# NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

## Appraisal consultation document

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

The Department of Health and Social Care has asked the National Institute for Health and Care Excellence (NICE) to produce guidance on using chlormethine gel in the NHS in England. The appraisal committee has considered the evidence submitted by the company and the views of non-company consultees and commentators, clinical experts and patient experts.

**This document has been prepared for consultation with the consultees.** It summarises the evidence and views that have been considered, and sets out the recommendations made by the committee. NICE invites comments from the consultees and commentators for this appraisal and the public. This document should be read along with the evidence (see the committee papers).

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 recommendations sound and a suitable basis for guidance to the NHS?
- Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?



Issue date: July 2020

**Note that this document is not NICE's final guidance on this technology. The recommendations in section 1 may change after consultation.**

After consultation:

- The appraisal committee will meet again to consider the evidence, this appraisal consultation document and comments from the consultees.
- At that meeting, the committee will also consider comments made by people who are not consultees.
- After considering these comments, the committee will prepare the final appraisal document.
- Subject to any appeal by consultees, the final appraisal document may be used as the basis for NICE's guidance on using chlormethine gel in the NHS in England.

For further details, see NICE's guide to the processes of technology appraisal.

**The key dates for this appraisal are:**

Closing date for comments: 26 August 2020

Second appraisal committee meeting: 08 September 2020

Details of membership of the appraisal committee are given in section 5.

# 1 Recommendations

1.1 Chlormethine gel is not recommended, within its marketing authorisation, for treating mycosis fungoides-type cutaneous T-cell lymphoma (MF-CTCL) in adults.

1.2 This recommendation is not intended to affect treatment with chlormethine gel that was started in the NHS before this guidance was published. People having treatment outside this recommendation may continue without change to the funding arrangements in place for them before this guidance was published, until they and their NHS clinician consider it appropriate to stop.

### Why the committee made these recommendations

Most treatments for mycosis fungoides-type cutaneous T-cell lymphoma (MF-CTCL) aim to relieve the skin symptoms. Options include topical treatments, which are applied to the skin, such as topical steroids, phototherapy (light therapy) and radiotherapy. Systemic treatment such as oral bexarotene can also be used to relieve skin symptoms if those treatments become unsuitable.

Clinical evidence shows that chlormethine gel relieves skin symptoms. But there is no robust evidence showing its effectiveness compared with phototherapy.

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, and
- the dose of chlormethine gel per application.

Because of these uncertainties, the committee was unable to estimate the cost effectiveness of chlormethine gel, so it is not recommended.

# 2 Information about chlormethine gel

## Marketing authorisation indication

2.1 Chlormethine gel (Ledaga, Recordati Rare Diseases and Helsinn Healthcare) is indicated for 'the topical treatment of mycosis fungoides-type cutaneous T-cell lymphoma (MF-type CTCL) in adult patients'.

## Dosing in the marketing authorisation

2.2 The dosage schedule is available in the summary of product characteristics.

## Price

2.3 The list price for chlormethine gel is £1,000 per 60 g tube (excluding VAT; BNF online accessed 17 July 2020). Costs may vary in different settings because of negotiated procurement discounts.

# 3 Committee discussion

The appraisal committee (section 5) considered evidence submitted by Recordati Rare Diseases and Helsinn Healthcare, a review of this submission by the evidence review group (ERG), the technical report, and responses from stakeholders. See the committee papers for full details of the evidence.

The appraisal committee was aware that several issues were resolved during the technical engagement stage, and agreed that:

- Phototherapy (PUVA and UVB bundled) is an appropriate comparator for chlormethine gel in the model.
- The company's estimate for phototherapy administration costs is acceptable for use in the model. Costs were derived from the mean of dermatology and oncology costs for consultant-led outpatient clinic cost of phototherapy and photochemotherapy (sourced from NHS reference costs 2017/18). The company and the ERG agreed that the PROCLIPI registry is an appropriate source of evidence to derive the distributions of PUVA and UVB phototherapy for the model.

- The Kim 2003 study is an acceptable data source to estimate time to progression to systemic treatment after a complete skin symptom response on chlormethine gel in the model. Study 201 is the current best available evidence for estimating complete and partial response rates in the chlormethine gel arm of the model. The company agreed with the ERG to use Phan et al. 2019 as the data source for complete and partial response rates in the phototherapy arm of the model.

The committee recognised that there were remaining areas of uncertainty associated with the analyses presented (see technical report, table 2, page 42), and took these into account in its decision making. It discussed the following issues: issue 1 (second part), issue 2 (second part), issue 3, issue 5, issue 6 (second part), issues 7 and 8, uncertainties in utility values, and uncertainty in the data used to estimate time to progression to systemic treatment after a partial skin symptom response on chlormethine gel, which were outstanding after the technical engagement stage.

## Clinical need

### There is a clinical need for chlormethine gel as an alternative treatment option for people with MF-CTCL

3.1 The patient expert explained in their written statement that mycosis fungoides-type cutaneous T-cell lymphoma (MF-CTCL) negatively affects many aspects of life including employment, leisure activities, relationships and day-to-day living. It can also have a psychosocial effect. Symptoms include itching, pain and fever, which can be distressing and are associated with fatigue, anxiety and depression. There is often a delay in being diagnosed with MF-CTCL, and people may already have tried several treatments to relieve their skin symptoms before their eventual diagnosis. The condition tends to return after treatment and people often cycle between treatments, including phototherapy and sometimes radiotherapy. This means people must travel for repeated hospital appointments and quality of life may be affected. The committee recognised the need for an alternative treatment option that may be more convenient for people and could be

particularly useful during the COVID-19 pandemic. It concluded that chlormethine gel could be an alternative treatment option for people who cannot have phototherapy or for whom it is more convenient because there is no need for regular hospital appointments.

## Treatment pathway

### Chlormethine gel relieves skin symptoms but is not a cure

3.2 Clinical experts explained that, in practice, chlormethine gel would be prescribed for up to a year, or for less than a year if there is a complete response in skin symptoms. For people with partial response in skin symptoms, treatment would be expected to stop after a year. People could potentially have further courses of treatment. The clinical experts also explained that, like the other treatments currently available for treating the skin symptoms of MF-CTCL, chlormethine gel is not a cure, and does not affect the spread of the disease to other organs in the body. They explained that there was a previous similar version of this treatment called nitrogen mustard which was withdrawn. The committee understood that there has been some experience of using it in the past and the benefit of this type of treatment on the skin has previously been shown. Although it is uncommon for skin symptoms to completely resolve, therapies can relieve skin symptoms and improve people's quality of life. The clinical experts explained that chlormethine gel does not affect the progression of the underlying disease or mortality. The committee concluded that chlormethine gel is not a disease-modifying treatment, but it relieves skin symptoms and improves quality of life.

### People with early stage MF-CTCL have multiple treatments until symptoms no longer respond

3.3 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. The aim of all these treatments is to reduce the burden of skin disease. The clinical experts explained that people with early stage MF-CTCL whose disease is confined to the skin cycle through the different treatments, and the sequence varies. 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.

## Clinical evidence

### The main trial shows chlormethine gel improves the skin symptoms of early stage MF-CTCL but compares it with a treatment that is no longer used

3.4 The main trial, Study 201, was a non-inferiority trial (a trial showing that a new treatment is not substantially worse than another treatment) comparing chlormethine gel with chlormethine ointment in 260 people with early stage MF-CTCL (stage 1A to 2A). Skin symptom response rate was scored on the Composite Assessment of Index Lesion Severity (CAILS) and the modified Severity Weighted Assessment Tool

(mSWAT). The overall response rate for chlormethine gel was 58.5% using CAILS and 46.9% using mSWAT. Using CAILS, 13.8% of people had a complete response in skin symptoms and 44.6% of people had a partial response in skin symptoms. The complete and partial response rates measured using mSWAT are confidential and cannot be reported. The committee understood that Study 201 shows that chlormethine gel improves the skin symptoms of early stage MF-CTCL. However, because the comparator ointment is no longer used in clinical practice, the committee concluded that Study 201 does not show how effective chlormethine gel is compared with standard care.

**The clinical effectiveness of chlormethine gel compared with phototherapy is not known**

3.5 The committee understood that phototherapy is the appropriate comparator for chlormethine gel. However, there was no evidence directly comparing chlormethine gel with phototherapy and no connected network for indirect comparison could be formed. Therefore the company did an unadjusted naive comparison. Most of the studies in the comparison were not randomised controlled trials and were of low quality. The overall response rates from the weighted average estimates of the 7 phototherapy studies identified by the company were higher for phototherapy than the response rates for chlormethine gel in Study 201. A systematic review on the clinical effectiveness of phototherapies (Phan et al. 2019) identified by the ERG also suggested higher response rates for phototherapy. Complete skin symptom response was also higher for phototherapy than partial skin symptom response (73.2% compared with 20.8%, as reported in the 7 phototherapy studies), but the reverse was the case for chlormethine gel (13.8% compared with 44.6% using CAILS). 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 committee understood that most studies included in Phan et al. 2019 were retrospective and at risk of bias. It also noted the ERG's concern that there was substantial heterogeneity across the included studies, including differences in how complete and partial response in skin symptoms were defined and measured. The committee concluded that the true clinical effectiveness of chlormethine gel compared with phototherapy is not known, given the high uncertainty associated with the unadjusted naive comparison.

**Study 201's results are not generalisable to people with advanced stage MF-CTCL**

3.6 The company stated in its submission that chlormethine gel is expected to be used:

- first line in early stage MF-CTCL and
- in combination with systemic therapies if the disease is at an advanced stage, to relieve skin symptoms.

The clinical experts explained that they may use chlormethine gel for people with advanced MF-CTCL if the skin disease was mild. Use of the treatment would be based on skin lesions rather than stage of the disease, and people with advanced MF-CTCL can have mild skin lesions suitable for treatment with a topical therapy. However, the committee noted that Study 201 only included people with early stage MF-CTCL and there was no comparative evidence evaluating the clinical effectiveness of chlormethine gel in people with advanced disease who may also be having chemotherapy. The clinical experts also explained that, even when used for people with advanced disease who had mild skin symptoms, the skin symptom response might not be the same as in early stage MF-CTCL. The committee acknowledged that there could be people with advanced disease who might benefit from chlormethine gel, however, no such people were included in Study 201. Because of this and the uncertainties about chlormethine gel's use in advanced stage MF-CTCL, the committee concluded that the results

from Study 201 could not be generalised to people with advanced MF-CTCL.

## Cost effectiveness

3.7 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. When the disease progressed they passed into the health state of 'progressed from 1L'. They then stayed in that state, taking bexarotene or peginterferon alfa for their remaining life years. However, as noted in section 3.3, in clinical practice people have repeated courses of treatments and switch between the different types. Chlormethine gel would not replace phototherapy, and the choice would not be between just one round of either chlormethine gel or phototherapy followed by bexarotene or peginterferon alfa if symptoms relapsed. The committee concluded that the model structure over-simplified the treatment pathway. The committee also noted that participants of Study 201 received only one course of chlormethine gel, while in clinical practice people with MF-CTCL could have repeated courses of treatments or switch between them. After subsequent treatment the skin symptom response may be different, but this was not accounted for in the model. Also, in the model, chlormethine gel was used for up to 3 years in people who had a partial skin symptom response. The clinical experts noted that people would have chlormethine gel for up to 1 year (see section 3.2) and not as maintenance during partial skin symptom response. Therefore the model did not reflect what would be expected in clinical practice. Also, the effect of extended duration of treatment on costs and disease state in the model was unclear. The committee concluded that the assumptions about sequential treatment and time on treatment meant that the model did not accurately reflect clinical practice.

### The assumption in the model about progression to bexarotene or peginterferon alfa after a complete or partial symptom response is not clinically realistic

3.8 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. The higher complete response rate in the phototherapy arm than in the chlormethine gel arm resulted in a faster transition to bexarotene or peginterferon alfa after phototherapy than chlormethine gel. People whose symptoms had a partial response, which was more common in the chlormethine gel arm, had a delayed entry into the 'progressed from 1L' health state where they had bexarotene or peginterferon alfa for their remaining life years. The effect of these assumptions was that phototherapy accumulated greater costs and quality of life decrements over a lifetime horizon than chlormethine gel. 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. The patient expert also explained that a watch and wait approach is typical in practice if symptoms are limited and not affecting someone's functioning. The committee therefore questioned the assumption that people with a complete skin symptom response fared worse and were more likely to progress to subsequent treatments earlier than those who had a partial symptom response. The committee concluded that the model's assumptions about progression to bexarotene or peginterferon alfa after a complete or partial symptom response were counterintuitive and not clinically realistic.

### The mean daily dose of chlormethine gel is uncertain

3.9 Dose estimates from the clinical experts, the company model, and the ERG were all different. The ERG used a mean daily dose of 2.8 g in the model. The ERG sourced this information from the summary of product

characteristics for Valchlor (the US brand name of chlormethine gel) from Study 201. The company modelled a lower mean daily dose, which was taken from individual patient data based on the number of returned empty tubes per follow-up visit from Study 201. The ERG's estimate of 2.8 g substantially increased the number of tubes used per year, particularly for those with a high skin burden in early stage disease. This estimate increased even more for those with advanced disease who were assumed to have a higher burden of skin disease. The clinical experts explained 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. 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. Increasing the mean daily dose of chlormethine gel to the ERG's preferred 2.8 g substantially increased the cost-effectiveness estimate because chlormethine gel stopped being cost saving while the quality-of-life benefit remained the same. The resulting incremental cost-effectiveness ratio (ICER) was above what NICE considers a cost-effective use of NHS resources (£20,000 to £30,000 per quality-adjusted life year gained). The committee concluded that the average daily dose of chlormethine gel, and therefore the costs, were uncertain.

**The committee would have preferred utility values derived from patient-reported outcomes**

3.10 The company generated utility values from a de novo vignette study and used EQ-5D-5L responses from clinicians, mapped to EQ-5D-3L

and valued using the UK general population time-trade off tariffs. The committee understood that chlormethine gel does not aim to cure, but to relieve the skin symptoms of people and improve quality of life. The committee considered patient-reported outcomes important in assessing quality-of-life benefits. The committee concluded that it would have preferred patient-reported outcomes to responses from clinicians to be used for deriving health state utility values.

### The cost effectiveness estimates are uncertain and depend on the time horizon affecting the duration of subsequent treatment

3.11 The committee recalled that in the company's model people in the 'progressed from 1L' health state of the model had bexarotene or peginterferon alfa and remained on them for the rest of their life (see section 3.7). The committee was not convinced that this assumption reflected clinical practice and these long periods incurring costs added to the uncertainty in the cost-effectiveness estimates. The ERG did scenario analyses with time horizons of 5 years, 10 years and 20 years and found that shorter time horizons were associated with much higher cost-effectiveness estimates. The committee also saw confidential information that included a patient access scheme discount applied to bexarotene. Including this discount in the model resulted in a substantial increase in the ICERs. 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.

## Conclusion

### Chlormethine gel is not recommended for treating MF-CTCL

3.12 The committee acknowledged that there is a clinical need for chlormethine gel as an alternative treatment option and that it may benefit people with MF-CTCL. But the model structure does not reflect the clinical treatment pathway for people with the condition, and its true

clinical effectiveness relative to phototherapy is unknown. 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. There are many uncertainties, including about the assumptions on time to progression to a permanent disease state, and the dosage calculation for chlormethine gel. Because of this high level of uncertainty, the committee was unable to recommend chlormethine gel for treating MF-CTCL.

# 4 Proposed date for review of guidance

4.1 NICE proposes that the guidance on this technology is considered for review by the guidance executive 3 years after publication of the guidance. NICE welcomes comment on this proposed date. The guidance executive will decide whether the technology should be reviewed based on information gathered by NICE, and in consultation with consultees and commentators.

Jane Adam
Chair, appraisal committee
July 2020

# 5 Appraisal committee members and NICE project team

## Appraisal committee members

The 4 technology appraisal committees are standing advisory committees of NICE. This topic was considered by committee A.

Committee members are asked to declare any interests in the technology to be appraised. If it is considered there is a conflict of interest, the member is excluded from participating further in that appraisal.

The minutes of each appraisal committee meeting, which include the names of the members who attended and their declarations of interests, are posted on the NICE website.

## NICE project team

Each technology appraisal is assigned to a team consisting of 1 or more health technology analysts (who act as technical leads for the appraisal), a technical adviser and a project manager.

**Faye Sheldon**
Technical lead

**Yelan Guo**
Technical adviser

**Thomas Feist**
Project manager

ISBN: [to be added at publication]