefore proposes that the wording on comparators in the draft scope is updated in the final scope to the following:<br>• *Therapies used to treat the skin symptoms associated with MF-CTCL e.g. phototherapy (PUVA, UVB)* | |
| | British Association of Dermatologists | Yes topical steroids are not a suitable comparator – these should be tried before Ledaga<br>Phototherapy or TSEBT are suitable comparators but phototherapy requires attendance to hospital 2-3 x week for 12-16 weeks and TSEBT up to 5 weeks in attendance increases the risk of other skin cancers such that the number of treatments are limited. Interferon alpha and bexarotene should also be considered as comparators as these are first line systemic options when SDTs are contraindicated or ineffective. | Thank you for your comments. The background section was updated considering all comments we received on comparators in the scope. |
| Outcomes | NCRI Lymphoma Clinical Study Group and Royal College of Physicians | No, Overall survival is a totally unsuitable outcome measure in this setting. HRQoL is the strongest indicator of benefit and this relates to various economic benefits such as ability to work and fulfil family and social responsibilities.<br>Response rate and duration of response are important as these have a direct bearing upon the utilisation of medical resources eg other medication, GP and hospital visits and call upon community medical services.<br>Adverse effects of treatment is of course important | Thank you for your comments. The scope was updated considering all comments we received on outcomes in the scope. |

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| | Lymphoma Action | Consider including complete or partial improvement in the 'CAILS' score, which takes into account different features of MF, such as the size and appearance of the skin damage.<br>In this low-grade, long-term condition, health-related quality of life outcomes are particularly important. | Thank you for your comments. The scope was updated considering all comments we received on outcomes in the scope. |
| | Recordati Rare Diseases/Helsinn Healthcare SA | The skin pathology associated with MF-CTCL involves flat, scaly, oval patches which form on the skin and can progress to thicker plaques and/or tumours. These patches, plaques and tumours can lead to pruritus (itching) and can also be painful for the patient, leading to decrements in patient quality of life. Therefore, monitoring and managing the skin symptoms of MF-CTCL is very important in assessing and controlling the disease, and ultimately improving patient outcomes.<br><br>The aim of treatment with chlormethine gel is to treat the skin symptoms of MF-CTCL. This treatment goal is supported by the fact that clinical evidence for the efficacy of chlormethine gel investigates clinical endpoints relating to the severity and extent of coverage of skin symptoms. On this basis, Recordati/Helsinn Healthcare SA requests that outcomes measuring the degree of skin involvement in this disease are included within the final scope, as these are the most appropriate way of assessing the efficacy of chlormethine gel and the relevant comparators. In Study 201, which investigated chlormethine gel in patients with MF-CTCL, the Composite Assessment of Index Lesion Severity (CAILS) and the Modified Severity Weighted Assessment Tool (mSWAT) were used to assess treatment efficacy. CAILS is based on an assessment of four clinical features (erythema, scaling, plaque elevation and surface area) of five index lesions. mSWAT is derived by weighting body surface area (BSA) involvement for patches, plaques and tumours, and summing the scores for each category.[6] These indices are commonly used measures when investigating treatments for MF-CTCL and their relevance is supported by the literature in this disease area.[6-8] Therefore, Recordati/Helsinn Healthcare SA politely requests that both the CAILS and SWAT/mSWAT be included in the final scope.<br><br>Whilst further research may elucidate a role for the treatment of skin symptoms in delaying or preventing progression of the underlying condition to more advanced disease stages, there | Thank you for your comments. The scope was updated considering all comments received on outcomes in the scope. |

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| | | is currently a lack of evidence to support such benefits. As such, outcomes of overall survival (OS) and progression-free survival (PFS), whilst being relevant outcomes in the majority of oncology indications, are not suitable measures of the impact of therapies aimed at treating skin symptoms in MF-CTCL. This is especially the case in early disease stages; disease progression with MF-CTCL can be slow and hence at these early stages of disease, treatment for skin lesions is not given with consideration for its impacts on progression or survival, but rather for its impact on improving skin symptoms. Given the points above, Recordati/Helsinn Healthcare SA requests that OS and PFS be removed in the final scope. For the purposes of this appraisal, considering the role of chlormethine gel in the treatment of MF-CTCL, the decision problem should be viewed in terms of the treatment of the skin symptoms of the disease and not in terms of preventing or delaying progression of the underlying disease, or improving survival. Whilst PFS is not a relevant outcome for the reasons described above, time to skin symptom progression data may be included as assessed in Study 201 (i.e. relating to progression according to CAILS, rather than progressing to a more advanced disease stage).<br><br>Regarding time to relapse, Recordati/Helsinn Healthcare SA plan on presenting data relating to duration of the skin response (i.e. time to loss of the skin response to treatment).<br><br>Recordati/Helsinn Healthcare SA acknowledge that health-related quality of life should be included as a relevant outcome in the final scope. In the absence of patient-reported outcomes from Study 201, a separate study will be conducted in order to derive utility values informing the quality of life of patients with MF-CTCL. | |
| | British Association of Dermatologists | Yes, add pruritus score | Thank you for your comments. The scope was updated considering all comments we received on outcomes in the scope. |

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| Economic analysis | NCRI Lymphoma Clinical Study Group and Royal College of Physicians | Quality Adjusted Life Years are not the ideal economical tool as indicated above, as the impact on overall survival should not be the primary outcome measure here.<br>The true estimation of cost to NHS and social services can be difficult to accurately estimate in this disease | Thank you for your comments. No action needed. |
| | Recordati Rare Diseases/Helsinn Healthcare SA | Results of the economic analysis will be expressed in terms of incremental cost per quality-adjusted life year, with costs considered from an NHS and Personal Social Services perspective.<br><br>Recordati/Helsinn Healthcare SA will consider an appropriate time horizon to reflect any differences in costs or outcomes between chlormethine gel and the relevant comparators. | Thank you for your comments. No action needed. |
| Equality and Diversity | NCRI Lymphoma Clinical Study Group and Royal College of Physicians | Currently across the UK, there is inequality of access to photo therapy. This leaves a significant deficit in the quality of care for a particular group of patients. Availability of Chlormethine will provide an equivalently efficacious treatment for this group of patients | Thank you for your comment. This comment has been included on the scoping EIA form. |
| | Recordati Rare Diseases/Helsinn Healthcare SA | Recordati/Helsinn Healthcare SA has not identified any issues related to equality that should be covered in the remit or scope of this appraisal. | Thank you for your comments. No action needed. |
| | British Association of Dermatologists | • could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which the treatment is licenced? No<br>• could lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the technology; No | Thank you for your comments. No action needed. |

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| | | • could have any adverse impact on people with a particular disability or disabilities. No | |
| Other considerations | NCRI Lymphoma Clinical Study Group and Royal College of Physicians | Chlormethine provides a local treatment to a number of symptomatic lesions by topical application. Characteristically, this may be a group of patients for whom topical steroid is no longer beneficial. In these patients whose disease is not sufficiently widespread to require photo therapy, Chlormethine will bring about disease control which can be prolonged. It also offers the flexibility that the intensity of treatment can be titrated against response. This is particularly relevant in the context of maintaining a long term response. | Thank you for your comments. No action needed. |
| | Recordati Rare Diseases/Helsinn Healthcare SA | No additional issues. | Thank you for your comment. No action needed. |
| Innovation | NCRI Lymphoma Clinical Study Group and Royal College of Physicians | This treatment is not new. It has been available in the past to a small percentage of suitable patients where there was capacity formulate this preparation in the local pharmacy. A number of clinicians therefore have experience in the successful use of this drug.<br>This “home made” system of preparation is no longer available and so this preparation of Chlormethine enables all suitable patients to have access to this important therapy | Thank you for your comments. No action needed. |
| | Recordati Rare Diseases/Helsinn Healthcare SA | There is a paucity of clear guidance on the treatment pathway for MF-CTCL; there are few licensed therapies with proven clinical efficacy through randomised controlled trials. Therefore, expanding the clinician armamentarium to include a treatment option that was developed specifically for MF-CTCL, is licensed for the treatment of this indication, and is supported by clinical trial evidence for its efficacy and safety, would represent a step change in the management of this condition.<br><br>Chlormethine has been used in the treatment of MF-CTCL since the 1930s, and clinicians in the UK have experience in prescribing this compound in alternative formulations. In addition, | Thank you for your comments. No action needed. |

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| | | chlormethine is the only topical therapy rated 1+ for evidence according to the BAD guidelines.[2] Thus, there is both trial evidence and experience from UK clinical practice supporting the efficacious use of this compound and its underlying safety profile.[1] However, there is not currently a chlormethine product available for use in UK clinical practice. This is due to the fact that the aqueous solution and ointment formulations that were previously the most commonly prescribed in clinical practice were unstable and associated with inconvenience for patients when applying to the skin, and for pharmacists when compounded (due to precaution required to avoid toxicity specific to these formulations).<br>By providing chlormethine in a gel formulation, the efficacious and tolerable nature of alternative formulations of chlormethine is preserved, whilst offering the convenience of safe, home application and decreased hospital visits. In addition, chlormethine gel may offer a distinct tolerability profile *versus* the relevant, current treatment options. For example, to date, no association between use of chlormethine gel and risk of secondary cancers has been reported; in contrast, phototherapy has been associated with squamous cell carcinomas and tumours even on non-exposed skin, including invasive penile tumours and basal cell carcinomas.[1, 2, 9-11] Therefore, chlormethine gel represents an innovation of formulation, and the availability of this therapy for patients would be expected to provide a valuable treatment option for patients with all stages of MF-CTCL, for whom current treatment options have considerable limitations.<br><br>The use of chlormethine gel in the UK may also offer additional non-health benefits that would not be captured in the QALY estimates. The convenience of home application, and consequent decreased requirement for hospital visits relative to a phototherapy comparator, may have a positive impact in decreasing absenteeism from work and hence aiding societal productivity, in addition to reducing both the financial and time-related costs of travel to appointments for individual patients. | |
| | British Association of Dermatologists | • Yes this is a much needed addition to our anti CTCL treatments, it is practical to use without trips to hospital nor risks of systemic effects and doesn't require monitoring<br>• Skindex is a better measure of HRQoL in CTCL, patients live with a high symptom burden not reflected by QALY<br>• Lessin SR, et al. JAMA Dermatol. 2013;149:25-32. | Thank you for your comments. No action needed. |

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| Questions for consultation | Recordati Rare Diseases/Helsinn Healthcare SA | Comments have been provided above with regards to the population, comparators and outcomes specified in the draft scope, as well as issues related to equality, and the innovativeness of chlormethine gel.<br><br>Answers to the additional questions for consultation on which Recordati Rare Diseases/Helsinn Healthcare SA wish to comment are provided below.<br><br>*Would chlormethine gel be used for people with advanced disease, including CD30-positive, mycosis fungoides-type stage IIB or over, cutaneous T-cell lymphoma?*<br>It is anticipated that patients would be treated with chlormethine gel irrespective of disease stage and CD30 status. Regarding disease stage, treatment would be based on the extent of skin symptoms rather than the progression status of underlying disease. Based on clinical expert opinion, chlormethine gel would be used to treat both early and late stage patients for the skin patches and plaques associated with their MF-CTCL, as treatments for these skin symptoms would be determined by physician and patient preference rather than disease stage only. Unlike brentuximab vedotin, chlormethine gel does not specifically target CD30 and therefore, patients can be treated with chlormethine gel for their skin symptoms of MF-CTCL irrespective of their CD30 status.<br><br>*Are there any subgroups of people in whom chlormethine gel is expected to be more clinically effective and cost-effective or other groups that should be examined separately?*<br>Recordati/Helsinn Healthcare SA do not consider there to be any clinically-relevant subgroups of patients for whom chlormethine gel will be more clinically- or cost-effective when compared to the overall population covered by the indication. However, as discussed above, there is a paucity of evidence investigating chlormethine gel in patients with advanced MF-CTCL, so this may lead to uncertainties in the clinical and cost-effectiveness analyses for this subgroup. Therefore, Recordati/Helsinn Healthcare SA consider that it may be relevant to assess the cost-effectiveness of chlormethine gel in both the full licensed population as well as subgroups of early and advanced stage patients separately.<br><br>*Where do you consider chlormethine gel will fit into the existing NICE pathway, Non-Hodgkin's lymphoma?*<br>The NICE guidelines for the management of non-Hodgkin's lymphoma includes guidance on the management of CTCL. However, these currently only recommend the use of | Thank you for your comments. The scope was updated considering all comments we received. |

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| | | brentuximab vedotin as an option for treating CD30-positive cutaneous T-cell lymphoma (CTCL) after at least 1 systemic therapy in adults, only if they have mycosis fungoides stage IIB or over, primary cutaneous anaplastic large cell lymphoma or Sézary syndrome. However, there are no additional guidelines or recommendations from NICE relating to the treatment of the skin patches and plaques that occur in MF-CTCL. Therefore, there is a lack of NICE-recommended treatment options for MF-CTCL specifically, across disease stages, and for the skin symptoms associated with this disease.<br>Chlormethine gel is anticipated to be used in patients with MF-CTCL at any stage of disease (and irrespective of CD30 status) for the treatment of skin symptoms related to their disease. Given the lack of NICE-recommended treatments in this setting, chlormethine gel may fulfil an unmet need in UK clinical practice.<br><br>*To help NICE prioritise topics for additional adoption support, do you consider that there will be any barriers to adoption of this technology into practice? If yes, please describe briefly.*<br>Recordati/Helsinn Healthcare SA do not anticipate any barriers to adoption, considering that chlormethine gel can be administered at home, with no training requirements.<br><br>*NICE intends to appraise this technology through its Single Technology Appraisal (STA) Process. We welcome comments on the appropriateness of appraising this topic through this process. (Information on the Institute's Technology Appraisal processes is available at http://www.nice.org.uk/article/pmg19/chapter/1-Introduction).*<br>Recordati/Helsinn Healthcare SA agrees that the appraisal of chlormethine gel for the treatment of adults with MF-CTCL is suitable for assessment via the STA process. | |
| | British Association of Dermatologists | Would chlormethine gel be used for people with advanced disease, including CD30-positive, mycosis fungoides-type stage IIB or over, cutaneous T-cell lymphoma?<br>They may be used for early stage lesions in patients with advanced disease – most CD30 positive lesions are advanced lesions<br><br>Where do you consider chlormethine gel will fit into the existing NICE pathway, Non-Hodgkin's lymphoma? | Thank you for your comments. Topical corticosteroids were removed from the list of comparators. |

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| | | After topical corticosteroids as a reasonable alternative to phototherapy or for patients resistant to other SDT<br><br>To help NICE prioritise topics for additional adoption support, do you consider that there will be any barriers to adoption of this technology into practice? If yes, please describe briefly.<br>No | |
| Additional comments on the draft scope | NCRI Lymphoma Clinical Study Group and Royal College of Physicians | No additional comment | Thank you for your comments. No action needed. |
| | Recordati Rare Diseases/Helsinn Healthcare SA | No additional comments on the draft scope. | Thank you for your comments. No action needed. |
| | British Association of Dermatologists | **Background**<br>Lymphomas are cancers of the lymphatic system. They are broadly divided into Hodgkin's and non-Hodgkin's lymphomas. Cutaneous T-cell lymphoma is a rare type of non-Hodgkin's lymphoma that affects the skin. It is caused by the uncontrolled growth of T-lymphocytes within the skin. Many types of cutaneous T-cell lymphoma start as flat red patches or plaques on the skin, which are scaly and may be weepy. They may progress to larger skin tumours, or spread to extensively involve the skin termed erythroderma. The lesions are frequently itchy and sometimes painful. Some people with cutaneous T-cell lymphoma experience swelling of the lymph nodes. Systemic spread may occur with lymphomatous involvement of lymph nodes or internal organs. | Thank you for your comments. The background section was updated considering all comments received on the background section of the scope. |

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| | | Within the group of cutaneous T-cell lymphoma, there are distinct subtypes. Mycosis fungoides is the most common type of cutaneous T-cell lymphoma. Between 2009 and 2013, 1,659 people were newly diagnosed with cutaneous T-cell lymphomas in UK of which around 55% were mycosis fungoides.[1] It is usually a very slow-growing type of lymphoma that often only affects the skin and can stay under control for many years.<br><br>In England in 2017, there were around 12,065 new cases of non-Hodgkin's lymphomas and 796 people had a primary diagnosis of peripheral or cutaneous T-cell lymphoma.[2] There were 107 men and 72 women diagnosed with mycosis fungoides cutaneous T-cell lymphoma, in England in 2017.[2] Median survival with early stage disease, stage IA, IB and IIA, is reported as 35.5, 21.5 and 15.8 years, respectively. The prognosis is worse when the condition is not limited to the skin at the time of initial diagnosis (stages IIB through IV). Median survival for late stage disease, stages IIB, IIIA and IIIB, is reported to be 4.7, 4.7 and 3.4 years, respectively, and decreases further for stage IV disease.[3]<br><br>Current management of cutaneous T-cell lymphoma consists of skin directed therapies and systemic therapies. Skin directed therapies are the main treatment for Stage IA, IB or IIA disease and include skin directed therapies (SDT) photo therapy (such as psoralen and ultraviolet A treatment [PUVA] and narrow band ultraviolet B treatment [UVB]), total skin electron beam therapy, topical chemotherapy agents (chlormethine), and topical corticosteroids.<br><br>Systemic therapies are aimed at treating late stage disease or early stage when SDT is contraindicated or refractory or include | |

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| | | immunotherapy (interferon alpha) or retinoids (bexarotene) before chemotherapy (such as<br>methotrexate, gemcitabine, liposomal doxorubicin or multi-agent chemotherapy–cyclophosphamide, doxorubicin, vincristine, and prednisolone).<br>TA577 recommends brentuximab vedotin for treating CD30-positive, mycosis fungoides-type stage IIB or over, cutaneous T-cell lymphoma after at least one prior systemic therapy. Stem cell or bone marrow transplant (such as allogeneic-SCT) and extracorporeal photopheresis (ECP) may also be a treatment option for some people. Treatment options for cutaneous T-cell lymphoma can be used either alone or in combination. People may have multiple sequential treatments and remain on maintenance therapy with palliative intent although there is no established standard of care.<br><br>**The technology**<br>Chlormethine gel is a topical chemotherapy. It is an alkylating agent with antineoplastic and immunosuppressive properties. The product under appraisal (Ledaga, Recordati Rare diseases/Helsinn Healthcare SA) is an anhydrous gel that is applied topically to the affected skin area and can be self-administered by patients.<br>Chlormethine gel has a marketing authorisation for the topical treatment of mycosis fungoides-type cutaneous T-cell lymphoma in adult patients.<br><br>**Comparators:**<br>Other skin directed therapies such as photo therapy (PUVA, UVB), total skin electron beam therapy, topical chemotherapy, and first line systemic choices for stage IA-IIA such as interferon alpha and bexarotene. | |

**The following consultees/commentators endorsed submitted comments:**

The RCP endorsed the response submitted by the British Association of Dermatologists (BAD).