NICE National Institute for Health and Care Excellence

Professional organisation submission

Dupilumab for treating adults with moderate to severe atopic dermatitis

[ID1048]

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature.

To help you give your views, please use this questionnaire. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

Information on completing this submission

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 13 pages.

About you	
1. Your name	**Drs Pamela McHenry, Michael Ardern-Jones, Carsten Flohr, Sara Brown, Sarah Wakelin, Gabriela Petrof and Profs Michael J. Cork and Catherine Smith on behalf of the Therapy & Guidelines and A*STAR sub-committees**

2. Name of organisation	**British Association of Dermatologists (the BAD)**
3. Job title or position	**Consultant Dermatologists**
4. Are you (please tick all that apply):	☒ an employee or representative of a healthcare professional organisation that represents clinicians? ☒ a specialist in the treatment of people with this condition? ☒ a specialist in the clinical evidence base for this condition or technology? ☐ other (please specify):
5a. Brief description of the organisation (including who funds it).	The BAD's charitable objectives are the practice, teaching, training and research of Dermatology. It works with the Department of Health, patient bodies and commissioners across the UK, advising on best practice and the provision of Dermatology services across all service settings. It is funded by the activities of its Members.
5b. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No.
The aim of treatment for this condition	
6. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition,	To reduce disease severity and burden, and improve quality of life. Clinical experience suggests that achieving good control of disease *may* be disease-modifying, inducing long-term remission, a reduced number of flares and preventing the development and/or reducing the severity of comorbidities including asthma, allergies and depression.

or prevent progression or disability.)	
7. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount.)	Research studies have shown that the minimal clinically important difference in disease extent as measured by the Eczema Area and Severity Index (EASI) is a reduction of 6.6/72, and for disease symptom improvement as measured by the Patient Oriented Eczema Measure (POEM) is 3.4/28 [Schram et al. Allergy. 2012 Jan;67(1):99-106] However, for pragmatic reasons, we propose that in clinical practice a more conservative estimate of the benefit should be applied and suggest that the treatment should induce: • **A reduction in the Eczema Area and Severity Index (EASI) of 6 points** (the minimum clinically important difference), **at 16 weeks** or • **A reduction in the Eczema Area and Severity Index (EASI) of 50% (i.e. EASI50), at 16 weeks** (N.B. AD is a heterogenous disease and the response of some patients to dupilumab is much slower than others. These are usually the patients with the most severe AD who start with a very high absolute EASI score. In the SOLO dupilumab trial, some patients did not reach EASI50 at week 16, but described it as "life-changing" and "I am cured" compared to their previous life. Subsequently, these patients are cleared of their AD after approximately 9 months on dupilumab. We are in the era of stratified medicine where one size/rule does not fit all and this applies to the rate at which biologic drugs such as dupilumab exert their effect in different types of patients) or less critically • **A reduction in the Patient Oriented Eczema Measure (POEM) of 25% (i.e. POEM25), at 16 weeks**
8. In your view, is there an unmet need for patients and	There is an enormous unmet need for new therapies for patients with atopic dermatitis (AD). This is shown by evidence of high disease burden, increased healthcare resource utilisation and complications of ineffective treatment with current modalities [Eckert et al. J Am Acad Dermatol. 2017 Oct 7. Epub ahead of print].

healthcare professionals in this condition?	Current systemic treatments for severe AD, e.g. immunosuppression, are complicated by the significant risk of side effects. In some individuals, the disease burden is such that despite the documentation of toxicity, the immunosuppression needs to be continued. An alternative treatment with a good adverse event profile is to be welcomed for the treatment of severe AD.
What is the expected place of the technology in current practice?	
9. How is the condition currently treated in the NHS?	AD is a common inflammatory skin condition that effects approximately 5% of adults in industrialized countries, of which approximately 15-23% have moderate-to-severe disease (Flohr et al., 2014; Saeki et al., 2009). The mainstay of treatment in primary care remains topical steroids and emollients. Second-line therapies include topical calcineurin inhibitors and phototherapy; however, topical calcineurin inhibitors may not be suitable for widespread AD and phototherapy requires frequent hospital attendances. Systemic therapy is considered for patients who fail to respond, develop side effects or have moderate-to-severe disease. Despite the high prevalence of moderate-to-severe AD, there are limited systemic treatment options. Historically, ciclosporin has been the only systemic drug licensed for AD (short courses up to 8 weeks); however, other agents have been used off-license to treat moderate-to-severe AD, including methotrexate, azathioprine and mycophenolate mofetil (Roekevisch et al., J Allergy Clin Immunol. 2014 Feb;133(2):429-38). Therefore, there is very considerable unmet need in this severely disabling, life-affecting condition. In particular, ciclosporin cannot be used long-term; recommendations in NICE CG153 suggested treatment beyond 1 year is relatively contraindicated and there is no reason to indicate that the risk of renal impairment (the primary driver for this recommendation in psoriasis) should not be the same in AD. Recently, the International Eczema Council have published recommendations on when to consider systemic therapy, and this document also outlines the standard approach to management [Simpson et al., J Am Acad Dermatol. 2017 Oct;77(4):623-633]
• Are any clinical guidelines used in the treatment of the	SIGN guidelines – Management of atopic eczema in primary care

condition, and if so, which?	
• Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	The pathway of care is well defined (see above) and consensus amongst specialists about the optimal approach and treatment options [Taylor et al., Br J Dermatol. 2017 Jun;176(6):1617-1623]. There is, however, great variability in the delivery of care across the U.K. due to current pressures on dermatology departments, and variable access to secondary care.
• What impact would the technology have on the current pathway of care?	The reported adverse effects profile of dupilumab appears superior to all currently available systemic therapies for AD. Unlike all other options, this treatment does not immunosuppress. Current data suggest that dupilumab is likely to be at least as effective as currently available treatments. Clearly, for those patients where standard treatments have been ineffective or are relatively contraindicated, treatment with dupilumab is indicated. For those who tolerate the currently available systemic therapies for AD, the drugs have very different adverse effects profiles. It is currently accepted that after 1 year of therapy with: • ciclosporin, the risk of irreversible nephrotoxicity is significant. [Chakravarty et al., Rheumatology (Oxford) 2008 Jun;47(6):924-5] • azathioprine, the risk of skin malignancy is significant [Meggitt et al., Br J Dermatol. 2011 Oct;165(4):711-34] • methotrexate, the risk of significant complications (e.g. liver fibrosis) at 1 year is low, but is thought to be proportional to the cumulative dose and presence of other risk factors (evidence from other inflammatory diseases)

	The precise risks attached to extending time of immunosuppression (e.g. by cycling through different immunosuppressants) have not been determined but it is well established that with regard to malignancy the risk is proportional to the length of immunosuppression [Madeleine et al., Br J Dermatol. 2017 Oct 10. doi: 10.1111/bjd.15931.Epub ahead of print]. Additionally, the severity of AD can be a factor associated with an increased risk of lymphoma [Arellano et al., J Invest Dermatol. 2007 Apr;127(4):808-16]. Therefore, we suggest that dupilumab is indicated for treatment of moderate-to-severe* AD when: • standard systemic (immunosuppressive) therapies such as methotrexate, ciclosporin and azathioprine have failed to achieve an adequate improvement in disease severity and/or quality of life or • standard systemic (immunosuppressive) therapies such as methotrexate, ciclosporin and azathioprine are contraindicated at baseline or during treatment due to significant co-morbidities, such as renal or liver disease, or previous malignancy or • there is concern about a significantly increased risk of malignancy due to the cumulative use of immunosuppressive treatments, particularly azathioprine and ciclosporin, for longer than 1 year. *e.g. EASI score of 16 and Physician's Global Assessment (PGA) score of at least 3
10. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	This technology is only currently available in selected centres via compassionate scheme and/or clinical trial. Use of biologic therapy is a well-established modality for other inflammatory conditions (psoriasis, urticaria, hidradenitis suppurativa) and therefore would be easily incorporated into current clinical practice.
• How does healthcare resource use differ	The healthcare resource used for moderate-to-severe disease currently involves phototherapy or systemic therapy that requires frequent monitoring, and, because it is of limited effectiveness in many patients, additional costs are often incurred due to management of poorly controlled disease (frequent GP/hospital visits, infections, hospital

between the technology and current care?	admissions). For patients who are controlled on dupilumab, these costs would be expected to be reduced significantly.
• In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	Dermatologists in a hospital setting
• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	Training of dermatologists and specialist nurses to prescribe and monitor the treatment. However, dermatologists and specialist nurses are familiar with biologic therapies (generally) and so this should not represent any major investment.
11. Do you expect the technology to provide clinically meaningful benefits compared with current care?	Yes.
• Do you expect the technology to increase length of life more than current care?	Yes, life-saving in some patients because severe atopic dermatitis is associated with increased rates of depression and suicide [Yu et al., Journal of Investigative Dermatology (2015) 135, 3183–3186].
• Do you expect the technology to increase health-related quality of	Yes, substantially. Pooled results from two RCTs [Simpson, Dermatol Ther (Heidelb). 2017 Jun;7(2):243-248] reported that AD patients (n=1379) had significantly impaired baseline health-related quality of life (HRQoL), which was slightly worse than the HRQoL reported for moderate-to-severe psoriasis, as well as the general population norms for the UK and US. Patients treated with dupilumab at different dosing regimens reported significant

life more than current care?	improvements in HRQoL by week 16, compared to placebo. These increases resulted in scores that approached population norms, were in the same range as that of biologic agents for psoriasis and were clinically meaningful, as they exceeded the reported minimal clinically important difference outlined in the study.
12. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	Yes, there are different ethnic groups that have different cytokine pathways in AD, so it may be more effective in some than others. The Th2 cytokines IL-4 and IL-13 predominate in most populations, however, in some Asian populations IL-17 predominates [Noda et al., J Allergy Clin Immunol. 2015 Nov;136(5):1254-64]
The use of the technology	
13. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability	Easier to use as less monitoring required. Formal assessment methods of disease severity and treatment outcome will be needed. Some training of nurses will be required to be able to complete disease assessment and be aware of side effects.

or ease of use or additional tests or monitoring needed.)	
14. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	Response to therapy will be evaluated formally using validated tools for disease severity (e.g. EASI, POEM, DLQI). These are part of the normal clinical assessments used and no additional testing (over and above those done when starting any systemic therapy) would be required. For patients not responding to treatment then dupilumab would be stopped. Data from trials and clinical experience suggest that where there has been an initial response at 3 months, the full response (for example reduction in lichenification, return to normal skin) can take longer.
15. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	Yes, it has been shown to transform patients' lives from suicidal (been for euthanasia) – to very happy and from unemployable to successful career. Results from RCT [Tsianakas et al., Br J Dermatol. 2017 Aug 27. doi: 10.1111/bjd.15905. Epub ahead of print; Simpson et al., N Engl J Med. 2016 Dec 15;375(24):2335-2348; Bruin-Weller et al., Dupilumab with concomitant topical corticosteroids in adult patients with atopic dermatitis who are not adequately controlled with or are intolerant to ciclosporin A, or when this treatment is medically inadvisable: a placebo-controlled, randomized phase 3 clinical trial (LIBERTY and CAFÉ)". British Journal of Dermatology, accepted] indicate that patients treated with dupilumab experienced rapid relief from clinical signs such as AD and their concomitant subjective symptoms, including sleep loss and pruritus. Importantly, dupilumab also significantly improved the HRQoL of patients as measured by Quality of life Index (QoLIAD). Of note, a significant improvement in QoLIAD score was already achieved after 4 weeks of dupilumab treatment, which was the earliest measured time point after baseline. Dupilumab was also found to reduce pruritus significantly and as a result leads to improvements in sleep, resulting in less daytime sleepiness and fatigue, which negatively affects functional activities, mood and overall mental and physical health. In both SOLO1 and SOLO2 trials, dupilumab q2w treatment has led to a significant ($p<0.001$) reduction (improvement) in the measure of anxiety and depression (HADS total score) at week 16 compared to placebo (mean ± SD: -5.2 ± 0.5

	vs. -3.0 ± 0.7, and -5.1 ± 0.4 vs. -0.8 ± 0.4 in SOLO1 and SOLO2, respectively). This has also been shown in the CAFÉ trial for dupilumab q2w + TCS vs. placebo + TCS (-6.1 ± 0.54 vs. -2.3 ± 0.56). In addition, the percentage of patients achieving HADS-A and HADS-D score of <8 at week 16 was significantly (p<0.001) higher in dupilumab q2w-treated patients vs. placebo-treated ones (41% vs. 12%, and 40% vs. 6% in SOLO1 and SOLO2, respectively). For the same parameter, in CAFÉ trial for dupilumab q2w + TCS vs. placebo + TCS-treated patients (62.5% vs. 36.7%), a statistical level of significance of p=0.0072 has been reached [Simpson et al., N Engl J Med. 2016 Dec 15;375(24):2335-2348; Bruin-Weller et al., Dupilumab with concomitant topical corticosteroids in adult patients with atopic dermatitis who are not adequately controlled with or are intolerant to ciclosporin A, or when this treatment is medically inadvisable: a placebo-controlled, randomized phase 3 clinical trial (LIBERTY and CAFÉ)". British Journal of Dermatology, accepted]
16. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met?	Yes, this is a highly innovative therapy – the first, targeted biologic mAb in AD, and targets a highly relevant pathway in the disease.
• Is the technology a 'step-change' in the management of the condition?	This therapy is the greatest advance in the treatment of AD since the introduction of topical corticosteroids.

• Does the use of the technology address any particular unmet need of the patient population?	Yes; it treats patients with AD who could not be treated with any currently available systemic therapy. This includes patients who have failed to respond to all current systemic therapies and /or had adverse events precluding their further use.
17. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	There are few side-effects. Conjunctivitis is reported in around 10% of the trial population and may require temporary treatment cessation and/or review with an ophthalmologist for severe cases. Part of the mechanism is that IL-13 is required for lacrimal secretions production and blocking IL-13 therefore results in reduced lacrimal secretions and a dry eye syndrome. The use of prophylactic tears can be used to reduce/prevent this problem in some patients.
Sources of evidence	
18. Do the clinical trials on the technology reflect current UK clinical practice?	The core trial reflects UK practice.
• If not, how could the results be extrapolated to the UK setting?	N/A
• What, in your view, are the most important outcomes, and were they measured in the trials?	• EASI (physician-assessed) • POEM (patient-assessed) Both are measured in the clinical trials.

• If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	N/A
• Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	No
19. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No
20. Are you aware of any new evidence for the comparator treatment(s) since the publication of NICE technology appraisal guidance [TAXXX]? [delete if there is no NICE guidance for the comparator(s)	No HTA

and renumber subsequent sections]	
21. How do data on real-world experience compare with the trial data?	The real-world experience is much better than the impression given by trial data. The most severe patients take much longer to clear than the 16-week primary efficacy endpoint in the trials.
Equality	
22a. Are there any potential equality issues that should be taken into account when considering this treatment?	No
22b. Consider whether these issues are different from issues with current care and why.	N/A
Topic-specific questions	
23 [To be added by technical team at scope sign off. Note that topic-specific questions	

will be added only if the treatment pathway or likely use of the technology remains uncertain after scoping consultation, for example if there were differences in opinion; this is not expected to be required for every appraisal.] **if there are none delete highlighted rows and renumber below**	
Key messages	

24. In up to 5 bullet points, please summarise the key messages of your submission.

- This therapy is the greatest advance in the treatment of AD in the past 50 years.
- This therapy effectively controls patients' AD in the majority of cases, often even when it has been unresponsive to all conventional systemic therapies.
- The adverse effect profile of the new therapy is substantially better than existing systemic treatments.
- For some of those who have been treated with the new therapy who also have severe depression (and have attempted suicide) it has been life-saving.

Thank you for your time.

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