NICE National Institute for Health and Care Excellence

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

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

	Please read the checklist for submitting comments at the end of this form. We cannot accept forms that are not filled in correctly. The Appraisal Committee is interested in receiving comments on the following: • has all of the relevant evidence been taken into account? • are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? • are the provisional recommendations sound and a suitable basis for guidance to the NHS? NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the preliminary recommendations may need changing in order to meet these aims. In particular, please tell us if the preliminary recommendations: • could have a different impact on people protected by the equality legislation than on the wider population, for example by making it more difficult in practice for a specific group to access the technology; • could have any adverse impact on people with a particular disability or disabilities. Please provide any relevant information or data you have regarding such impacts and how they could be avoided or reduced**.**
Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	British Association of Dermatologists (the BAD)
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**None**
Name of commentator person completing form:	Prof Nick Levell on behalf of the BAD's Therapy & Guidelines sub-committee

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

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

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	Dermatol. 2019;155(3):335–341. doi:10.1001/jamadermatol.2018.5204 2. Scarisbrick JJ, Quaglino P, Prince HM, et al. The PROCLIPI international registry of early-stage mycosis fungoides identifies substantial diagnostic delay in most patients. *Br J Dermatol*. 2019;181(2):350-357. doi:10.1111/bjd.17258 3. Lessin SR, Duvic M, Guitart J, et al. Topical chemotherapy in cutaneous T-cell lymphoma: positive results of a randomized, controlled, multicenter trial testing the efficacy and safety of a novel mechlorethamine, 0.02%, gel in mycosis fungoides. *JAMA Dermatol*. 2013;149(1):25-32. doi:10.1001/2013.jamadermatol.541 4. Kim YH, Martinez G, Varghese A, Hoppe RT. Topical nitrogen mustard in the management of mycosis fungoides: update of the Stanford experience. *Arch Dermatol*. 2003;139(2):165-173. doi:10.1001/archderm.139.2.165 5. Monk BE, Vollum DI, du Vivier AW Combination topical nitrogen mustard and photochemotherapy for mycosis fungoides. *Clin Exp Dermatol.* 1984;9243- 247 6. E Parry; data unpublished; presented to Genopharm sponsored nitrogen mustard workshop, London

Insert extra rows as needed

Checklist for submitting comments

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

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

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

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