# Aberdeen HTA Group

## Dupilumab for treating moderate to severe atopic dermatitis

# Erratum

**Completed** 23 February 2018

This report was commissioned by the NIHR HTA Programme as project number 16/168/08.

This document is intended to replace pages 8, 13, 18, 68, 84 and 101 of the original ERG assessment report for *Dupilumab for treating moderate to severe atopic dermatitis*, which contained a few inaccuracies. The main issues relate to changes in phrasing to avoid misunderstanding. The amended pages follow in order of page number below.

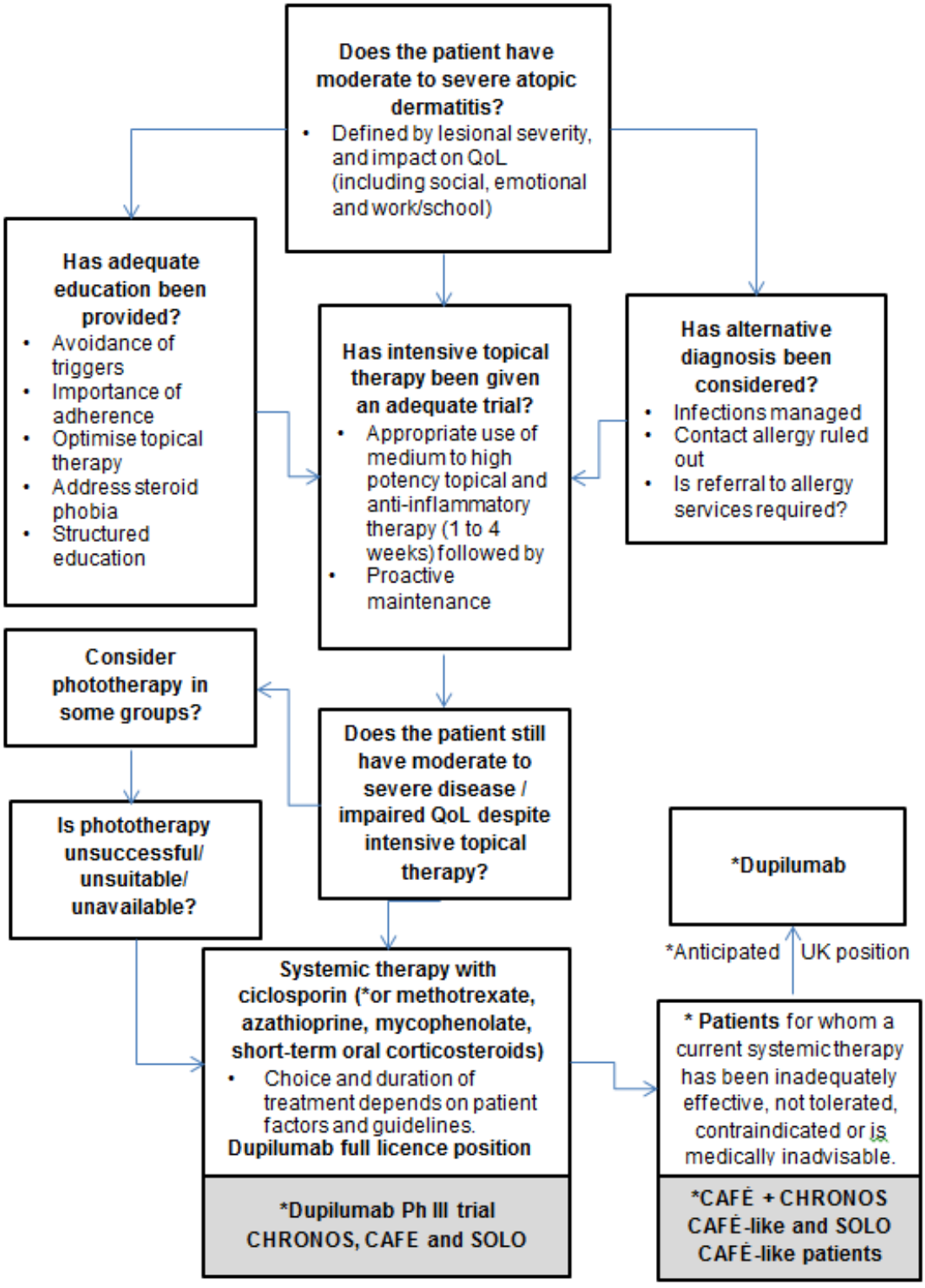
# 2 Background

## *2.1 Critique of company's description of underlying health problems*

The company's description of atopic dermatitis (AD) in terms of prevalence, symptoms and complications appears generally accurate and appropriate to the decision problem. Atopic dermatitis is a chronic, pruritic, inflammatory dermatitis that is remitting-relapsing in nature.[1] It is characterised by chronic or relapsing red and inflamed skin (erythema), thickened and leathery skin (lichenification), dry skin (xerosis) and an intense itch (pruritus).[2] Atopic dermatitis can be a major burden for patients due to sleep loss, psychosocial challenges and missed work.[3] The terms 'atopic dermatitis' and 'atopic eczema' are synonymous and tend to be used interchangeably in the literature.

Incidence or lifetime prevalence of atopic eczema symptoms in the UK increased by more than 10% between 1990 and 2010 .[4] Atopic dermatitis is more common in children and the majority of children with AD no longer have symptoms by adulthood .[5] Prevalence of AD in adults in the UK has been reported as 2.5% with 53% to 67% of those having moderate to severe disease (depending upon the instrument of assessment of severity).[6] In contrast, the company reports that 7% of people diagnosed and treated for AD have moderate-to-severe AD, based on data which was not available to the ERG.

Hospital Episode Statistics for Admitted Patient Care in England from 2016-2017 show that there were 1,258 finished consultant episodes and 1,135 admissions for "AD, unspecified" and "other AD" (codes L20.8 and L20.9).[7] The mean age of "other AD" patients was 16 years and the 227 finished consultant episodes and 197 admissions resulted in 41 day cases. The mean length of stay was 3 days. Patients who were categorised with "AD, unspecified" were older, with a mean age of 29 years, and stayed for a mean of 4 days. For these patients, there were 1,031 finished consultant episodes, 938 admissions and 568 day cases. Of all patients who had outpatient appointments, 2,353 of attendances were classified "other AD" (code L20.8) and 5,521 were "AD, unspecified" (code L20.9). It should be noted that, according to NHS Digital, primary diagnosis is not a mandated field in the outpatient dataset, and,




*Sanofi adaptation

**Figure 1 Company's anticipated positioning of dupilumab in clinical practice (adapted from the IEC algorithm) (reproduced from Figure 1.6 of the company's submission)**

*present a comparison with indirect comparison (MAIC) in* 13 *ciclosporin using a mixed adjusted scenario analysis*.

The company's justification for not including phototherapy or oral steroids as comparators was that they are short-term treatment options only and not for chronic, long-term continuous treatment of AD. In addition, the company points out that the recent International Eczema Council treatment algorithm places phototherapy after intensive topical therapy has failed and before systemic therapy. The ERG's clinical expert agrees that phototherapy is not a long-term treatment option but is of the opinion that phototherapy can be a constituent of BSC in clinical practice in the UK, as it can be used in the short-term to induce remission and can have lasting effects. The ERG's clinical expert agrees that alitretinoin is not a valid comparator as it is licensed for hand eczema only, which is a distinct condition in its own right. The company did not include ciclosporin as a comparator, with the justification that the evidence base of dupilumab compared to ciclosporin is sparse and that the treatments would not, in any case, occupy the same place in the treatment pathway. The company compared ciclosporin with dupilumab in a scenario analysis assuming equivalent efficacy over the common treatment period. Ciclosporin is currently the only licenced therapy for AD. Other immunosuppressive therapies (azathioprine and methotrexate) are currently used in UK clinical practice if ciclosporin fails.

### *3.4 Outcomes*

The outcomes specified in the NICE final scope were: measures of disease severity; measures of symptom control; disease-free period/maintenance of remission; time to relapse/prevention of relapse; adverse effect of treatment; health-related quality of life. The company stated: *clinical outcomes supported by evidence from the LIBERTY AD trial programme are reported addressing all the points raised in the scope.* The trials in the LIBERTY AD programme reported time to first rescue treatment as opposed to disease-free period/maintenance of remission or time to relapse/prevention of relapse; 18 the ERG's clinical expert considers

these outcomes to be equivalent. The outcomes used by the company in the economic model were stated as: measures of disease severity (for example, according to absolute EASI or IGA scores); measures of symptom control according to relative EASI scores (reduction in absolute score);

predict utility values for the pooled base case populations; and 3) dichotomise the fitted values by responder status (in the dupilumab arm). As an alternative approach, the company apply the observed rather than regression fitted values as a sensitivity analysis.

*Sources of health-related quality of life data*

Table 3.9 in Document B of the CS summarises and compares the results of a systematic literature review (SLR) to identify relevant HRQoL data. These include published dupilumab studies[31, 33] as well as previous technology appraisals which report utility data for adults with various severities of AD.

Simpson[33] *"reports findings from a Phase IIb trial for dupilumab across seven countries; 380 patients with moderate-to-severe AD provided EQ-5D-3L data. Baseline utilities ranged from 0.578 to 0.658 and mean utility increments at 16 weeks were reported for placebo (0.028) and for the intervention (range: 0.106 to 0.240)."*

Simpson[31] conducted a pooled analysis of EQ-5D response data from 1,379 patients enrolled in the SOLO 1 and SOLO 2 trials. Baseline utilities ranged from 0.607 to 0.629 and mean utility increments at 16 weeks were reported for placebo (0.031), dupilumab 300 mg once weekly (0.207) and dupilumab 300 mg every two weeks (0.210).

Whilst the company's systematic literature review did not identify any published studies focusing specifically on the analysis of EQ-5D data from the CAFÉ or CHRONOS trials, the company have presented further analyses of these data in their submission. The company note that the utility data in the LIBERTY AD trials were collected using the EQ-5D-3L instrument and valued using the UK general population tariff. Apart from the published dupilumab studies, few other studies identified in the company's literature review used the EQ-5D instrument directly to measure HRQoL in patients with moderate to severe AD. The ERG agree that the LIBERTY AD trial data represents the best available source of utility data for the current appraisal.

GP or optometrist visit prior to referral. However, the small additional cost of a pre-referral visit to a GP would unlikely have a significant impact on results.

**Indirect costs**

The model includes an option to consider indirect costs as a sensitivity analysis. The company submission indicates that indirect costs are based on estimates of absenteeism for the UK, and a reported three-fold increase in the rate of absenteeism for people with moderate-to-severe AD in the 2013 National Health and Wellness survey. The average number of days lost to work in the UK for 2016 was 4.3.[51] Therefore, the company submission states that 4.3 and 12.9 days of lost productivity per year have been implemented in the model for responders and non-responders, respectively. The ERG identified a mismatch between these reported days of lost productivity and those provided in the company model (11.7 and 53.7 for responders and non-responders), which were derived from the AWARE study (Sanofi Genzyme, unpublished data, 2017). However, upon closer inspection the ICERs reported by the company do derive from the stated 4.3 and 12.9 days of lost productivity per year.

The weighted average of full and part-time employment wages (per hour) from the ONS,[52] were used in conjunction with the percentage of individuals employed in the AWARE study, and the weighted average of full and part-time employment hours per work day,[52] to obtain a unit cost per day of work lost in the model.

### 5.2.8 Cost effectiveness results

All the final data inputs and assumptions applied in company base case analyses are summarised in Table 3.38 and Table 3.39 of the company submission (Document B, pages 206-212).

*Company base case results*

The company base case results are reproduced below for the CAFÉ + CHRONOS CAFÉ-like population and the SOLO CAFÉ-like populations. These results relate to the base case population of "*patients who have been optimised on topical therapies and an immunosuppressant but for whom these therapies have failed, are contraindicated or are not tolerated*" (company submission, section B 3.6.1). The presented results include the confidential patient access scheme.

The ERG checked the model calculations and carried out a number of diagnostic checks. Whilst no calculation errors were found, the ERG did identify a mismatch between the reported number of days of absenteeism in the company submission and the number actually applied in the model. However, the reported ICERs do derive from the input values stated in the company submission and only apply in two sensitivity analyses that incorporate indirect costs. In addition, the company applied a value of 0.25 A&E admissions per patient year in the model (for non-responders), but the original data source suggests a value of 0.1. This has a negligible impact on results. The ERG also conducted a number of checks to ensure coherence of the QALY and life-year calculation. It was not possible to assess the external validity of the model due to a lack of available existing longitudinal data on the long-term quality and response status of moderate-to-severe AD patients. The biggest assumption of the model is the setting of health state utility to baseline in BSC patients during the extrapolation, rather than carrying forward the observed placebo arm utility gain, and this cannot be verified by observed longitudinal data.

### *5.3 Exploratory and sensitivity analyses undertaken by the ERG*

Given that the NICE DSU guidance seems to favour a multiplicative approach to adjusting and combining health state utilities for age and comorbidities, the ERG first of all reproduced the company's tables of deterministic sensitivity analysis using this method. These results are presented in Table 32 for the CAFÉ + CCL cohort and Table 33 for the SOLO CAFÉ-like cohort. As noted previously, the ERG were unable to reproduce two of the scenarios based on the information provided in the company submission: i) Scenario 15, which assumed an additional efficacy assessment at 24 weeks for partial responders to dupilumab at 16 weeks; and ii) an analysis that incorporated costs based on market research (described in section B 3.4.4 of the submission) to elicit dermatologists' perceptions of the resource use requirements for responders and non-responders. The impact that these changes had when using the additive approach to utility adjustment, can be reviewed in Tables 26 and 27 above.

It can be noted that the ICERs in all assessed deterministic scenarios increase slightly with the multiplicative approach to age adjustment of utility (Tables 32 and 33) compared with the additive approach (Tables 26 and 27).