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Advising on new medicines for Scotland
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NHS SCOTLAND
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dupilumab 300mg solution for injection in pre-filled syringe (Dupixent®)

SMC2011

Sanofi

10 August 2018

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 NHS Scotland. The advice is summarised as follows:

ADVICE: following a full submission assessed under the orphan medicine process

dupilumab (Dupixent®) is accepted for restricted use within NHSScotland.

Indication under review: the treatment of moderate-to-severe atopic dermatitis in adult patients who are candidates for systemic therapy.

SMC restriction: patients who have had an inadequate response to existing systemic immunosuppressants such as ciclosporin, or in whom such treatment is considered unsuitable.

Four phase III studies demonstrated superiority of dupilumab in improving signs and symptoms of atopic dermatitis when compared with placebo, as monotherapy or in combination with topical corticosteroids in patients with moderate to severe atopic dermatitis.

This SMC advice takes account of the benefits of a Patient Access Scheme (PAS) that improves the cost-effectiveness of dupilumab. This advice is contingent upon the continuing availability of the PAS in NHS Scotland or a list price that is equivalent or lower.

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

Chairman
Scottish Medicines Consortium

Published 10 September 2018

Indication

The treatment of moderate-to-severe atopic dermatitis in adult patients who are candidates for systemic therapy.[1]

Dosing Information

An initial dose of 600mg (two 300mg injections) is recommended in adults, followed by 300mg administered every other week by subcutaneous injection. Dupilumab can be used with or without topical corticosteroids. Topical calcineurin inhibitors may be used, but should be reserved for problem areas only, such as the face, neck, intertriginous and genital areas.

If a dose is missed, it should be administered as soon as possible; thereafter, dosing should resume at the regular scheduled time.

Consideration should be given to discontinuing treatment in patients who have shown no response after 16 weeks of treatment, Some patients with initial partial response may subsequently improve with continued treatment beyond 16 weeks.

Treatment should be initiated by healthcare professionals experienced in the diagnosis and treatment of atopic dermatitis.[1]

Product availability date

December 2017

Dupilumab received a positive scientific opinion under the Early Access to Medicines Scheme with the Medicines and Healthcare Products Regulatory Agency on 13 March 2017. The indication was in adult patients with severe atopic dermatitis who have failed to respond, or who are intolerant of or ineligible for all approved therapies.

Dupilumab meets SMC orphan equivalent criteria.

Summary of evidence on comparative efficacy

Dupilumab is a recombinant human IgG4 monoclonal antibody and is the first biologic medicine approved specifically for this condition.[2] Dupilumab inhibits signalling of interleukin-4 and interleukin-13, two key cytokines involved in atopic dermatitis.[1]

The submitting company has requested that SMC considers dupilumab when positioned for use in adult patients with moderate-to-severe atopic dermatitis not adequately controlled by topical therapies and who are contra-indicated to, intolerant of, have had an inadequate response to or for whom it is otherwise medically inadvisable to receive treatment with a systemic immunosuppressant.

Evidence to support the use of dupilumab for the treatment of atopic dermatitis comes from four randomised, double-blind, placebo-controlled, phase III studies CHRONOS, SOLO 1, SOLO 2 and CAFÉ. All studies enrolled patients aged ≥18 years, with moderate to severe atopic dermatitis

meeting the American Academy of Dermatology Consensus Criteria. Patients had moderate to severe disease at baseline defined by an investigator's global assessment (IGA) score of ≥3 (moderate=3, severe=4), an eczema area severity index (EASI) score of ≥16 (≥20 in CAFÉ study), pruritus Numerical Rating Scale (NRS) average score for maximum itch intensity of ≥3 and ≥10% body surface area (BSA) involvement.[3-6] In three studies (CHRONOS, SOLO 1 and SOLO 2), eligible patients had an inadequate response to topical medication.[3-5] In the fourth study (CAFÉ), eligible patients had a history of inadequate response to topical corticosteroids and inadequate response or intolerance to ciclosporin, or were ciclosporin-naive and ciclosporin treatment was medically inadvisable.[6]

In all studies, patients were randomised to receive a loading dose of subcutaneous dupilumab 600mg, followed by 300mg weekly or the loading dose followed by 300mg every other week (the licensed dose) or placebo. Randomisation was stratified by baseline disease severity (IGA=3 or IGA=4) in all studies, by geographical region in CHRONOS, SOLO 1 and SOLO 2 and by previous ciclosporin use in CAFÉ. In CHRONOS, patients were randomised in a 3:1:3 ratio; study treatment was used in combination with topical corticosteroids and treatment was continued for 52 weeks. In SOLO 1 and SOLO 2, patients were randomised equally; study treatment was used as monotherapy and treatment continued for 16 weeks. In CAFÉ, patients were randomised equally; treatment was used in combination with topical corticosteroids and treatment was continued for 16 weeks. In all studies, patients could receive rescue treatment if needed but were then considered non-responders for the primary analyses. [3-6]

Studies CHRONOS, SOLO 1 and SOLO 2 had two co-primary outcomes of proportion of patients with IGA 0 or 1 plus a reduction from baseline of ≥2 points at week 16 and 75% improvement in EASI (EASI-75) from baseline to week 16. Key secondary outcomes across these studies included proportion of patients achieving peak pruritus NRS reduction ≥4 and ≥3 from baseline at week 16.[3-5] Only the licensed dose of dupilumab (300mg every other week) will be considered further. Results for primary and key secondary outcomes significantly favoured dupilumab compared with placebo as detailed in table 1 below.

Table 1: Primary and selected key secondary outcomes from CHRONOS and SOLO 1 and SOLO 2 studies.[3-5]

	CHRONOS		**SOLO 1**		**SOLO 2**	
	Dupilumab (n=106)	**Placebo (n=315)**	**Dupilumab (n=204)**	**Placebo (n=224)**	**Dupilumab (n=233)**	**Placebo (n=236)**
Co-primary outcomes at week 16						
IGA 0 or 1 and ≥2 point reduction	39%	12%	38%	10%	36%	8.5%
EASI-75	69%	23%	51%	15%	44%	12%
Selected key secondary outcomes						
IGA 0 or 1 and ≥2 point reduction at 52 weeks	36%	13%	-	-	-	-
EASI-75 at 52 weeks	65%	22%	-	-	-	-
Pruritus NRS≥4	59%	20%	41%	12%	36%	9.5%

improvement at 16 weeks*						
Pruritus NRS≥3 improvement at 16 weeks*	66%	28%	47%	17%	51%	13%

p<0.001 for all comparisons versus placebo. EASI=Eczema Area and Severity Index. EASI-75=≥75% improvement in EASI score from baseline. IGA=Investigator's Global Assessment. NRS=numerical rating scale. * patients analysed with a baseline score ≥3 or ≥4 (where appropriate).

Results from the CAFÉ study support the proposed positioning by the company for patients with moderate-to-severe atopic dermatitis not adequately controlled by topical therapies and who are contra-indicated to, intolerant of, have had an inadequate response to or for whom it is otherwise medically inadvisable to receive treatment with a systemic immunosuppressant. The CAFÉ study had EASI-75 at week 16 as its primary outcome. Results for the primary and key secondary outcomes significantly favoured dupilumab compared with placebo as detailed in table 2 below.[6]

Table 2: Primary and selected secondary outcomes from the CAFÉ study at week 16.[6]

	dupilumab (n=107)	**placebo (n=108)**
Primary outcome		
Proportion of patients achieving EASI-75	63%	30%
Selected secondary outcomes		
Change from baseline in EASI	-80%	-47%
Change from baseline in weekly average of peak pruritus NRS score	-54%	-25%
Change from baseline in SCORAD score	-62%	-30%
Proportion of patients who achieved improvement ≥4 points from baseline in weekly average of peak pruritus NRS score*	46%	14%
Change from baseline in percent of BSA affected	-39%	-20%
Proportion of patients who achieved both IGA 0 or 1 and reduction from baseline of ≥2 points	40%	14%
Mean weekly dose of topical corticosteroid used	15g	25g

p<0.001 for all comparisons versus placebo. BSA: body surface area, DLQI: Dermatology Life Quality Index, EASI: Eczema Area and Severity Index, EASI-75: ≥75% improvement from baseline in EASI Score, IGA: Investigator's Global Assessment, NRS: numerical rating scale, SCORAD: Scoring Atopic Dermatitis. * patients analysed with a baseline score ≥4.

In CHRONOS, results from a subgroup of patients who had an inadequate efficacy response to oral ciclosporin, were intolerant to oral ciclosporin or who did not receive prior oral ciclosporin treatment because ciclosporin was contraindicated or otherwise medically inadvisable support the proposed positioning. The European Public Assessment Report (EPAR) states that a clinically relevant improvement in signs and symptoms of atopic dermatitis in patients in this subgroup was identified at week 16 and these results were sustained at week 52.[3]

A number of patient reported outcomes were included in the pivotal studies. Pruritus NRS results are summarised with secondary endpoints in tables 1 and 2 above. In CHRONOS, a significant difference in least squares (LS) mean change from baseline for Dermatology Life Quality Index (DLQI) and Patient-Oriented Eczema Measure (POEM) score at week 16 was identified favouring dupilumab when compared with placebo. There were no significant differences in Hospital Anxiety

and Depression Scale (HADS) score LS mean change from baseline at week 16. LS mean change from baseline for DLQI, POEM and HADS at week 52 favoured dupilumab compared with placebo, however statistical significance was not claimed due to the hierarchical testing procedure.[4] Statistically significant differences favouring dupilumab over placebo were identified in SOLO 1, SOLO 2 and CAFÉ studies for patient reported outcomes relating to DLQI, POEM and HADS score at week 16.[5, 6]

All patients who completed the studies described above were eligible to enter an open-label extension study (LIBERTY AD OLE), which is ongoing and is expected to be completed in December 2018.[4] Patients from SOLO 1 and SOLO 2 could either enter a maintenance study (SOLO CONTINUE) or the open label extension study (OLE). The SOLO CONTINUE study was a phase 3, randomised, double-blind, placebo-controlled study enrolling only patients who achieved high-level clinical response (IGA 0 or 1 or EASI-75) after 16-week treatment in either SOLO 1 or SOLO 2. SOLO CONTINUE compared the ability of increased dosing intervals to maintain the high level of response achieved after 16 weeks of dupilumab treatment in the SOLO studies. Patients received dupilumab 300 mg weekly, every two weeks, every four weeks, every eight weeks, or placebo for 36 weeks followed by a 12 week follow-up period. The co-primary endpoints were the mean change between baseline and week 36 in percent change in EASI Score from parent study baseline, and percent of patients with EASI-75 at week 36 for patients with EASI-75 at baseline. The results showed that the best effect in maintaining clinical response was achieved by patients who continued on the same dose regimen received in the SOLO 1 and SOLO 2 studies (300mg weekly or every other week) while efficacy of other dose regimens reduced in a dose-dependent manner.[3]

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

Summary of evidence on comparative safety

Safety data are available for 52 weeks of dupilumab treatment from the CHRONOS study. A similar proportion of patients in the dupilumab licensed dose and placebo groups experienced adverse events (88% [97/110] and 84% [266/315], respectively), with serious adverse events being experienced by 4% (4/110) and 5% (16/315) of patients, respectively. Treatment was discontinued due to adverse events in 2% (2/110) of patients given dupilumab and in 8% (24/315) given placebo. Infections and infestations were the most common adverse effects in the dupilumab licensed dose and placebo groups (57% [63/110] and 58% [182/315], respectively). Of these, nasopharyngitis was reported most frequently in 23% (25/110) and 19% (61/315) of the respective groups. Eye disorders were experienced by 31% (34/110) and 15% (46/315) of patients in the respective groups. Injection site reactions were reported more frequently in the dupilumab group than the placebo group, 15% (16/110) compared with 8% (24/315).[4]

In the CAFÉ study, whose full population reflects the proposed positioning, safety data are available for 16 weeks of treatment with dupilumab. An adverse event was reported in 72% (77/107) of patients in the dupilumab licensed dose group and 69% (75/108) of the placebo group. One patient in the placebo group discontinued treatment due to an adverse event. Serious adverse events occurred in two patients in each group.[6]

Infections and infestations were reported in 46% (49/107) of patients in the dupilumab group and 41% (44/108) of the placebo group. Of these, nasopharyngitis was the most common, reported in 21% (22/107) and 17% (18/108) of patients in the respective groups. Conjunctivitis was reported

in 11% (12/107) of the dupilumab group compared with 2.8% (3/108) of the placebo group. Skin disorders were reported by 21% (22/107) and 19% (21/108) and eye disorders by 20% (21/107) and 14% (15/108) of the respective groups.[6]

It is noted in the EPAR that analysis of the safety of dupilumab in atopic dermatitis patients who are not adequately controlled by or were intolerant to oral ciclosporin, or for whom oral ciclosporin was not medically advisable was broadly comparable with that of patients who did not meet these criteria.[3]

Summary of clinical effectiveness issues

Atopic dermatitis is an inflammatory skin disease that can be either chronic, or chronically relapsing, and is characterised by pruritus, dry skin, redness and eczematous lesions. Itching and skin infections are often a complication. These symptoms can lead to pain, sleep disruption, anxiety and depression, impairing health and quality of life.[2, 3]

Treatment options for atopic dermatitis are limited; topical treatments include emollients, corticosteroids and calcineurin inhibitors such as tacrolimus. The mainstay of treatment is with topical corticosteroids, however topical corticosteroids are not recommended for continuous, long-term use due to side effects. Symptom control is often not achieved with topical corticosteroids in patients with moderate to severe atopic dermatitis and they frequently require systemic therapy with non-selective immunosuppressants such as systemic corticosteroids or ciclosporin. Clinical experts consulted by the Scottish Medicines Consortium (SMC) noted that methotrexate, azathioprine and mycophenolate are sometimes used, however these medications are not licensed for treatment of atopic dermatitis. Systemic immunosuppressants can be associated with severe toxicity and side effects.[2, 3] Alitretinoin, an oral retinoid, is available for severe chronic hand eczema only. Ultra violet (UV) phototherapy is also a potential treatment option.[9] Clinical experts noted that this would be a potential treatment option considered prior to systemic immunosuppressants, if appropriate.

Clinical experts consulted by SMC considered that dupilumab fills an unmet need in this therapeutic area, namely treatment of moderate to severe atopic dermatitis where current treatments are inadequate or inappropriate. Dupilumab, for this indication, meets orphan equivalent criteria.

The submitting company has requested that SMC considers this product when positioned for use in adult patients with moderate to severe atopic dermatitis not adequately controlled by topical therapies and who are contra-indicated to, intolerant of, have had an inadequate response to or for whom it is otherwise medically inadvisable to receive treatment with a systemic immunosuppressant.

The four phase III studies have shown that dupilumab was significantly more effective than placebo in terms of achieving IGA and EASI-75 responses and was also associated with a range of favourable patient reported outcomes.

The CHRONOS, SOLO 1 and SOLO 2 studies included patients with moderate to severe atopic dermatitis with a previous inadequate response to topical corticosteroids, which represents the patient population included within the dupilumab licence. This proposed positioning is in patients in whom systemic immunosuppressants are contra-indicated, intolerant of, have had an

inadequate response to or for whom it is otherwise medically inadvisable to receive treatment with a systemic immunosuppressant which is represented by the full CAFÉ study population. Subgroup analyses were conducted in CHRONOS, SOLO 1 and SOLO 2 in patients who were considered representative of the proposed positioning although patient numbers were small and the studies were not sufficiently powered. Use of dupilumab in combination with topical corticosteroids (CAFÉ and CHRONOS studies) is considered more relevant to clinical practice.

The primary analyses in the four pivotal studies considered patients who required rescue medication as non-responders. However the submitting company used all observed results regardless of rescue medication use in the economic model.

Long-term data are limited. Patients included in the CAFÉ study represent the proposed positioning however this was a 16-week study which is only sufficient to demonstrate short-term efficacy for a long-term condition. Results of 52 weeks of treatment in a subgroup population representative of the positioning are available from the CHRONOS study and are generally similar to the main population. Dupilumab can be given with or without topical corticosteroids, results are only available for short-term treatment (16 weeks) as monotherapy (from SOLO 1 and SOLO 2). Longer term data from extension studies are expected to become available. Patients who were unable to safely use topical corticosteroids were excluded from the CHRONOS and CAFÉ studies (due to the study design).

There were no active comparators in the pivotal studies. Best supportive care (BSC) was considered to be the appropriate comparator in the patient population represented by the proposed positioning. A number of other systemic immunosuppressants are used in the management of atopic dermatitis but they are not licensed for this indication and are used off-label.

Dupilumab would provide another treatment option for patients with moderate to severe atopic dermatitis not adequately controlled by topical therapies and who have had an inadequate response to existing systemic immunosuppressants such as ciclosporin, or in whom such treatment is considered unsuitable. Clinical experts consulted by SMC considered that dupilumab is a therapeutic advancement due to the novel mechanism of action and the place in therapy would be for patients with moderate to severe atopic dermatitis who have had an inadequate response to or are unsuitable for other treatments.

Dupilumab is the first biologic medicine licensed for the treatment of atopic dermatitis and its introduction will require routine use of objective measures e.g. SCORAD, EASI and DLQI in this patient group. It is given every two weeks by subcutaneous injection which can be administered by the patient or carer. It should be initiated by healthcare professionals experienced in the diagnosis and treatment of atopic dermatitis and training / education on injection technique would be required, however patient numbers may be small and therefore impact on dermatology clinics is likely to be low. The EPAR notes that the burden of bi-weekly subcutaneous injections is likely to be considered low by the patient against the background that no systemic and efficacious therapy is in place to date.[3]

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 dupilumab, as an orphan-equivalent medicine, in the context of treatments currently available in NHSScotland.

The key points expressed by the group were:

- Moderate/severe atopic dermatitis is a distressing and disabling long-term skin condition. Symptoms included extreme itching and painful skin which often leads to significant sleep disturbance. The condition can impact on ability to work, study, perform day-to-day activities and also participation in social or family activities. Scratching can cause skin to bleed and increases the risk of infection. The visual appearance of eczema can cause relationship issues, self-consciousness and social isolation. Mental health problems such as anxiety and depression have been reported commonly.
- Current treatment options are limited. There is significant unmet need in a proportion of patients who have failed topical treatment and have inadequate response, intolerance or contra-indication to existing systemic immunosuppressants.
- Dupilumab is a novel, specific treatment that has been shown to be effective in reducing signs and symptoms of atopic dermatitis and therefore has the potential to have a significant impact on patient quality of life.
- It can be self-administered by the patient by a fortnightly subcutaneous injection, and appears to be well tolerated with less side effects and monitoring requirements than existing immunosuppressants.
- Improving symptom control, for example improving the visual appearance, reducing itching and sleep disturbance, would lead to physical and mental health benefits for patients. This would also have a positive impact on family and carers as patients would become more independent, requiring less physical, emotional and psychological support.
- Long term data on efficacy of dupilumab are limited. Regular review of response to therapy including objective measures would be required and treatment only continued if a clinical benefit is observed.

Additional Patient and Carer Involvement
We received a patient group submission from the National Eczema Society. The National Eczema Society is a registered charity. The National Eczema Society has not received any funding from pharmaceutical companies in the past two years. Representatives from the National Eczema Society 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 submitting company presented a cost-utility analysis comparing dupilumab to BSC in adult patients with moderate to severe atopic dermatitis not adequately controlled by topical therapies and who are contra-indicated to, intolerant of, have had an inadequate response to or for whom it is otherwise medically inadvisable to receive treatment with a systemic immunosuppressant. The analysis was presented for two populations; patients receiving dupilumab in combination with

topical corticosteroids and patients who would receive monotherapy with dupilumab. BSC in the model was assumed to be comprised of treatments as used in the placebo arms of the clinical study programme (eg emollients, low to mid-potency topical corticosteroids and rescue medication with higher potency topical corticosteroids, oral corticosteroids or topical calcineurin inhibitors). A lifetime horizon was used for the analysis.

The economic modelling was carried out using an initial one-year decision tree followed by a Markov model with a yearly cycle. In the decision-tree, patients were evaluated for response at 16 weeks and dupilumab patients who did not respond to treatment were assumed to move to BSC. The Markov model included three states; maintenance treatment with dupilumab, BSC treatment and death. In the Markov phase of the model, costs and benefits of treatment for dupilumab patients were differentiated according to whether a patient was a responder or non-responder to treatment. For the comparator arm of the Markov model, costs were accrued according to the responder status of the patient, but the benefits of treatment were not differentiated according to whether the patient had responded to BSC or not and instead an averaged responder/ non-responder utility value was used. Background general population mortality was assumed equally in both arms of the model, and as such the benefits of dupilumab were mediated through quality of life impacts only.

Responder status in the economic model was assessed using a composite outcome measure of EASI- 50 plus DLQI>4 assessed at 16 weeks. As noted above, the economic model also used 'all observed' data rather than the 'primary analysis' data set where patients were considered non-responders after rescue medication. The data were also pooled across studies and in addition, the data pooled from the studies were selected to be more relevant to the proposed positioning for dupilumab. The company therefore termed the two patient groups as 'CAFÉ + CHRONOS CAFÉ-like' for patients treated in combination with topical corticosteroids, and 'SOLO CAFÉ- like' for the monotherapy patients. A discontinuation rate of 3.7% per year was applied to the dupilumab arm of the model.

Quality of life in the model was obtained from patient- level EQ-5D data in the 'all observed' data but using the full trial data for from the studies (ie not using CHRONOS- CAFÉ like or SOLO CAFÉ like subgroups). Regression analyses were used to estimate utilities in the various states of the model. For example, base line utility was 0.66 for patients in the CAFÉ and CHRONOS-CAFÉ like group, rising to 0.898 for a dupilumab responder or 0.797 for both a non-responder to dupilumab or a patient treated with BSC (regardless of whether a responder to BSC or not). In addition, the effects of quality of life were assumed to wane over time, with the treatment-waning effect estimated from expert opinion survey. It was noted that the assumptions would mean that everyone in the BSC arm of the model would have lost benefit by the end of year 4 but a high proportion of patients in the dupilumab arm would have the treatment benefit maintained. The company indicated that it was not unreasonable to expect such a sharp fall in utility for BSC as the levels of support achieved as part of the clinical trials wouldn't persist over time and thus any BSC effect would fall away.

Costs in the model related to treatment acquisition costs, costs of background treatments, costs of treating disease flares, health care professional visits and any inpatient care required. It should be noted that for some of the background treatment costs (eg emollients, topical corticosteroids etc) the company assumed that the costs for dupilumab responders would be lower than for non-responding patients. While there was some evidence of reduced usage of topical corticosteroids within the clinical study programme, for other aspects of resource use, the lower resource use was based on expert opinion or assumption. The cost of some adverse events were included;

injection site reactions with dupilumab were included as a one-off cost. The analysis also included a one-off cost for training to self-administer dupilumab based on band 6 nursing time.

A Patient Access Scheme (PAS) was proposed by the submitting company and assessed by the Patient Access Scheme Assessment Group (PASAG) as acceptable for implementation in NHS Scotland.

The results of the base case analysis are noted in table 5 below:

Table 5: Base case cost-effectiveness results - with PAS

	Incremental cost	Incremental quality adjusted life year (QALY)	Incremental cost-effectiveness ratio (ICER)
CAFÉ FAS+ CHRONOS CAFÉ-like pool population	£63,911	1.81	£35,351
SOLO CAFÉ-like pool population	£41,532	1.41	£29,504

A range of sensitivity analyses were presented by the company and the key findings are reported in table 6.

Table 6: selected sensitivity analysis results - with PAS

	Sensitivity analysis	ICER with PAS CAFÉ +CHRONOS CAFÉ- like pool	ICER with PAS SOLO CAFÉ-like pool
1	Change of utility measurement from regression analysis to observed changes from baseline EQ-5D from trials	£32,367	£27,888
2	Decline in utility for BSC patients does not decline beyond year 2 level	£44,403	£35,489
3	Linear decline in BSC utility to year 5	£37,260	£29,982
4	Utility values varying by responder status for both arms of the model, and same values used for dupilumab and BSC patients	£35,423	£29,888
5	5 year time horizon	£43,991	£36,052
6	Primary analysis data used for response	£35,387	£31,067
7	Removal of differences in background medication costs except topical corticosteroids	£36,849	£30,712
8	Ongoing annual injection site reactions	£35,002	£28,542
9	Use of EASI-75 as the outcome measure and the primary analysis data set	£37,349	£31,642
10	Treatment waning effect based on CHRONOS time to event analysis	£36,992	£35,309

11	Combined scenario analysis: common rather than treatment-specific utility values, time to event data used for treatment waning effect, ongoing injection site reaction costs and only topical corticosteroid background treatment costs allowed to reduce with response.	£40,089	£31,560

The following weaknesses were noted with the analysis:

- A number of differences were noted between the clinical study data and the data used in the economic model (eg pooled data, subgroups to match the proposed positioning and use of a composite outcome measure rather than the primary outcome of the trials). The use of the all observed data may not have exerted a large influence on the results (see sensitivity analysis 6 above) but combined with the use of the primary outcome, the ICERs rose (sensitivity analysis 9). It is noted that the EASI-75 outcome may be a less achievable target in clinical practice than the composite endpoint used in the modelling.
- There were a number of issues in relation to the utility values used in the analysis. The model used utility data from a regression equation rather than data from the EQ-5D directly, and there was the averaging of utility values for BSC patients rather than using values specific to patients being a responder or not. Further, dupilumab non-responders were assumed to have the level of benefit associated with BSC patients rather than specific values for dupilumab non-responders. The company provided a range of additional analyses in relation to these aspects, However, a revision to the analysis to allow utility values by responder status for both arms of the model and where the utility values for responders and non-responders were the same for dupilumab and BSC did not cause the ICERs to rise significantly. This may reflect that there was only a short period of time in the model that BSC patients maintained a response given the treatment waning assumptions. See analysis 4 above.
- Further, in relation to utility valuation, the assumptions made about the treatment waning effect had an important impact on the results, but were based on a small sample of clinical experts. The company provided some additional analysis on request where maintenance of treatment effect was based on CHRONOS time to event data. This increased the ICER (see analysis 10).
- In terms of costing, response to dupilumab was assumed to be associated with reductions in background therapies and health care professional visits. In the absence of available data, these reductions were commonly based on expert opinion or assumption rather than observed data. The company provided additional analysis on these aspects which is shown above as analysis 7.
- The company assumed that injection site reactions with dupilumab were one-off events. Revised analysis assuming an ongoing annual cost changed the ICERs slightly (see analysis 8 above).

The Committee considered the benefits of dupilumab in the context of the SMC decision modifiers that can be applied when encountering high cost-effectiveness ratios and agreed that a number of the criteria were satisfied: a substantial improvement in quality of life; and the absence of other treatments of proven benefit. In addition, as dupilumab is an orphan equivalent medicine, SMC can accept greater uncertainty in the economic case.

After considering all the available evidence, the output from the PACE process, and after application of the appropriate SMC modifiers, the Committee accepted dupilumab for restricted use in NHS Scotland.

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

Additional information: guidelines and protocols

All guidelines predate the availability of dupilumab, the first biologic treatment for the disease.

The Scottish Intercollegiate Guidelines Network (SIGN) published its national clinical guideline on the Management of atopic eczema in primary care (SIGN125) in 2011. The guideline relates only to primary care and notes that 'dermatitis' and 'eczema' are terms used interchangeably when referring to atopic dermatitis. For patients with moderate to severe disease, potent topical steroid is recommended until signs of improvement, when a reduction in frequency or potency should be considered.[10]

Additional information: comparators

No comparators exist in the positioning requested by the company.

Cost of relevant comparators

Medicine	Dose Regimen	Cost per year (£)
dupilumab	**600mg (two 300mg injections) initially, followed by 300mg every other week by subcutaneous injection**	**Year 1: £17,708 Subsequent years: £16,444**

Doses are for general comparison and do not imply therapeutic equivalence. Costs from electronic BNF and MIMS on 07 May 2018. Costs calculated using the full cost of vials/ampoules assuming wastage. Costs do not take any patient access schemes into consideration.

Additional information: budget impact

The submitting company estimated there would be 766 patients eligible for treatment with dupilumab in year 1, rising to 949 patients in year 5. The estimated uptake rate was 5% (38 patients) in year 1 rising to 38% (360 patients) in year 5 but the company also assumed a further 20 patients per year would receive treatment as a consequence of already having received dupilumab through compassionate use or open label extension studies. This gave a total treated population of 58 and 380 in years 1 and 5 respectively.

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.

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This assessment is based on data submitted by the applicant company up to and including 15 June 2018.

**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 drug 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 NHS Scotland 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 NHS Scotland 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.