

chlormethine hydrochloride 160 micrograms/g gel (Ledaga®)

Recordati Rare Diseases UK Ltd

9 April 2021

The Scottish Medicines Consortium (SMC) has completed its assessment of the above product and advises NHS Boards and Area Drug and Therapeutic Committees (ADTCs) on its use in NHSScotland. The advice is summarised as follows:

ADVICE: following a full submission under the orphan medicine process

chlormethine hydrochloride (Ledaga®) is accepted for use within NHSScotland.

Indication under review: for the topical treatment of mycosis fungoides-type cutaneous T-cell lymphoma (MF-type CTCL) in adult patients.

In a single-blind, randomised, phase II study, chlormethine gel was non-inferior to a compounded chlormethine ointment based on $\geq 50\%$ improvement in Composite Assessment of Index Lesion Severity (CAILS) score confirmed after 4 weeks.

This advice applies only in the context of an approved NHSScotland Patient Access Scheme (PAS) arrangement delivering the cost-effectiveness results upon which the decision was based, or a PAS / list price that is equivalent or lower.

This advice takes account of the views from a Patient and Clinician Engagement (PACE) meeting.

Chairman
Scottish Medicines Consortium

Indication

For the topical treatment of mycosis fungoides-type cutaneous T-cell lymphoma (MF-type CTCL) in adult patients.¹

Dosing Information

A thin film of chlormethine gel should be applied once daily to the affected areas of skin.

Treatment with chlormethine gel should be stopped for any grade of skin ulceration or blistering, or moderately severe or severe dermatitis (e.g. marked skin redness with oedema). Upon improvement, treatment can be restarted at a reduced frequency of once every 3 days. If reintroduction of treatment is tolerated for at least 1 week, the frequency of application can be increased to every other day for at least 1 week and then to once-daily application if tolerated.

The summary of product characteristics (SPC) gives instructions for patients and caregivers when applying chlormethine gel. Refer to the SPC for details.

Treatment with chlormethine gel should be initiated by an appropriately experienced physician.¹

Product availability date

May 2020

Chlormethine gel was granted EU orphan designation (EU/3/12/963) on 22 May 2012 for the treatment of cutaneous T-cell lymphoma and this was maintained at the time of marketing authorisation.²

Chlormethine gel meets SMC orphan criteria.

Summary of evidence on comparative efficacy

Chlormethine, also known as nitrogen mustard or mechlorethamine, is an alkylating chemotherapy agent which has antineoplastic and immunosuppressive properties and has been used clinically for many decades. This gel formulation is the first topical medicine to be granted a marketing authorisation for the treatment of mycosis fungoides cutaneous T-cell lymphoma (MF-CTCL) in adult patients.^{1,3}

The key evidence to support chlormethine gel in MF-CTCL comes from a multicentre, randomised, observer-blinded, phase II study (Study 201) which evaluated the non-inferiority of chlormethine 0.02% gel compared with a compounded chlormethine 0.02% ointment. Enrolled patients (n=260) had a diagnosis of stage IA, IB or IIA MF-CTCL confirmed by skin biopsy and had been previously treated with at least one skin-directed therapy for MF-CTCL, including topical corticosteroids, psoralen and ultraviolet A (PUVA) or ultraviolet B (UVB). They could not have received any

previous treatment with carmustine, previous treatment with chlormethine in the preceding 2 years, radiation therapy in the preceding year or topical or systemic therapies including corticosteroids in the preceding 4 weeks. They were randomised equally to receive chlormethine 0.02% gel (n=130) or chlormethine 0.02% ointment compounded in Aquaphor (n=130) applied once daily and continued for up to 12 months. The treatment area was decided by the investigator but, in general, patients with stage IA disease applied study treatment to all affected lesions and patients with stage IB or IIA disease or those with new developing lesions meeting the criteria for progressive disease (that is $\geq 25\%$ worsening), to the whole body with the exception of around the mouth and mucous membranes. The frequency of administration could be reduced to manage grade 3 or 4 skin toxicity or irritation. Concomitant therapy with topical or systemic corticosteroids was prohibited (with the exception of topical corticosteroids [up to 1% strength only] allowed only on non-MF lesions). Randomisation was stratified according to disease stage (IA versus IB/IIA).^{3, 4}

The primary outcome was response rate (complete and partial response) according to the Composite Assessment of Index Lesion Severity (CAILS) score and confirmed after 4 weeks. A complete response was 100% reduction from baseline to a CAILS score of 0 and a partial response was $\geq 50\%$ to $< 100\%$ reduction. The CAILS score was calculated by summing the scores of up to five index lesions at baseline and throughout the study for severity of scaling (0 to 8), erythema (0 to 8), plaque elevation (0 to 3), and surface area (0 to 18) (range: 0 to 185). The CAILS response rate was assessed in the intention to treat (ITT, n=260) and efficacy evaluable (n=185) populations and non-inferiority was considered demonstrated if the lower bound of the 95% confidence interval for the ratio of response rate between treatments was ≥ 0.75 . In each population, non-inferiority was demonstrated as detailed in table 1. A major protocol violation at one study centre meant that 18 patients were incorrectly assigned to treatment based on their stage of disease. An analysis was performed in the ITT population with patients from this site excluded (n=242) which confirmed the results.³

The key secondary outcome was the modified Severity Weighted Assessment Tool (mSWAT) response rate defined as $\geq 50\%$ improvement in the baseline SWAT score on at least two consecutive assessments over at least 4 weeks. The mSWAT was calculated by measuring each lesion as a percentage of total body surface area (BSA) and multiplying it by a severity-weighting factor of 1 for patch, 2 for plaque or 4 for tumour and summing the results for all lesions (range 0 to 300). Non-inferiority of chlormethine gel to chlormethine ointment was demonstrated in each population; see table 1.

Table 1: Results for the primary outcome and selected secondary outcomes in Study 201^{1, 3, 4}

	Chlormethine gel	Chlormethine ointment	Ratio (95% CI)
Primary outcome: confirmed CAILS response rate % (n/N)			
ITT population (n=260)	58% (76/130)	48% (62/130)	1.23 (0.97 to 1.55)
Efficacy evaluable population (n=185)	77% (69/90)	59% (56/95)	1.30 (1.06 to 1.61)
Key secondary outcome: confirmed mSWAT response rate % (n/N)			
ITT population (n=260)	47% (61/130)	46% (60/130)	1.02 (0.78 to 1.32)
Efficacy evaluable population (n=185)	63% (57/90)	56% (53/95)	1.14 (0.89 to 1.45)
Other secondary outcomes			
Time to confirmed 50% CAILs response (ITT population)	26 weeks	42 weeks	
Percentage BSA response rate (ITT population)	45% (58/130)	43% (56/130)	1.04 (0.79 to 1.37)

ITT=intention-to-treat; CI=confidence interval; CAILS=composite assessment of index lesion severity; mSWAT=modified Severity Weighted Assessment Tool; BSA= body surface area

A complete CAILS response was achieved by 14% and 12% respectively of the ITT population and 19% and 15% respectively of the efficacy evaluable population. While a complete mSWAT response was achieved by 6.9% and 3.1% of the ITT population and by 8.9% and 4.2% of the efficacy evaluable population respectively.^{3, 4}

Other secondary endpoints also supported the non-inferiority of chlormethine gel to chlormethine ointment; see table 1. The duration of CAILS response (defined as time from the first appearance of the response to loss of response) was assessed in the 76 patients treated with chlormethine gel and 62 patients treated with chlormethine ointment who had achieved a response and found similar durations in both groups.^{3, 4}

Patients who had completed up to 12 months of study treatment in Study 201 and had not achieved a complete response could enter an open-label, 7-month extension study (Study 202). However this assessed the efficacy and safety of a higher strength of chlormethine gel (0.04%) and is not relevant to this submission.³

The submitting company presented a naïve indirect comparison of chlormethine gel with phototherapy for the treatment of patients with MF-CTCL. The indirect comparison included two sources: Study 201, described above, and a published systematic review and meta-analysis of phototherapy. Results of the naïve indirect comparison were not provided but the mSWAT response rates from Study 201 and undefined response rates from the meta-analysis were used within the economic case.^{4, 5}

Summary of evidence on comparative safety

In Study 201, the median duration of treatment in the chlormethine gel group was 51.7 weeks and in the chlormethine ointment group was 52 weeks and patients were followed up for a further 12 months for safety. The mean daily use of chlormethine gel was 2.8g, the median daily use was 1.8g and the maximum individual daily use was 10.5 g.^{1, 3}

Any treatment-emergent adverse event was reported by 84% (108/128) of patients in the chlormethine gel group and 91% (115/127) in the chlormethine ointment group and these were considered treatment-related in 62% and 50% respectively. In the chlormethine gel and chlormethine ointment groups respectively, patients with a reported serious adverse event were 11% versus 8.7%, patients with any dose frequency reduction due to treatment emergent adverse events were 23% versus 12%, patients with an adverse event that led to dose interruptions were 34% versus 20% and patients discontinuing therapy due to an adverse event was 20% versus 17%.³

The most frequently reported treatment-emergent adverse events of any grade in the chlormethine gel group versus the chlormethine ointment group were associated with the skin; specifically dermatitis (55% and 57%), pruritus (20% and 17%), skin infections (12% and 11%), skin hyperpigmentation (5.5% and 7.1%), skin ulceration or blistering (6.3% and 3.9%) and actinic keratosis (3.9% and 1.6%). There was a higher incidence of moderate to moderately severe dermal irritation in the chlormethine gel compared with ointment group. Other reported adverse events included: upper respiratory tract infection (8.6% and 7.9%), nasopharyngitis (0.8% and 4.7%), fatigue (2.3% and 4.7%), sinusitis (4.7% and 2.4%), nausea (4.7% and 2.4%).³

Given the known mechanism of action of chlormethine, as an alkylating agent, patients were monitored for developing secondary non-melanoma skin cancers during Study 201 and its 12-month follow-up period. A total of 11 patients (three in the chlormethine gel and eight in the chlormethine ointment group) were found to have 20 non-melanoma skin cancers including 10 basal cell carcinomas (five in treatment areas), nine squamous cell carcinomas (one in treatment areas) and one Merkel cell carcinoma.⁴ None of these cases were considered to be related to chlormethine treatment but since skin directed therapy for MF-CTCL has been associated with secondary skin cancers, the SPC recommends that chlormethine-treated patients should be monitored.

Cutaneous hypersensitivity reactions were reported in 2.3% of patients in the chlormethine gel group and 1.6% of patients in the chlormethine ointment group and all were considered related or possibly related to study treatment and led to discontinuation in Study 201.³

The European Medicines Agency noted that the safety and tolerability of topical chlormethine are well known and that no new concerns were raised from Study 201. The safety profile was considered well tolerated and manageable.³

Summary of clinical effectiveness issues

Cutaneous T-cell lymphomas (CTCL) are a heterogeneous group of lymphoproliferative diseases characterised by infiltration of the skin by malignant T-cells. CTCL is a rare type of tumour with an estimated prevalence of 2.7 cases per 10,000. Mycosis fungoides (MF) is an epidermotropic form of CTCL and is the most common subtype accounting for 60% of new CTCL cases. The prognosis varies with stage of the disease and median overall survival for patients with early stage disease (stage IA, IB and IIA) is reported as 35.5, 21.5 and 15.8 years, respectively. When MF-type CTCL is more advanced and not limited to the skin (stages IIB to IV), median survival is shorter and has been reported as 4.7 years for stages IIB and IIIA and 3.4 years for stage IIIB. Treatment is guided by the stage of the disease and ranges from skin directed therapies (including topical agents, phototherapy and radiotherapy) for early-disease (stage IA to IIA) to systemic treatments (including biologics, chemotherapy and stem cell transplantation) for more advanced disease, which may be combined with skin directed therapy. Therapeutic options for topical agents include topical corticosteroids or topical chemotherapy with chlormethine or carmustine (BCNU). Topical chlormethine was only available when prepared by specialist pharmacy departments. Chlormethine gel is the first topical medicine to be granted a marketing authorisation for the treatment of MF-CTCL in adult patients.^{1-3, 6} Clinical experts consulted by SMC considered that chlormethine gel fills an unmet need offering a licensed topical treatment for these patients. Chlormethine gel meets SMC orphan criteria.

Although topical chlormethine has been used for many decades and is recommended in clinical guidelines, there is limited prospective, controlled evidence. The key direct evidence from Study 201 has demonstrated that chlormethine gel was non-inferior to compounded chlormethine ointment in terms of CAILS response rate. The European Medicines Agency considered this an acceptable primary outcome. However, it is limited to the assessment of up to five lesions identified at the beginning and monitored throughout the study. The results were supported by the key secondary outcome, mSWAT response rate, which also assessed the affected BSA to capture the severity and extent of disease. These and other secondary outcomes supported non-inferiority.^{3, 4}

Study 201 had a number of limitations including its phase II, single-blinded design. There was a major protocol violation due to a randomisation problem at one centre, but analysis of outcomes excluding the affected patients found consistent results. The controlled study period was 12 months and there are no controlled data to support longer term treatment or retreatment after an initial course. Study 201 was performed in the United States and results may not be completely generalisable to the Scottish population.^{3, 4}

The study population was narrower than the licensed indication. Study patients were required to have early disease (stages IA to IIA) and patients with more advanced disease were excluded but the marketing authorisation does not restrict use by disease stage. There are, therefore, no controlled data on the use of chlormethine gel in patients with more advanced disease. However,

the EMA noted that relevant differences were not expected and considered that the safety and efficacy of chlormethine was established for treatment of patients at any stage of the disease. The submitting company has provided some limited real-world data to support use in these patients. The quantity of gel applied during the study was low (mean 2.8g/day) and may not reflect the amounts required by patients in practice with varying extents of cutaneous disease.

The company suggests that chlormethine gel is expected to be used as a treatment option from the point of diagnosis of MF-CTCL, at which point, patients would likely have already received prior treatment with topical corticosteroids. In Study 201 patients were required to have received at least one previous treatment. Most study patients had received previous topical corticosteroids (87%) but 40% had received phototherapy and 18% had received oral or topical bexarotene. Notably, 12% of patients in the chlormethine gel group and 10% of patients in the chlormethine ointment group had received previous topical chlormethine >2 years before study entry. A minority of patients in each group had also received interferon, methotrexate or radiation therapy. These factors may affect the generalisability of the study results to the first-line treatment of eligible patients in clinical practice.

During the study, patients were only allowed to use low potency topical corticosteroid on non-MF lesions. In addition, there are no controlled data to support the use of chlormethine gel when used in combination with systemic treatments. These factors may affect the generalisability of the study results to patients eligible for treatment in clinical practice.^{1, 3, 4}

The chlormethine ointment used as a control in Study 201 is no longer used in practice and there are no direct comparative data versus a relevant comparator. Due to a lack of available evidence to perform a more robust comparison, the submitting company presented a naïve indirect comparison with phototherapy.^{4, 5} Relative results were not presented but the company stated that the response rates were used to calculate transition probabilities for use in the economic model. There are limitations with this indirect comparison including the naïve methods, the study selection process, the quality and heterogeneity of the studies included in the meta-analysis of phototherapy and the lack of a definition of response making the appropriateness of comparison of outcomes between the sources unclear. Response rates were lower with chlormethine gel than with phototherapy. Both Study 201 and the meta-analysis of phototherapy included patients with early stage disease and these results may not be generalisable to patients with more advanced stage disease. The submitting company concluded that the results of the indirect comparison are uncertain due to the naïve methods but can be considered a conservative approach. Given the limitations outlined, the results of the naïve indirect comparison with phototherapy are highly uncertain.

The introduction of chlormethine gel would offer patients with MF-CTCL a licensed topical option as a skin directed therapy. This would provide a manufactured formulation giving patients the option of a local therapy which could be used at home. This may offer advantages to the patient and service over phototherapy sessions at treatment centres. Clinical experts consulted by SMC

considered that chlormethine gel is a therapeutic advancement offering an additional treatment option for these patients.

Patient and clinician engagement (PACE)

A patient and clinician engagement (PACE) meeting with patient group representatives and clinical specialists was held to consider the added value of **chlormethine hydrochloride**, as an **orphan medicine**, in the context of treatments currently available in NHSScotland.

The key points expressed by the group were:

- MF-type CTCL is a rare, chronic and often incurable cancer associated with distressing symptoms that includes skin lesions, pain and itching, which often lead to sleep disturbance. This condition has substantial physical, functional, psychological and social impact for the patients and their carers.
- The few available treatments for MF-type CTCL may improve symptoms only for a short period of time. These include topical corticosteroids that can lead to significant side effects if used over prolonged periods, and phototherapy that requires frequent hospital attendance and may have variable accessibility around Scotland. There is a high unmet need for patients with MF-type CTCL, namely for an effective and convenient topical therapy.
- Chlormethine gel has been shown to effectively reduce symptoms, and this may lead to improvements in patients' quality of life. It is expected that this would be the case irrespectively of the disease stage. Chlormethine gel may also help delay the need for systemic treatment and the potential associated toxicities, this would be valued by patients.
- Chlormethine gel would offer an additional accessible and convenient topical treatment. It can be administered at home, with no need for additional hospital appointments, and has the potential to reduce the impact of treatment on patients and their carers.
- The service implications and side-effects burden associated with chlormethine gel use are expected to be low.

Additional Patient and Carer Involvement

We received a patient group submission from Lymphoma Action, which is a registered charity. Lymphoma Action has received 12.7% pharmaceutical company funding in the past two years, including from submitting company. A representative from the organisation participated in the PACE meeting. The key points of their submission have been included in the full PACE statement considered by SMC.

Summary of comparative health economic evidence

The company submitted a cost-utility analysis comparing chlormethine gel versus phototherapy for the topical treatment of MF-CTCL in adult patients. The base case analysis was provided for the licensed population and a lifetime time horizon was used.

A cost-effectiveness model comprising of a state-transition Markov model was used to evaluate the cost-effectiveness of chlormethine gel versus phototherapy in adult patients across all disease stages of MF-CTCL. Patients entering the model were defined as either low or high skin burden within each of the three disease stages (stage IA, stage IB/IIA or stage IIB+) and experience different degrees of response to treatment (complete- CR or partial- PR), including relapse of skin lesions or no change. Patients experiencing a CR transition to 'no skin burden' from where they could relapse and transition to the skin direct therapy (SDT) health state after waiting for 8 months in the 'watch and wait' state. However, patients experiencing a PR transition to 'reduced skin burden' health state from where they could either transition to SDT if their disease progresses (PD) or transition to 'no skin burden' if they achieve a CR. Patients who show no response to treatment (no CR or PR, but PD) in the chlormethine gel arm transition to the SDT health state. Those experiencing PD following phototherapy transition to the systemic therapy health state. All patients in SDT either transition to systemic therapy if their disease progresses or move to 'no skin burden' or 'reduced skin burden' if they achieve a CR or PR respectively. Throughout the model time horizon, patients continue to transition between these subsequent health states while also gradually transitioning into the next disease stages in a sequential manner. A cycle length of 1 month is used for the Markov model, whereas patients are assessed for progression of skin burden on chlormethine gel at 6 months, and on phototherapy at 3 months.

There was no direct clinical evidence available for chlormethine versus phototherapy as described above. Furthermore, external literature sources or clinical expert opinion were used where there was paucity of data or the evidence was not reflective of current practice in the UK. In the model, all efficacy estimates and time to response data from Study 201 were utilised to generate transition probabilities (TPs) between various health states of varying degree of skin burden (low or high), but also between disease stages (IA-IV). The TPs between health states for advanced stage disease patients (IIB- IV) were assumed to be the same as stage IA and stage IB/IIA for low skin and high skin burden groups respectively in the absence of alternative data. Lastly, for both arms, the TPs between disease stages and the disease-specific mortality were derived from a separate published study.⁷

Health-related quality of life (HRQoL) data were not collected in Study 201 and given MF-CTCL is a rare disease, no relevant utilities for health states based on skin burden were identified. Hence, a vignette study was conducted to derive utility values associated with the health states. To this end, 12 distinct vignettes were prepared to describe typical patients in different disease stages with varying levels of skin burden, covering the range of health states used in the cost-effectiveness model. HRQoL data were obtained through an indirect elicitation method using

proxy-reporting via clinicians using proxy version 2 of the EQ-5D-5L questionnaire. Baseline utility values for each initial health state were determined using baseline mean mSWAT scores obtained from the PROCLIP registry with standard deviations available from Study 201.⁸ As for utility loss due to adverse events, the disutility for contact dermatitis, erythema and skin irritation was assumed to be based on the disutility for rash reported in a published study.⁹

Acquisition, administration and resource use costs for chlormethine and phototherapy were included in the analysis. Likewise, the cost of subsequent treatments once patients transitioned into the systemic therapy health state and any background treatments for patients on advanced disease stage irrespective of skin burden were included. Additionally, costs associated with treating adverse events and end-of-life care costs were also included in the base case analysis.

A Patient Access Scheme (PAS) was proposed by the submitting company and accepted by the patient access scheme assessment group (PASAG) as acceptable for implementation in NHSScotland. Under the PAS, a simple discount is offered on the list price of the medicine. The base case analysis presented by the submitting company estimated that chlormethine gel was dominant (i.e. cost saving and more effective than phototherapy) with the PAS.

The company provided deterministic sensitivity analysis, scenario analysis and probabilistic sensitivity analysis. Results showed the base case result to be robust to exploration of model parameter and structural uncertainty, and the adoption of alternative assumptions. However, the additional scenario analyses requested showed how cost-effectiveness of chlormethine decreased as the severity of disease increased. The scenario analyses also showed that chlormethine is less cost-effective in advanced stage disease patients. As for the early stage disease patients involving stage IB/IIA, the likelihood of chlormethine being cost effective would depend on how well all the other assumptions made in the model hold true. Selected results from the scenario analyses are presented in tables 1-4 below.

Table 1: Full population (includes all stages) analyses

	Scenario	ICER (£/QALY)	NMB
1	Base case	Chlormethine dominant	£54,446
2	Time horizon: 5 years	193,765	-£997
3	Time horizon: 10 years	Chlormethine dominant	£16,866
4	Chlormethine gel dosing from Valchor [®] SmPC	Chlormethine dominant	£40,308

Abbreviations: ICER: incremental cost-effectiveness ratio; NMB: net monetary benefit; PAS: patient access scheme; QALYs: quality-adjusted life years.

Table 2: Early disease stage population (includes stage IA, IB, IIA) analyses

	Scenario	ICER (£/QALY)	NMB
1	Base case	Chlormethine dominant	£66,098
2	Time horizon: 5 years	Chlormethine dominant	£958
3	Time horizon: 10 years	Chlormethine dominant	£20,620
4	Chlormethine gel dosing from Valchor® SmPC	Chlormethine dominant	£50,483

Abbreviations: ICER: incremental cost-effectiveness ratio; NMB: net monetary benefit; PAS: patient access scheme; QALYs: quality-adjusted life years.

Table 3: Only disease stage IB and IIA population analyses

	Scenario	ICER (£/QALY)	NMB
1	Base case	Chlormethine dominant	£65,212
2	Time horizon: 5 years	125,986	-£5,196
3	Time horizon: 10 years	Chlormethine dominant	£16,644
4	Chlormethine gel dosing from Valchor® SmPC	Chlormethine dominant	£46,202

Abbreviations: ICER: incremental cost-effectiveness ratio; NMB: net monetary benefit; PAS: patient access scheme; QALYs: quality-adjusted life years.

Table 4: Advanced disease stage population (only stage IIB+) analyses

	Scenario	ICER (£/QALY)	NMB
1	Base case	Chlormethine dominant	£8,851
2	Time horizon: 5 years	2,078,502	-£8,215
3	Time horizon: 10 years	14,203	£2,452
4	Chlormethine gel dosing from Valchor® SmPC	27,929	£489
5	Duration of Watch and Wait: 12 months	3,415	£6,097
6	Alternative phototherapy proportions scenario (PUVA: 60.7%, UVB: 39.3%)	10,950	£3,612

Abbreviations: ICER: incremental cost-effectiveness ratio; NMB: net monetary benefit; PAS: patient access scheme; QALYs: quality-adjusted life years.

Weaknesses in the economic analysis were as follows:

- There is high uncertainty due to the analysis relying on a naïve indirect comparison. Due to this, the relative effectiveness of chlormethine versus phototherapy is unknown across disease stages irrespective of skin burden or for different degrees of skin burden irrespective of the disease stage.
- The cost-effectiveness for chlormethine has been evaluated using a wider patient population than the one used in study 201 where patients in advanced disease stages (IIB+) were not included. This means that QALYs and treatment costs could differ considerably in the real world, which makes the cost-effectiveness estimates quite uncertain.
- The transition probabilities derived from efficacy sources for both chlormethine and

phototherapy included only early stage (IA, IB, IIA) disease patients and so their applicability to advanced stage (IIB+) disease patients is uncertain. The justification that skin burden is independent of disease stages does reduce this uncertainty to some extent; however, the issue of patient compliance with treatment due to change in circumstances given other disease complications, or how systemic therapy in general may confound the SDT efficacy, have not been addressed.

- Relative effectiveness of chlormethine versus phototherapy on repeated use has been assumed to be similar to initial efficacy estimates. This may be unlikely, especially in the case of high skin burden patients and may bias the results in favour of chlormethine.
- A linear chronological flow was assumed for disease stage progression, that is, all stage IA patients would progress to stage IB/IIA and all stage IB/IIA patients would progress to stage IIB+. This might not be the case in the real world since some patients could move to the advanced stages rather rapidly which would have a knock on effect on their QALYs and cost of treatment leading to further uncertainty in the model.
- Baseline QALYs and gain in QALYs associated with different health states entirely relies on the vignette study conducted by the company and it is not possible to compare these with any external literature source. This can potentially lead to considerable uncertainty in the base case results.
- Due to the inflexibility of the model structure, a few requested scenario and sensitivity analyses could not be undertaken. This limited the interpretation of the findings of the analysis, especially in the case of advanced disease stage patients or those who have high skin burden in the model.

The Committee considered the benefits of chlormethine gel in the context of the SMC decision modifiers that can be applied when encountering high cost-effectiveness ratios and agreed that as chlormethine gel is an orphan medicine, SMC can accept greater uncertainty in the economic case.

After considering all the available evidence and the output from the PACE process, the Committee accepted chlormethine gel for use in NHSScotland.

Additional information: guidelines and protocols

The British Association of Dermatologists and the UK Cutaneous group published guidelines on the management of primary cutaneous lymphomas in September 2018.⁶ This guideline makes the following recommendation for MF-type CTCL:

- Treatment aims are to control disease and symptoms with the minimum of interventions.
- For stage IA to IIA mycosis fungoides skin directed therapy, including topical nitrogen mustard (chlormethine), phototherapy and local radiotherapy are the standard of care. Total skin electron beam radiotherapy (TSEB) and biologic therapy are options for refractory disease. There is no evidence to support the use of maintenance phototherapy. SDTs are recommended as ‘first-line’ treatment options for all disease stages.
- Patients with stage IIB mycosis fungoides can have an unpredictable clinical course: some

patients develop only small and infrequent skin tumours and often obtain durable responses to localized radiotherapy and other SDT options for persistent patches and plaques; other patients develop extensive bulky skin tumours and rapidly progressive disease requiring TSEB and systemic chemotherapy.

- Following treatment, patients with advanced mycosis fungoides may develop recurrent, low-grade disease where SDT is a treatment option.
- Patients with erythrodermic mycosis fungoides (stage III) and Sézary Syndrome (stage IVA1) often require single or combination systemic therapies such as methotrexate, photopheresis, bexarotene and interferon-alpha as first-line treatment.
- For stage IVA2–B mycosis fungoides / Sézary Syndrome, radiotherapy (including TSEB) for selected stage IV patients) and single-agent chemotherapy regimens are the preferred option, but response duration is often short.
- Brentuximab offers an effective option for refractory stage IB disease and advanced stages of mycosis fungoides/ Sézary Syndrome with tumour CD30 expression.
- All patients with early refractory or advanced mycosis fungoides / Sézary Syndrome should be offered participation in clinical trials.
- Reduced-intensity allogeneic HSCT should be considered for selected groups of patients with advanced mycosis fungoides / Sézary Syndrome to consolidate treatment responses.
- Treatment for CD30+ primary cutaneous anaplastic large cell lymphoma (ALCL) consists of surgical excision and/or radiotherapy for localized disease.
- Combination chemotherapy or brentuximab may be appropriate for patients with CD30+ primary cutaneous ALCL with extensive cutaneous disease or those with systemic progression.

The European Society for Medical Oncology (ESMO) published “Primary cutaneous lymphomas: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up” in 2018.¹⁰ This guideline makes the following recommendations for patients with MF-CTCL:

- patients with early-stage disease (stage IA–IIA) should be treated with skin-directed therapies including topical steroids, PUVA, narrow-band-UVB or mechlorethamine (chlormethine). Narrow-band-UVB can be used in patients with patches or very thin plaques. In patients with thicker plaques, PUVA therapy is preferred.
- in patients developing one or few infiltrated plaques or tumours (stage IIB), additional low-dose local radiotherapy may suffice; local radiotherapy can be curative in patients with unilesional MF and pagetoid reticulosis.
- For patients with more extensive infiltrated plaques and tumours or patients refractory to skin-directed therapies, a combination of PUVA and interferon-alfa or PUVA and retinoids (including bexarotene), a combination of interferon-alfa and retinoids or TSEBT can be considered.
- In patients with advanced and refractory disease, gemcitabine or liposomal doxorubicin may be considered, but responses are generally short-lived.
- Multi-agent chemotherapy is only indicated in MF patients with effaced lymph nodes or visceral involvement (stage IV), or in patients with widespread tumour stage MF, which cannot be controlled with skin-targeted and immunomodulating therapies or who failed

single-agent chemotherapy.

- Local palliation of cutaneous and as well as extracutaneous lesions may be achieved with local radiotherapy.
- In relatively young patients with refractory, progressive MF alloSCT should be considered. The optimal conditioning regimen and timing for an allogeneic transplant are currently unknown.

The European Organisation for Research and Treatment of Cancer (EORTC) published updated consensus recommendations for the treatment of mycosis fungoides/Se´zary syndrome in 2017.¹¹ The recommendations are similar and in general recommend that patients with early stage disease should primarily be treated with skin directed therapy (including topical corticosteroids, UVB, PUVA, local radiotherapy, and topical mechlorethamine [chlormethine]) and on relapse to the skin receive further courses of the same or another skin directed therapy. Systemic therapy should be mainly considered for patients with advanced stages and for refractory cutaneous disease and includes retinoids, interferon-alfa, TSEB, low-dose methotrexate and chemotherapy. Ideally, patients with advance-stage disease should have the option to enter multicentre clinical trials.

Additional information: comparators

Other skin directed therapy, including topical corticosteroids, phototherapy and radiotherapy.

Additional information: list price of medicine under review

Medicine	Dose Regimen	Cost per year (£)
Chlormethine 0.02% gel	A thin film applied once daily	17,000

Costs from BNF online on 7 December 2020. The cost will vary depending on the size of the affected area and the duration of treatment. In Study 201, patients used a mean amount of 2.8g gel per day which equates to 1,019g per year at a cost of £17,000. Costs do not take patient access schemes into consideration.

Additional information: budget impact

The estimated number of patients eligible for treatment was 336 in year 1 increasing to 352 in year 5. Treatment uptake was estimated at 5% in year 1 (17 patients) rising to 15% in year 5 (53 patients).

SMC is unable to publish the with PAS budget impact due to commercial in confidence issues. A budget impact template is provided in confidence to NHS health boards to enable them to estimate the predicted budget with the PAS.

*Other data were also assessed but remain confidential.**

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This assessment is based on data submitted by the applicant company up to and including 19 February 2021.

**Agreement between the Association of the British Pharmaceutical Industry (ABPI) and the SMC on guidelines for the release of company data into the public domain during a health technology appraisal: http://www.scottishmedicines.org.uk/About_SMC/Policy*

Medicine prices are those available at the time the papers were issued to SMC for consideration. SMC is aware that for some hospital-only products national or local contracts may be in place for comparator products that can significantly reduce the acquisition cost to Health Boards. These contract prices are commercial in confidence and cannot be put in the public domain, including via the SMC Detailed Advice Document. Area Drug and Therapeutics Committees and NHS Boards are

therefore asked to consider contract pricing when reviewing advice on medicines accepted by SMC.

Patient access schemes: A patient access scheme is a scheme proposed by a pharmaceutical company in order to improve the cost-effectiveness of a medicine and enable patients to receive access to cost-effective innovative medicines. A Patient Access Scheme Assessment Group (PASAG), established under the auspices of NHS National Services Scotland reviews and advises NHSScotland on the feasibility of proposed schemes for implementation. The PASAG operates separately from SMC in order to maintain the integrity and independence of the assessment process of the SMC. When SMC accepts a medicine for use in NHSScotland on the basis of a patient access scheme that has been considered feasible by PASAG, a set of guidance notes on the operation of the scheme will be circulated to Area Drug and Therapeutics Committees and NHS Boards prior to publication of SMC advice.

Advice context:

No part of this advice may be used without the whole of the advice being quoted in full.

This advice represents the view of the Scottish Medicines Consortium and was arrived at after careful consideration and evaluation of the available evidence. It is provided to inform the considerations of Area Drug & Therapeutics Committees and NHS Boards in Scotland in determining medicines for local use or local formulary inclusion. This advice does not override the individual responsibility of health professionals to make decisions in the exercise of their clinical judgement in the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.