NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Final appraisal document

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

1 Recommendations

1.1 Chlormethine gel is recommended as an option for treating early stage (stage 1A, 1B, and 2A) mycosis fungoides-type cutaneous T-cell lymphoma (MF-CTCL) in adults, only if the company provides chlormethine gel according to the commercial arrangement (see section 2).

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 early stage MF-CTCL aim to relieve the skin symptoms. Options depend on the extent of the skin affected, but include treatments applied to the skin, such as topical steroids, phototherapy (light therapy) and radiotherapy. Systemic treatment that targets the whole body, such as oral bexarotene, can also be used to relieve skin symptoms if those treatments do not work, no longer work, or become unsuitable.

Clinical evidence shows that chlormethine gel improves skin disease. It may particularly benefit people who have skin disease over a limited area of the body or for whom whole body phototherapy is unsuitable. However, there is no robust

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evidence for its effectiveness compared with other treatments or showing if it is more effective for people with limited skin disease.

Some things are still uncertain, including the true effectiveness of phototherapy, which was used as a comparator in the model, and the average amount of chlormethine gel used per day.

But the cost-effectiveness estimates for chlormethine gel in early stage disease, using the preferred assumptions and the company's updated patient access scheme, are within the range NICE considers cost effective. Therefore, chlormethine gel is recommended in early stage disease.

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).

2.4 The company has a commercial arrangement (simple discount patient access scheme). This makes chlormethine gel available to the NHS with a discount. The size of the discount is commercial in confidence. It is the company's responsibility to let relevant NHS organisations know details of the discount.

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3 Committee discussion

The appraisal committee 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.

Clinical need

There is a clinical need for chlormethine gel as an alternative treatment option for people with MF-CTCL, particularly in people with low skin burden

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. Symptoms include itching, pain and fever, can be

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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. Consultation responses noted that there is no gold standard treatment and that initial treatment depends on various factors including burden or stage of skin disease, availability of therapy, clinician speciality, location and personal experience, and patient preference. The effects of existing skin-directed treatments, including phototherapy and sometimes radiotherapy, are not long lasting and people often cycle between treatments. This means people must travel for repeated hospital appointments and their quality of life may be affected. A new option which could be used at home would be welcomed. People with early disease (which consists of patches or plaques on the skin but no disease elsewhere in the body) have a particular unmet need because existing skin-directed treatments are limited, and systemic treatments are onerous and associated with side effects. Clinical experts noted that they may be offered topical steroids or emollients, but these only relieve the symptoms of itchiness and redness and do not reduce the patches or plaques. The only options for treating the patches are localised radiotherapy, which is not ideal for younger people, and phototherapy. There is a particular disadvantage of phototherapy for people with limited skin disease (disease covering less than 10% of the skin surface), because the whole skin is exposed to the UV radiation, which carries a long-term risk of inducing skin cancer. These people would prefer an effective topical treatment applied only to the disease area. The committee also recognised the need for an alternative treatment option that may be more convenient and could be particularly useful during the COVID-19 pandemic. It concluded that chlormethine gel would be particularly useful for people who have limited skin disease who want to avoid whole body phototherapy, or people for whom phototherapy is not effective or who have exceeded the maximum safe UV exposure for

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phototherapy. It could also be helpful for those who find it difficult to attend hospital for courses of phototherapy.

Treatment pathway

Chlormethine gel relieves skin symptoms but is not a cure

3.2 Clinical experts explained that, in practice, the impact of chlormethine gel would be assessed after the first 4 to 6 months. Treatment would stop if the skin disease resolved because there would be no remaining patches to treat. For people with a partial response, treatment would be expected to stop after a year, although if there was clear benefit it might be continued for longer. People could have further courses of treatment with chlormethine gel, or move onto other skin-directed treatments, such as phototherapy if the chlormethine gel was not effective or the skin disease recurred. Clinical experts also explained that, like the other skin-directed treatments available for MF-CTCL, chlormethine gel is not a cure, and does not affect the spread of the disease to other organs in the body or mortality from the disease. However, if the skin disease cannot be controlled, people are offered systemic therapy even if the disease has not spread to other areas, so effective skin-directed therapies are important because systemic treatments are expensive and toxic. If another skin-directed therapy were available, it could keep the skin disease under control for longer, which could improve the quality of life of patients. The clinical experts explained that there was a previous similar version of this treatment in the form of a nitrogen mustard ointment. The committee understood that people had benefited from treatment with nitrogen mustard, and that up until recently it was still being used in parts of the UK. Therefore clinicians have experience with using similar topical treatments. The clinical experts explained that, although it is uncommon for skin symptoms to completely resolve, therapies can relieve skin symptoms and improve people's quality of life. The committee concluded that chlormethine gel is not a disease-modifying treatment, but it relieves skin symptoms and improves quality of life.

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People with early stage MF-CTCL have multiple treatments

3.3 Clinical experts explained that skin-directed therapy decisions for MF-CTCL are based on the extent of the skin involvement, not just the overall stage of disease. As noted in section 3.1, people with early stage disease and a low skin burden (less than 10%; typically stage 1A but other stages may also have low skin burden) have a particular unmet need because of the disadvantages of whole body phototherapy when the extent of the disease is limited. Clinical experts explained that some people with stage 1B disease may have a skin burden greater than 10% but it still may be relatively limited (around 15% to 17%) so topical treatments may be preferable to whole body treatments. People with early stage disease and more extensive skin burden (a proportion of patients with stage 1B or 2A may also have high skin burden) are usually offered topical treatments, phototherapy or localised radiotherapy. The clinical experts also explained that people with early stage MF-CTCL, whose disease is confined to the skin, cycle through available treatments with periods of active monitoring (watch and wait) between therapies, with the sequence depending on the response in skin symptoms. Because individual treatments are typically not long lasting, multiple courses of treatment are usually necessary, although the number of courses of phototherapy is limited by the cumulative UV dose. It is therefore likely that repeated courses of chlormethine gel would be offered, and in practice phototherapy could be followed by chlormethine gel or vice versa. If the skin disease becomes refractory to skin-directed treatments, or the maximum safe UV exposure has been reached, or if the condition progresses to an advanced stage, systemic therapies such as oral bexarotene and peginterferon alfa are offered. The committee concluded that treatment in clinical practice depends on the level of skin burden and the extent of the underlying disease. But, in practice, people with early MF-CTCL have multiple treatments in different sequences until symptoms no longer respond or the disease spreads beyond the skin.

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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). People with advanced stage disease were not included in the trial. 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 current alternative treatments.

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

3.5 The company compared phototherapy with chlormethine gel in its submission. However, there was no evidence directly comparing chlormethine gel with phototherapy and no connected network for an indirect comparison could be formed. Therefore the company did an unadjusted naive comparison. However, most of the studies available to provide estimates of phototherapy's effectiveness are of low quality and there was considerable debate about the most appropriate source to use.

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The company initially used overall response rates from the weighted average estimates of 7 phototherapy studies. But it then used results from a systematic review on the clinical effectiveness of phototherapies (Phan et al. 2019) identified by the ERG in its base case after technical engagement. The response rates in the 7 studies identified by the company and in the systematic review were higher for phototherapy than the response rates for chlormethine gel in Study 201. Complete skin symptom response was also higher for phototherapy than partial skin symptom response (73.2% and 20.8% respectively, as reported in the 7 phototherapy studies), but the reverse was the case for chlormethine gel (13.8% and 44.6% respectively, 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. Responses to consultation noted that the early studies of chlormethine in ointment form, which are all retrospective studies, had response rates comparable to those from the phototherapy studies. They suggested that the lower response rates in Study 201 may be because many patients (39%) in the trial had already had phototherapy. 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.

Cost effectiveness

Clinical practice is better represented in the company's revised model

3.6 The company updated its model substantially in response to the first consultation, and then again after the second consultation, to better reflect

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the treatment pathway for people with MF-CTCL in clinical practice. After the first consultation, the company introduced a skin-directed therapy state for people whose symptoms were refractory to chlormethine gel or for people whose skin symptoms relapse after responding to treatment. The ERG considered that when people whose condition is refractory to chlormethine gel go to the skin-directed therapy state but people whose condition is refractory to phototherapy go straight to systemic therapy, chlormethine gel has an unfair advantage. In response to the second consultation, the company amended its base case model to reflect the ERG and committee's preferred assumptions. These were that people with disease refractory to chlormethine gel or phototherapy move to systemic treatment but those in the chlormethine arm have 1 course of phototherapy first. The company noted however that, although it had incorporated the committee's preferences into its base case, it did not agree that this better reflects clinical practice. The company considered it an oversimplification because it does not allow for more than 1 course of phototherapy and does not capture the range of responses to phototherapy. The clinical experts consulted by the company had noted that the number of courses of phototherapy may differ depending on the type of phototherapy and duration of response to initial courses of treatment. The company also did not agree with the ERG that delaying transition to the systemic therapy state for people whose condition was refractory to chlormethine gel gave an unfair advantage to chlormethine gel. However, it acknowledged that the health state utility in the skin-directed therapy state might differ for relapsed compared with refractory disease so presented several scenarios with different utilities. The committee concluded that the company's revised model better reflected clinical practice and incorporated the committee's preferred assumptions.

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Models based on skin burden are preferred but the company's updated models for stage 1A and early stage disease are suitable for decision making

3.7 At the second meeting, the committee noted that the company's model, which included early and late-stage disease, resulted in uncertainty in costs. This was because of the variability in costs within the model, with people who have different levels of skin disease using different amounts of gel, and because people at different skin stages may start costly subsequent systemic treatments at different times. The committee had concluded that the company's model did not reflect who may benefit the most from chlormethine gel (people with a low skin burden, see section 3.1). In response to the second appraisal consultation, the company changed its approach, and excluded people with advanced disease (stage 2B and later). Instead, it presented 2 models: one for stage 1A disease and another for early stage disease (stages 1A, 1B, and 2A). The company explained that it was unable to model by skin burden alone because of the way the previous model was developed. The ERG agreed that the company's model was difficult to amend to represent low skin burden because of its structure and the difficulty in populating the required transition probabilities. The ERG noted that a decision based on disease stage is the most robust, given the model structure. The committee considered that a model based on skin burden would be more appropriate but concluded that the company's models based on disease stage were suitable for decision making.

Phototherapy's effectiveness may be overestimated in the model

3.8 The committee noted that the high levels of uncertainty about the true clinical effectiveness of phototherapy (see section 3.5) made the benefits of chlormethine gel compared with phototherapy in the model uncertain. However, the committee concluded at the second meeting that, while it did not consider that any data source was robust, it preferred the ERG's approach of using one data source for all outcome measures because it

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ensured the same consistent source of data for response rates and duration, reducing potential bias. The company preferred Whittaker et al. (2012), which reports lower response rates than Phan et al. and is a controlled, prospective study that used an objective scoring system. The ERG was concerned about the quality of all sources of data for the effectiveness of phototherapy. It was particularly concerned about the company's use of Whittaker et al. (2012) because it had a small sample size and excluded people with stage 1A disease. The ERG preferred to use Phan et al. (2019), despite its limitations (see section 3.5), because of the availability of data for all outcome measures and because it separates outcomes by type of phototherapy and stage of disease. The company considered that the estimates from Phan et al. (2019) overestimate the effectiveness of phototherapy, resulting in a 'worst case' for chlormethine gel. But, in response to consultation, it used Phan et al. (2019) in its base case for complete response, partial response, progressed disease and duration response, as preferred by the committee and ERG. The committee acknowledged the uncertainty around capturing the effectiveness of phototherapy in the model, given the poor data available. It concluded that the true clinical effectiveness of phototherapy was not known and that the parameters used in the model could mean that the model may have overestimated the effectiveness of phototherapy.

The mean daily dose of chlormethine gel is uncertain

3.9 The clinical experts explained that the amount of gel used depends on skin burden, not disease stage. The committee noted that the population included in the trial had mixed skin burdens, which made it difficult to accurately estimate gel usage. 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 original model. It sourced this information from the summary of product characteristics for Valchlor (the US brand name of chlormethine gel) from Study 201. The company used a lower mean daily dose in its original model, which was taken from individual patient data based on the number of returned empty tubes per follow-up

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visit from Study 201. The clinical experts estimated that people with limited disease need at least 6 tubes a year (1 every 2 months) because of the shelf-life of the product. But they said it was not uncommon for people to use 1 tube every month with a mean daily dose of approximately 1 g, up to 2 g. They added that usage was difficult to predict and relates to the body surface area affected. However, it was unlikely that people with more extensive skin burden (needing more than 2 tubes a month) would want to take the time to put this on their whole body. They may use it for exposed areas like the hands and face, which could have a big impact on their quality of life. In the company's revised models, the company used the ERG's estimate of 2.8 g but noted that it was likely to be a substantial overestimate of gel used. The committee concluded that the average daily dose of chlormethine gel, and therefore the costs, were uncertain but preferred the ERG's estimate of 2.8 g.

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 early stage disease model is most appropriate to decision making

3.11 The company's stage 1A model represents a population with low skin burden but excludes a proportion of people who have stage 2A disease with low skin burden. The company's early stage model represents both low and high skin burden. The ERG noted that, while the early stage model applies to people with both low and high skin burden, the combined

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state of stage 1B/2A assumes that all have high skin burden. The company considered the early stage model to be conservative because it includes people with a higher skin burden who would use more gel and therefore have higher costs. The ERG noted that, because the differential treatment effect of low compared with high skin burden is unknown, it is not clear if the early stage model is conservative. The company explained that it preferred the early stage model over the stage 1A model because it includes people with low skin burden in stages other than stage 1A and because skin burden is not the only factor influencing disease stage. The ERG noted that there was no evidence to suggest that the results from the stage 1A model could be applied to low skin burden in other stages. Clinical experts noted that there are difficulties with accurately staging disease, particularly in differentiating between stage 1A and stage 1B. The committee noted that the evidence base for this disease was poor and that splitting the data down into substages within early stage disease increases the uncertainty in the modelling. The committee also considered the difficulties in differentiating between stages and the difficulty there would be in implementing a recommendation only for stage 1A. It concluded that the early stage disease model was most appropriate for decision-making.

Cost-effectiveness estimates and conclusion

Chlormethine gel is cost effective for early stage MF-CTCL and therefore recommended

3.12 There are updated patient access schemes for chlormethine gel (agreed in response to the second consultation) and a patient access scheme for the subsequent treatment, bexarotene. Therefore all costs and incremental cost-effectiveness ratios (ICERS) are confidential and cannot be presented. The cost-effectiveness estimates for early stage disease are uncertain but below what NICE normally considers an acceptable use of NHS resources. The committee was aware of the uncertainty associated with the effectiveness estimates of phototherapy and dosage

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used. However, it agreed that the most plausible ICER is unlikely to be above what NICE normally considers an acceptable use of NHS resources. It therefore recommended chlormethine gel as an option for treating adults with early stage (stage 1A, 1B, and 2A) MF-CTCL.

4 Implementation

4.1 Section 7 of the National Institute for Health and Care Excellence (Constitution and Functions) and the Health and Social Care Information Centre (Functions) Regulations 2013 requires clinical commissioning groups, NHS England and, with respect to their public health functions, local authorities to comply with the recommendations in this appraisal within 3 months of its date of publication.

4.2 The Welsh ministers have issued directions to the NHS in Wales on implementing NICE technology appraisal guidance. When a NICE technology appraisal recommends the use of a drug or treatment, or other technology, the NHS in Wales must usually provide funding and resources for it within 2 months of the first publication of the final appraisal document.

4.3 When NICE recommends a treatment 'as an option', the NHS must make sure it is available within the period set out in the paragraphs above. This means that, if a patient has early stage mycosis fungoides-type cutaneous T-cell lymphoma and the doctor responsible for their care thinks that chlormethine gel is the right treatment, it should be available for use, in line with NICE's recommendations.

5 Review of guidance

5.1 The guidance on this technology will be considered for review 3 years after publication. The guidance executive will decide whether the technology should be reviewed based on information gathered by NICE, and in consultation with consultees and commentators.

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Jane Adam
Chair, appraisal committee
August 2021

6 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.

Heather Stegenga and Faye Sheldon
Technical leads

Joanna Richardson and Yelan Guo
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