Healthcare Improvement Scotland | SMC Advice on new medicines

SMC2337

baricitinib 2mg and 4mg film-coated tablets (Olumiant®)

Eli Lilly and Company

07 May 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

baricitinib (Olumiant®) is accepted for restricted use within NHSScotland.

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

SMC restriction: treatment of moderate to severe atopic dermatitis in adult patients who are candidates for systemic therapy who have failed at least one current systemic immunosuppressant due to intolerance, contraindication or inadequate disease control.

Four phase III studies demonstrated superiority of baricitinib 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 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.

Chairman
Scottish Medicines Consortium

Indication

For the treatment of moderate to severe atopic dermatitis in adult patients who are candidates for systemic therapy.[1, 2]

Dosing Information

The recommended dose is 4mg once daily taken orally with or without food and may be taken at any time of the day. A dose of 2mg once daily is appropriate for patients such as those aged ≥75 years and may be appropriate for patients with a history of chronic or recurrent infections. A dose of 2mg once daily should be considered for patients who have achieved sustained control of disease activity with 4mg once daily and are eligible for dose tapering.

Baricitinib can be used with or without topical corticosteroids. The efficacy can be enhanced when given with topical corticosteroids. Topical calcineurin inhibitors may be used, but should be reserved for sensitive areas only, such as the face, neck, intertriginous and genital areas.

Consideration should be given to discontinuing treatment in patients who show no evidence of therapeutic benefit after 8 weeks of treatment.

Treatment should be initiated by physicians experienced in the diagnosis and treatment of atopic dermatitis.

See Summary of product characteristics (SPC) for further information.[1, 2]

Product availability date

19 October 2020

Summary of evidence on comparative efficacy

Baricitinib is a selective Janus kinase (JAK) inhibitor of JAK1 and JAK2. Within the intracellular pathway, JAKs phosphorylate and activate signal transducers and activators of transcription (STATs). The JAK-STAT pathway is a major signal transduction pathway for several cytokines involved in the pathogenesis of atopic dermatitis and interruption of these pathways may have a therapeutic effect on the signs and symptoms of atopic dermatitis.[2, 3]

The submitting company has requested that SMC considers baricitinib when positioned for the treatment of moderate to severe atopic dermatitis in adult patients who are candidates for systemic therapy who have failed at least one current systemic immunosuppressant due to intolerance, contraindication or inadequate disease control.

Evidence to support the efficacy and safety of baricitinib for the treatment of moderate to severe atopic dermatitis comes from four randomised, multicentre, double-blind phase III studies BREEZE-AD1, BREEZE-AD2, BREEZE-AD7 and BREEZE-AD4. All studies recruited patients aged ≥18 years with a diagnosis of atopic dermatitis as defined by the American Academy of Dermatology criteria

for at least 12 months before screening. Patients had moderate to severe disease defined as an Eczema Area and Severity Index (EASI) score of ≥16, Validated Investigator's Global Assessment of Atopic Dermatitis (vIGA-AD) ≥3 (3=moderate, severe=4) and ≥10% body surface area involvement at screening and randomisation. In BREEZE-AD1, BREEZE-AD2 and BREEZE-AD7, eligible patients had an inadequate response to topical therapies, defined as the inability to achieve mild disease after use of at least a moderate potency topical corticosteroid for at least 4 weeks (or for the maximum duration recommended by the product prescribing information), failure to respond to systemic immunosuppressant therapies (such as ciclosporin, methotrexate, azathioprine or mycophenolate mofetil) or a clinically significant reaction to topical corticosteroids (BREEZE-AD1 and BREEZE-AD2 only). In BREEZE-AD4, patients had an inadequate response to topical therapies and a documented history of an inadequate response, intolerance, or contraindication to ciclosporin.[3-6]

Patients were randomised to receive orally once daily baricitinib 1mg (BREEZE-AD1, BREEZE-AD2 and BREEZE-AD4 only), baricitinib 2mg, baricitinib 4mg or matching placebo. Randomisation was stratified according to geographical region and baseline disease severity (vIGA-AD score of 3 or 4). In BREEZE-AD1 and BREEZE-AD2, patients were randomised in a 1:1:1:2 ratio; study treatment was used as monotherapy and continued for 16 weeks. In BREEZE-AD7, patients were randomised equally and study treatment continued for 16 weeks. In BREEZE-AD4 patients were randomised in a 1:2:1:1 ratio, the primary and key secondary endpoints were measured at 16 weeks but treatment period continued for 52 weeks. Patients in BREEZE-AD7 and BREEZE-AD4 received study treatment in combination with topical corticosteroids. The use of topical calcineurin inhibitors and topical phosphodiesterase-4 inhibitors was allowed in the place of topical corticosteroids if deemed appropriate by the investigator. In all studies rescue treatment was permitted if patients experienced unacceptable or worsening symptoms.[3-7]

The primary outcome for BREEZE-AD1, BREEZE-AD2 and BREEZE-AD7 was the proportion of patients that achieved a vIGA-AD score of 0 (clear) or 1 (almost clear) with a ≥2-point improvement from baseline at week 16. The vIGA-AD is a static 5-point scale ranging from 0 (clear) to 4 (severe) that assesses the physician's overall impression of disease severity. Key secondary outcomes included the proportion of patients with at least a 75% change from baseline in EASI score (EASI75) and a ≥4-point improvement on the Itch NRS among patients with a baseline score of ≥4. A hierarchical testing procedure was applied to the primary and key secondary outcomes in all studies with no formal testing after the first non-significant outcome in the hierarchy. The primary analyses for the four key studies was conducted using the primary censoring rule with patients censored as non-responders when rescue therapy was required. The economic base case used data based on secondary censoring rules where patients were not considered non-responders if they used topical corticosteroids as rescue treatment. The submitting company considered this a better reflection of clinical practice as it anticipated that baricitinib will be used concomitantly with topical corticosteroids. Only baricitinib 4mg will be considered further as the EMA concluded that this was the most effective dose.[3-5, 8]

A significantly higher proportion of patients achieved a vIGA-AD score of 0 or 1 with a ≥2-point improvement from baseline at week 16 in the baricitinib group compared with placebo. This was supported by a number of key secondary outcomes, the results are presented in Table 1.[3-5]

Table 1: Primary and selected key secondary outcomes from BREEZE-AD1, BREEZE-AD2 and BREEZE-AD7 studies.[3-5]

	BREEZE-AD1		BREEZE-AD2		BREEZE-AD7	
	Baricitinib 4mg (n=125)	Placebo (n=249)	Baricitinib 4mg (n=123)	Placebo (n=244)	Baricitinib 4mg + TCS (n=111)	Placebo + TCS (n=109)
Primary outcome at week 16						
vIGA-AD 0 or 1 and ≥2 point improvement	17%[A]	4.8%	14%[A]	4.5%	31%[B]	15%
Selected key secondary outcomes at week 16						
EASI75 response, %	25%[A]	8.8%	21%[A]	6.1%	48%[A]	23%
EASI90 response, %	16%[A]	4.8%	13%[A]	2.5%	24%	14%
LSM percent change from baseline in EASI	-59%[A]	-35%	-55%[A]	-29%	-67%[A]	-45%
Proportion with Itch NRS ≥4-point improvement	22%[A]	7.2%	19%[A]	4.7%	44%[A]	20%
SCORAD75 response, %	10%[A]	1.2%	11%[A]	1.6%	18%	7.3%

[A] p≤0.001 for baricitinib versus placebo when adjusted for multiplicity, [B]p≤0.05 for baricitinib versus placebo when adjusted for multiplicity. TCS=topical corticosteroid, vIGA-AD= Validated Investigator's Global Assessment of Atopic Dermatitis, EASI75/90=75%/90% improvement from baseline in Eczema Area and Severity Index, LSM=least squares mean, NRS=numeric rating scale, SCORAD75= 75% improvement in SCORing Atopic Dermatitis. The EASI score is a validated, investigator-assessed composite scale that assesses the extent and severity of atopic dermatitis on the head and neck, trunk, upper extremities and lower extremities. The Itch NRS is a patient assessed 11-point horizontal scale ranging from 0 to 10, with 0 representing no itch and 10 representing the worst imaginable itch. Only patients with an Itch NRS baseline severity of 4 or more were included in the analysis. The SCORAD index measures disease severity using six clinical characteristics with higher scores representing higher disease burden.

Evidence to support the proposed positioning comes from BREEZE-AD4. The primary outcome for BREEZE-AD4 was the proportion of patients achieving an EASI75 at 16 weeks. Baricitinib demonstrated superiority compared with placebo for the primary outcome, this was supported with a number of key secondary outcomes. The results are presented in Table 2.[3, 6]

Table 2: Primary and selected key secondary outcomes from BREEZE-AD4[3, 6, 9]

	Baricitinib 4mg+TCS (n=92)	Placebo + TCS (n=93)
Primary outcome at week 16		
EASI75 response, %	32%[A]	17%
Selected key secondary outcomes reported at week 16		
LSM percent change from baseline in EASI	-63%[B]	-43%
Itch NRS ≥4 point improvement	38%[B]	8.2%

Proportion with vIGA-AD 0 or 1 and ≥2 point improvement	22%	9.7%
SCORAD75 response, %	7.0%	1.0%

[A] p≤0.05 for baricitinib versus placebo. [B] p≤0.001 for baricitinib versus placebo EASI=Eczema Area and Severity Index, LSM= least squares mean, NRS= numeric rating scale, SCORAD75=75% improvement in SCORing, TCS=topical corticosteroid, vIGA-AD= Validated Investigator's Global Assessment of Atopic Dermatitis.

A vIGA-AD 0 or 1 and EASI75 response was apparent after 2 to 4 weeks as monotherapy or in combination with a topical corticosteroid. A lack of response at 8 weeks was considered predictive for a lack of response at later time points and the SPC advises consideration should be given to discontinuing treatment in patients who show no evidence of therapeutic benefit after 8 weeks.[2, 3]

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

A number of patient reported outcomes were assessed as secondary outcomes in the four key studies, the results for the Itch NRS at week 16 have been reported above in Tables 1 and 2. In BREEZE-AD1, BREEZE-AD2 and BREEZE-AD4, significant differences favouring the baricitinib 4mg group compared with placebo were observed for least squares (LS) mean change from baseline in the Skin Pain NRS at week 16 and Atopic Dermatitis Sleep Scale (ADSS) – frequency of night-time wakening (item 2) at week 16. In BREEZE-AD7, the between group differences numerically favoured baricitinib 4mg. Other patient reported outcomes assessed included the mean change from baseline in the Patient Orientated Eczema Measure (POEM) and the Dermatology Life Quality Index (DLQI); these favoured the baricitinib group compared with placebo.[3-6]

Patients from BREEZE-AD1, BREEZE-AD2 and BREEZE-AD7 were eligible to participate in BREEZE-AD3, an ongoing long-term extension study. Patients from these studies were identified as responders (vIGA-AD of 0 or 1 and did not receive rescue treatment), partial responders (vIGA-AD score of 2 and did not receive rescue treatment) or non-responders (vIGA-AD score of 3 or 4 or had received rescue treatment). This classification determined if they remained on the same treatment and dose or were re-randomised to receive baricitinib 2mg or 4mg for an initial treatment period of 52 weeks. The primary outcome of BREEZE-AD3 was the proportion of patients that achieved a vIGA-AD score of 0 or 1 at week 16, week 36 and week 52. The key secondary outcome was EASI75 at week 16. Interim results from responders and partial responders demonstrated that the proportion of patients achieving a vIGA-AD score of 0 or 1 was higher in the baricitinib 2mg group (67% [30/45]) compared with the baricitinib 4mg (38% [24/64]) and placebo groups (23% [11/47]) at week 36 for patients on monotherapy and week 24 for patients on combination therapy (45% [14/31] in the baricitinib 2mg group compared with 36% [9/25] in the baricitinib 4mg group and 40% [6/15] in the placebo group). This was supported by the proportion of patients that achieved an EASI75 and consistently demonstrated the response was numerically greater in the baricitinib 2mg group compared with the other treatment groups.[3]

In the absence of direct evidence with an active comparator, the submitting company presented three pairwise Bucher indirect treatment comparisons (ITCs). The ITCs compared baricitinib with dupilumab as monotherapy and in combination with a topical corticosteroid in adult patients with

moderate to severe atopic dermatitis who have experienced failure with, are intolerant to, or are contraindicated to ciclosporin. Data for baricitinib were taken from BREEZE-AD4 and a subgroup of BREEZE-AD4-like patients (a subgroup of patients with ciclosporin failure, intolerance or contradiction) from BREEZE-AD1, BREEZE-AD2 and BREEZE-AD7. Data for dupilumab were taken from CAFÉ[11] and a subgroup of CAFÉ-like patients from SOLO-1[12], SOLO-2[12] and CHRONOS[13]. The outcomes included in the analysis were: the proportion of patients that achieved an EASI50, EASI75 and EASI90 response and the proportion of patients with a ≥4-point improvement in itch NRS, all outcomes were measured at 16 weeks. Outcome data were compared using primary and secondary censoring rules. The results of the ITC suggest that for most outcomes baricitinib and dupilumab have similar efficacy when used in combination with a topical corticosteroid or as monotherapy. Across all outcomes, results produced using the secondary censoring rule were broadly consistent with the primary analyses. These secondary censoring data were used to inform the economic base case.

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

Summary of evidence on comparative safety

Overall, the EMA considered that the safety profile of baricitinib for the treatment of atopic dermatitis is consistent with that already known for the treatment of rheumatoid arthritis.[3]

A pooled analysis assessed the safety of baricitinib compared with placebo during the 16-week placebo-controlled period for patients in a phase II study and four phase III studies including BREEZE-AD1, BREEZE-AD2, BREEZE-AD4 and BREEZE-AD7. The median duration of treatment was 113 days for the baricitinib 4mg and placebo groups. Any treatment-emergent adverse event (AE) was reported by 51% (300/489) in the baricitinib 4mg group and 43% (388/743) in the placebo group. In both groups, 2.3% reported a serious AE and the proportion of patients that discontinued treatment because of an AE was 2.1% in the baricitinib 4mg group and 1.4% in the placebo group. The most frequently reported treatment-emergent AEs in the pooled safety analysis with an adjusted incidence ≥5% in the baricitinib 4mg group versus placebo were: nasopharyngitis (11% versus 9.5%) and headache (6.3% versus 3.3%).[8]

In BREEZE-AD4, whose full population reflects the proposed positioning, safety data are available for 16 weeks of treatment with baricitinib. Any treatment-emergent AE was reported by 75% (69/92) in the baricitinib 4mg group and 54% (50/93) in the placebo group. In each group respectively, 6.5% and 2.2% reported a serious AE and the proportion of patients that discontinued treatment due to an AE was 1.1% in both groups. The most frequently reported treatment-emergent AEs in BREEZE-AD4 with an incidence ≥5% in the baricitinib 4mg group versus placebo were: nasopharyngitis (26% versus 13%), headache (7.6% versus 6.5%), influenza (6.5% versus 2.2%), upper abdominal pain (5.4% versus 2.2%), diarrhoea (5.4% versus 3.2%) and oral herpes (5.4% versus 3.2%).[3, 6]

Treatment with baricitinib was associated with a higher incidence of infections, elevations in lipid parameters including total cholesterol, low-density lipoprotein cholesterol (LDL) and high-density lipoprotein cholesterol (HDL), increased hepatic transaminases and creatine phosphokinase. A risk management plan is in place and a post authorisation study has been proposed to assess the long-term safety profile for the treatment of atopic dermatitis.[3] Please see SPC for further information on adverse events and monitoring guidance.[2]

Summary of clinical effectiveness issues

Atopic dermatitis is a chronic, relapsing, heterogeneous, inflammatory skin disease that is characterised by eczematous skin lesions, itch, pain and other atopic conditions such as asthma and allergic rhinitis. Itch is considered the most debilitating manifestation and failure to gain adequate control can result in scratching, superimposed skin inflammation, infections, sleep disturbance, anxiety, depression and has a substantial impact of quality of life.[3]

Treatment for atopic dermatitis includes initial therapy with emollients and topical corticosteroids. A topical calcineurin inhibitor may be considered for moderate to severe disease that has not been controlled by topical corticosteroids or where there is a serious risk of important adverse effects from further use. If topical agents fail to control skin inflammation and alleviate symptoms, additional treatment options may be required including phototherapy and systemic immunosuppressants. Oral ciclosporin is licensed for the treatment of severe atopic dermatitis and due to its safety profile, is recommended for intermittent use. Other oral immunosuppressants used off-label include methotrexate, azathioprine and mycophenolate mofetil. Subcutaneous dupilumab is licensed for moderate to severe atopic dermatitis and has been accepted for restricted use by SMC in adult patients who have had an inadequate response to existing systemic immunosuppressants such as ciclosporin, or in whom such treatment is considered unsuitable (SMC2011).[3, 14, 15] Clinical experts consulted by SMC considered that baricitinib fills an unmet need in this therapeutic area, namely for the treatment of moderate to severe atopic dermatitis.

The submitting company has requested that SMC considers baricitinib when positioned for use for patients who have failed at least one current systemic immunosuppressant due to intolerance, contraindication or inadequate disease control.

The baricitinib 4mg dose demonstrated superiority compared with placebo as monotherapy in BREEZE-AD1 and BREEZE-AD2 and in combination with a topical corticosteroid in BREEZE-AD7 and BREEZE-AD4 for the primary outcome of a vIGA-AD score of 0 or 1 or EASI75 response at 16 weeks. This was supported by a favourable response for a number of patient reported outcomes. The treatment effect was considered modest in the monotherapy studies and patients frequently required rescue treatment with topical corticosteroids, however, the EMA indicated it was clinically relevant. The treatment effect can be enhanced by concomitant use with topical corticosteroids.[4-6] Interim results from long-term extension study BREEZE-AD3 demonstrated that the treatment effect was largely maintained from week 16 over 52 weeks for patients on monotherapy or combination therapy and the effect was similar for patients continuing on the

2mg or 4mg dose. Therefore, patients on baricitinib 4mg who have achieved sustained control of disease activity may be considered for dose tapering to the lower 2mg dose.[2, 3]

The proposed positioning of baricitinib is in patients who have failed at least one current systemic immunosuppressant due to intolerance, contraindication or inadequate disease control. This subpopulation of patients is represented in the full study population of BREEZE-AD4, although this study only included patients that had failed ciclosporin and no other systemic immunosuppressants. A post hoc subgroup analysis of patients from BREEZE-AD1, BREEZE-AD2 and BREEZE-AD7 with ciclosporin failure, intolerance or contraindication also supports the proposed positioning; however, the number of patients in these subgroups were small and the studies were not powered for subgroup analyses. Overall, the EMA noted that previous failure of ciclosporin did not seem to have a negative influence on the treatment effect of baricitinib 4mg.[3]

Clinical experts consulted by SMC suggested that baricitinib may be used after treatment failure with dupilumab but a limited number of patients in the BREEZE-AD studies had received previous treatment with dupilumab. However, the EMA noted there was no indication that treatment with baricitinib would be ineffective if patients had previously used dupilumab.[3]

Long-term data are limited as BREEZE-AD4 and long-term extension study BREEZE-AD3 are ongoing. The clinical impact of treatment cessation or down-titration of doses remains uncertain and this is being studied in BREEZE-AD3. Further data will be available in 2023 when final results are available.[3]

There were no active comparators in the key studies. Best supportive care and dupilumab are considered the most relevant comparators for the patient population based on the proposed positioning. A number of oral systemic immunosuppressants are used in the treatment of atopic dermatitis but these are not licensed for this indication and are used off-label. Bucher ITCs compared baricitinib with dupilumab.

A number of limitations affect the validity of the ITCs, including the clinical and methodological heterogeneity across the studies. BREEZE-AD4 and BREEZE-AD7 included a higher proportion of Asian patients compared with CAFÉ and CHRONOS. As geographic region appears to be an effect modifier, a sensitivity analysis was conducted using data from European patients from BREEZE-AD4. There was also heterogeneity in topical corticosteroid washout and censoring rules applied in the baricitinib and dupilumab studies. The ITC is based on pooled data from post-hoc subgroups from BREEZE-AD1, -AD2, -AD7 and CHRONOS, SOLO-1 and SOLO-2 and this may also affect the validity of the results. Results could only be explored in the short-term (16 weeks) and long-term efficacy of baricitinib versus dupilumab is uncertain. There were also no safety or health-related quality of life outcomes included in the analysis. Due to these limitations, the company's conclusions are uncertain.

Clinical experts consulted by SMC considered that baricitinib is a therapeutic advancement due to its novel mechanism of action. They also indicated that it would provide patients with an additional treatment where options are currently limited. It is anticipated that baricitinib will be

used for patients who have failed or are intolerant to oral systemic immunosuppressants. Clinical experts suggested that baricitinib would be used in patients who have also failed dupilumab, although they noted that treatment choice would depend on considerations such as patients' characteristics, preferred route of administration and side effects. Baricitinib is a once daily oral treatment which some patients and carers may find advantageous compared with an alternative injectable option.

Summary of comparative health economic evidence

The submitting company presented a cost-utility analysis evaluating baricitinib within its licensed indication, with the additional restriction to patients who have failed at least one current systemic immunosuppressant due to intolerance, contraindication or inadequate disease control. Comparisons were provided against dupilumab and best supportive care (BSC).

A cohort-level Markov state transition model was presented representing four main health states ('induction', 'maintenance', 'non-response' and 'death') across two lines of treatment (line 1: active treatment with baricitinib/dupilumab; line 2: best supportive care). Patients entered the model in induction, and after 16 weeks the proportion of patients estimated to achieve an EASI75 response transitioned into the 'maintenance' state. The remaining patients transitioned to the next line of treatment, entering line 2 at 'induction' or line 3 in the 'no response' health state. Patients could discontinue maintenance treatment with baricitinib or dupilumab and move to the next treatment line. A simplifying assumption of no discontinuation in the BSC maintenance state was applied, to reflect the waxing and waning nature of patients achieving and losing a response to BSC over the time horizon. A four-week cycle length and lifetime time horizon was used.

Clinical effectiveness data were mainly derived from a pooled analysis of the BREEZE-AD4 and BREEZE-AD4-like patients from the BREEZE-AD7 study[5, 6]. An indirect comparison (as described above) was utilised to provide treatment response data for dupilumab. This suggested a probability of response at week 16 of 42% for baricitinib, 57% for dupilumab and 22% for best-supportive care. Baricitinib and dupilumab discontinuation rates up to 52 weeks were based on conditional probability of EASI75 response in patients achieving a response at week 16, following which all-cause discontinuation rates at 52 weeks was used to calculate a constant discontinuation rate from year 2 onwards.

EQ-5D-5L data were collected in the BREEZE-AD4 and BREEZE-AD7 studies and valued using the crosswalk algorithm and the UK value set.[16, 17] Patient-level utilities were included in a mixed-model repeated measures analysis to estimate the change in utility score at week 16 for an EASI response and non-response. This resulted in health state utility values of 0.62 for induction, 0.84 for the maintenance health state and 0.76 for the non-response health state. A waning in utility was also applied for both responders and non-responders, where to reflect patient adherence to treatment, a proportion of patients were assumed to revert to baseline utility over time. This resulted in nearly all BSC-treated patients in the maintenance health state and non-response

states reverting to baseline utilities, versus a minority of baricitinib and dupilumab patients (96% versus 8%).

Medicines costs included the acquisition and administration costs of baricitinib and dupilumab, alongside costs of concomitant medicines (emollients, topical corticosteroids and topical calcineurin inhibitors). A stopping rule was applied for baricitinib which assumed all patients who do not achieve an EASI75 response at week 16 will discontinue treatment (in contrast to the use of a composite outcome of EASI50 and DLQI≥4, as used in the previous SMC submission for dupilumab). Costs of managing specific adverse events were also included (for injection site reactions, allergic conjunctivitis, infectious conjunctivitis, oral herpes and upper respiratory tract infections). Resource use included routine outpatient, community and inpatient appointments, phototherapy and psychological services.

A Patient Access Scheme (PAS) was submitted by the company and assessed by the Patient Access Scheme Assessment Group (PASAG) as acceptable for implementation in NHSScotland. Under the PAS, a discount was offered on the list price. A PAS discount is in place for dupilumab and this was included in the results used for decision-making by using estimates of the comparator PAS price.

The base case results are shown below for the comparisons with best supportive care and dupilumab (Table 3). The QALYs are primarily driven by the increased quality of life in the maintenance health state for dupilumab and baricitinib for the BSC comparison, and the reduced proportion of baricitinib patients achieving a response for the dupilumab comparison. Cost differences between baricitinib and the two comparators are primarily a result of differences in costs of medicines acquisition.

The results presented do not take account of the PAS for dupilumab or the PAS for baricitinib but these were considered in the results used for decision-making. SMC is unable to present the results provided by the company which used an estimate of the PAS price for dupilumab due to commercial confidentiality and competition law issues.

Table 3: Base case results

Comparator	Pairwise ICER (£/QALY)
BSC (at list price)	£65,466
Dupilumab (at list prices)	£113,459 (SW Quadrant)

QALYs: Quality-adjusted life year; ICER: Incremental cost-effectiveness ratio; BSC: best supportive care; SW Quadrant: south-west quadrant (baricitinib is less effective and less costly)

A number of sensitivity analyses were provided and the key scenarios are summarised in Table 4. The comparison with best supportive care was highly sensitive to the impact of the utility waning assumption and the positioning of baricitinib in the treatment pathway. The comparison with dupilumab provided more stable results which were consistent with the base case.

Table 4: Key scenario analyses

	Scenario	Base case approach	Scenario approach	ICER vs BSC (list price)	ICER vs dupilumab (all list price)
	Base case	-	As base case	£65,466	£113,459 (SW Quadrant)
1.	**Monotherapy**	Baricitinib modelled in combination with topical corticosteroids	Baricitinib modelled for use as a monotherapy	£85,675	£119,200 (SW Quadrant)
2.	**Utility waning**	Waning of utility applied on treatment-specific basis	No waning applied to any treatment	£298,043	£286,739 (SW Quadrant)
3.			No waning in utility values beyond year 2	£68,900	£102,523 (SW Quadrant)
4.	**Treatment sequencing (baricitinib used prior to dupilumab)**	Line 1: baricitinib: Line 2: BSC	Line 1: baricitinib Line 2: dupilumab Line 3: BSC	£65,466	£57,341 (SW Quadrant)
5.	**Stopping rule**	Patients who do not achieve EASI75 at week 16 discontinue baricitinib	Patients who do not achieve EASI50 at week 16 discontinue baricitinib	£80,898	£98,295 (SW Quadrant)
6.	**Alternative response criteria**	Response based on EASI75	Response based on EASI50 and DLQI>= 4 criteria	£69,076	£84,943 (SW Quadrant)

The economic analysis had a number of strengths, including the choice of appropriate comparators, and the approach to measuring and valuing health state utilities. A number of conservative approaches were also taken, particularly in the assumption of inferiority to dupilumab based on numerical differences in the ITC, and the omission of potential utility benefits for an oral therapy over a subcutaneous injection.

However, there were a number of limitations which could impact on the reliability of the results:

- The application of a utility waning effect is uncertain, particularly with respect to best supportive care. This assumed that, from year 5 onwards across the patient lifetime, patients achieving an EASI75 response to best supportive care will have negligible improvements in quality of life over non-responders. Although acknowledging that the modelling of response to best supportive care is an attempt to reflect the waxing and waning nature of AD, this approach may bias in favour of baricitinib. While the removal of this waning effect results in a substantially higher ICER (**Error! Reference source not found.**4, Scenario 2), this was felt to be overly conservative by the New Drugs Committee. An alternative approach to waning was obtained to align with the previous SMC assessment of dupilumab, which assumed no additional waning in effect from year 2 onwards. This resulted in a moderate increase to the ICER (Table 4, Scenario 3), although is subject to a degree of uncertainty.
- A stopping rule has been applied at sixteen weeks, which results in patients who do not achieve an EASI75 response transitioning to the low-cost best supportive care health state. EASI75 represents a relatively high target, and it is unclear whether all patients who achieve a degree of response (such as EASI50) will discontinue treatment. Alternative scenarios were requested which utilised a lower threshold of EASI50 (Table 4, Scenario 5), as well as the composite endpoint of EASI50 and DLQI50≥4 (Table 4, Scenario 6), which is consistent with the SMC guidance for dupilumab in the same indication. The former resulted in a moderate increase in the ICER, with a smaller increase in the latter.
- The submission focused on the use of baricitinib in combination with topical corticosteroids. The majority of expert responses received by SMC corroborated this approach. However, one expert suggested that it may also be used as a monotherapy, in which case the ICER increased for the BSC comparison (Table 4, Scenario 1).

Despite these weaknesses, the economic case was demonstrated.

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

Summary of patient and carer involvement

The following information reflects the views of the specified Patient Groups.

- We received patient group submissions from Allergy UK and National Eczema Society, which are both registered charities.
- Allergy UK has received 5.3% pharmaceutical company funding in the past two years, including from the submitting company. National Eczema Society has received 22% pharmaceutical company funding in the past two years, including from the submitting company.
- Atopic eczema is a chronic inflammatory skin condition. Its major symptom is itchiness, which can be intense, relentless and unbearable. Constant scratching causes the skin to split and bleed and increases the risk of infection. Individuals with eczema often find

sleeping extremely difficult. The condition can impact on their ability to perform daily activities as well as physical, social and psychological wellbeing.

- Current treatment options are limited. Eczema is a heterogeneous disease requiring a variety of treatment options. Second-line treatments such as immunosuppressants do not work for everyone, and some are not eligible to take them. There is a need for new treatments to reduce the lived impact of severe eczema.
- Baricitinib has a different mode of action to current treatments. It would provide a valued additional option to help people live with this condition, with the potential to improve symptoms and quality of life. AS an oral medicine, it would offer a more convenient treatment option that is likely to be preferred over injection. The safety profile is also felt to be manageable.

Additional information: guidelines and protocols

Consensus-based European guidelines for treatment of atopic eczema (atopic dermatitis) in adults and children: part II were published in 2018. This second part of the guideline covers various treatments including systemic therapy and states that systemic immunosuppressive treatment with ciclosporin, methotrexate, azathioprine and mycophenolate mofetil is an established option for severe refractory cases. It also recommends that biologicals such as dupilumab may be a safe and effective, disease modifying alternative when available. It is noted that JAK inhibitors are in development. This guideline pre-dates the availability of baricitinib.

The Scottish Intercollegiate Guidelines Network (SIGN) published Management of atopic eczema in primary care, a national clinical guideline (SIGN 125) in 2011. This guideline focuses on primary care and excludes treatments that are usually carried out in secondary care, such as phototherapy and systemic immunosuppressant drugs. SIGN 125 recommends that patients with atopic eczema should have ongoing treatment with topical emollients, once daily topical corticosteroids are also advised and patients with moderate to severe disease experiencing frequent relapses should be considered for twice weekly topical corticosteroid maintenance therapy. Topical tacrolimus should be considered, in patients aged two years and older, for short term, intermittent treatment of moderate to severe atopic eczema that has not been controlled by topical corticosteroids or where there is a serious risk of important adverse effects from further topical corticosteroid use, particularly skin atrophy.

Additional information: comparators

Dupilumab and best supportive care.

Additional information: list price of medicine under review

Medicine	Dose Regimen	Cost per year (£)
Baricitinib	**4mg once daily**	**10,472**
	2mg once daily	**10,472**

Costs from BNF online on 26 February 2021. Costs do not take patient access schemes into consideration.

Additional information: budget impact

The submitting company estimated there would be 768 patients eligible for treatment with baricitinib in year 1 and 778 patients in year 5, to which confidential estimates of treatment uptake were applied.

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. This template does not incorporate any PAS discounts associated with comparator medicines or PAS associated with medicines used in a combination regimen.

The savings from displacement of other medicines may also not be achieved, as clinical experts consulted by SMC suggest that baricitinib is likely to be positioned subsequent to dupilumab in the treatment pathway.

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

References

1. Eli Lilly and Company Limited. Baricitinib 2mg film-coated tablets (Olumiant®). Summary of product characteristics. Electronic Medicines Compendium https://www.medicines.org.uk/emc/product/2434/smpc last updated 07 December 2020.
2. Eli Lilly and Company Limited. Baricitinib 4mg film-coated tablets (Olumiant®). Summary of product characteristics. Electronic Medicines Compendium https://www.medicines.org.uk/emc/product/7486/smpc last updated 07 December 2020.
3. European Medicines Agency (EMA). European Public Assessment Report Type II Variation. Baricitinib (Olumiant®) EMA/520470/2020 17 September 2020. Available at: https://www.ema.europa.eu/en/documents/variation-report/olumiant-h-c-4085-ii-0016-epar-assessment-report-variation_en.pdf.
4. Simpson EL, Lacour JP, Spelman L, Galimberti R, Eichenfield LF, Bissonnette R*, et al.* Baricitinib in patients with moderate-to-severe atopic dermatitis and inadequate response to topical corticosteroids: results from two randomized monotherapy phase III trials. British Journal of Dermatology. 2020.
5. Reich. K., et al. Efficacy and Safety of Baricitinib Combined With Topical Corticosteroids for Treatment of Moderate to Severe Atopic Dermatitis. JAMA Dermatol. 2020;156(12):1333-1343.
6. Bieber. T., et al. Efficacy and Safety of Baricitinib in Combination With Topical Corticosteroids in Patients With Moderate-to-Severe Atopic Dermatitis Who Failed, Are Intolerant to, or Have Contraindication to Cyclosporine: Results From a Randomized, Placebo-Controlled, Phase 3 Clinical Trial (BREEZE-AD4). P0183. Presented at EADV Virtual Congress 29th - 31st October 2020. .
7. Eli Lilly and Company. I4V-MC-JAIN (BREEZE-AD4) Clinical Study Report (13th April 2020).
8. Bieber T, Thyssen JP, Reich K, et al. Pooled safety analysis of baricitinib in adult patients with atopic dermatitis from 8 randomized clinical trials. J Eur Acad Dermatol Venereol 2021;35:476-485.
9. U.S. National Library of Medicine ClinicalTrials.gov. A Long-term Study of Baricitinib (LY3009104) With Topical Corticosteroids in Adults With Moderate to Severe Atopic Dermatitis That Are Not Controlled With Cyclosporine or for Those Who Cannot Take Oral Cyclosporine Because it is Not Medically Advisable (BREEZE-AD4). NCT03428100. Last updated 19 January 2021. Available at: https://clinicaltrials.gov/ct2/show/results/NCT03428100?term=breeze-ad4&draw=2&rank=1.
10. Eli Lilly and Company. Data on file. .
11. de Bruin-Weller M, Thaci D, Smith CH, Reich K, Cork MJ, Radin A*, et al.* Dupilumab with concomitant topical corticosteroid treatment in adults with atopic dermatitis with an inadequate response or intolerance to ciclosporin A or when this treatment is medically inadvisable: a placebo-controlled, randomized phase III clinical trial (LIBERTY AD CAFE). The British journal of dermatology. 2018;178(5):1083-101. Epub 2017/12/02.
12. Simpson EL, Bieber T, Guttman-Yassky E, Beck LA, Blauvelt A, Cork MJ*, et al.* Two Phase 3 Trials of Dupilumab versus Placebo in Atopic Dermatitis. New England Journal of Medicine. 2016;375(24):2335-48.
13. Blauvelt A, de Bruin-Weller M, Gooderham M, Cather JC, Weisman J, Pariser D*, et al.* Long-term management of moderate-to-severe atopic dermatitis with dupilumab and concomitant topical corticosteroids (LIBERTY AD CHRONOS): a 1-year, randomised, double-blinded, placebo-controlled, phase 3 trial. The Lancet. 2017;389(10086):2287-303.
14. Scottish Intercollegiate Guidelines Network. Management of atopic eczema in primary care (SIGN125). March 2011. Available at: https://www.sign.ac.uk/media/1063/sign125.pdf [Last accessed: 15th March 2021]. [cited.

15. Wollenberg. A., et al. Consensus-based European guidelines for treatment ofatopic eczema (atopic dermatitis) in adults and children:part II. European Academy of Dermatology and Venereology 2018;32 p850-878.
16. van Hout B, Janssen MF, Feng YS, Kohlmann T, Busschbach J, Golicki D*, et al.* Interim scoring for the EQ-5D-5L: mapping the EQ-5D-5L to EQ-5D-3L value sets. Value in health : the journal of the International Society for Pharmacoeconomics and Outcomes Research. 2012;15(5):708-15. Epub 2012/08/08.
17. Dolan P. Modeling valuations for EuroQol health states. Medical care. 1997;35(11):1095-108. Epub 1997/11/21.

This assessment is based on data submitted by the applicant company up to and including 16 April 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.