Healthcare Improvement Scotland | SMC Advice on new medicines

SMC2417

# upadacitinib 15mg and 30mg prolonged-release tablets (Rinvoq®)

AbbVie Ltd

04 March 2022

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

**upadacitinib (Rinvoq®)** is accepted for restricted use within NHSScotland.

**Indication under review:** for the treatment of moderate to severe atopic dermatitis in adults and adolescents 12 years and older who are candidates for systemic therapy.

**SMC restriction:** patients who have had an inadequate response to at least one conventional systemic immunosuppressant such as ciclosporin, or in whom such treatment is considered unsuitable.

In patients with moderate to severe atopic dermatitis eligible for systemic therapy, upadacitinib was associated with significantly greater improvements in the signs and symptoms of atopic dermatitis in adults and adolescent patients in three placebo-controlled phase III studies and in adult patients in one phase III comparative study with a monoclonal antibody.

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 adults and adolescents 12 years and older who are candidates for systemic therapy.[1]

## Dosing Information

The recommended dose of upadacitinib for adults is 15mg or 30mg once daily based on individual patient presentation. A dose of 30mg once daily may be appropriate for patients with high disease burden or an inadequate response to 15mg once daily. The lowest effective dose for maintenance should be considered. For patients ≥65 years of age, the recommended dose is 15mg once daily.

The recommended dose of upadacitinib for adolescents (from 12 to 17 years of age) weighing at least 30kg is 15mg once daily.

Upadacitinib can be used with or without topical corticosteroids. Topical calcineurin inhibitors may be used for sensitive areas such as the face, neck, and intertriginous and genital areas.

Consideration should be given to discontinuing upadacitinib treatment in any patient who shows no evidence of therapeutic benefit after 12 weeks of treatment.

Treatment with upadacitinib should be initiated and supervised by physicians experienced in the diagnosis and treatment of conditions for which upadacitinib is indicated.[1]

## Product availability date

25 August 2021

# Summary of evidence on comparative efficacy

Upadacitinib is a Janus kinase (JAK) inhibitor; it selectively and reversibly inhibits JAK enzymes, which transmit cytokine or growth factor signals that are involved in a broad range of cellular processes including inflammatory responses, haematopoiesis and immune surveillance. Inhibiting JAK1 with upadacitinib reduces the signalling of many mediators which drive the signs and symptoms of atopic dermatitis.[1,2] The submitting company requested that SMC considers the use of upadacitinib when positioned for both:

- the full licensed indication, that is for the treatment of moderate to severe atopic dermatitis in adults and adolescents who are candidates for systemic therapy (referred to as systemic-eligible) and
- a subpopulation of the licensed indication, that is for the treatment of moderate to severe atopic dermatitis in patients in whom the disease has not responded to at least one other conventional systemic immunosuppressant therapy (ciclosporin, methotrexate, azathioprine or mycophenolate mofetil) or conventional systemic therapy is not suitable (referred to as systemic-exposed).

The evidence comes from three randomised, double-blind, placebo-controlled, phase III studies (Measure Up 1, Measure Up 2 and AD Up) and one randomised, double-blind, phase IIIb study comparing upadacitinib with dupilumab (Heads Up) in patients with moderate to severe atopic dermatitis. In all four studies, eligible patients had a diagnosis of chronic atopic dermatitis according to Hanifin and Rajka criteria with symptoms onset ≥3 years previously. They had moderate to severe disease (defined as meeting all of: ≥10% of body surface area affected by atopic dermatitis; Eczema Area and Severity Index [EASI] score of ≥16; validated Investigator's Global Assessment for Atopic Dermatitis [vIGA-AD] score of ≥3 and Worst Pruritus Numerical Rating Scale [WP-NRS] score of ≥4) and were considered eligible for systemic therapy. Measure Up 1, Measure Up 2 and AD Up enrolled patients aged 12 to 75 years (adolescents had to weigh ≥40kg); Heads Up enrolled adult patients (18 to 75 years) only.[2-5]

In Measure Up 1, Measure Up 2 and AD Up, eligible patients were randomised equally to receive upadacitinib 15mg, 30mg or placebo orally once daily for the 16-week double-blind period. All patients used a topical emollient twice daily. In AD Up, all patients also received topical corticosteroids which were stepped down over the study period. Randomisation was stratified by vIGA-AD score at baseline (3 or 4), age group (adolescent or adult) and geographical region. Rescue medication was permitted at the discretion of the investigator after week 4 in patients who did not achieve a ≥50% improvement in EASI response.[2-4]

There were two co-primary outcomes of the proportion of patients who achieved:

- a ≥75% improvement in EASI score (EASI 75) from baseline to week 16. The EASI score measures the extent and severity of signs of atopic dermatitis.
- a vIGA-AD response (defined as a score of 0 [clear] or 1 [almost clear] with ≥2-grade reduction from baseline) at week 16. The vIGA-AD is a global score assessed by the investigator.

Efficacy analyses were performed in the intention to treat (ITT) populations, which comprised all randomised patients. A hierarchical statistical testing strategy was applied to the co-primary and numerous secondary outcomes with no formal testing of outcomes after the first non-significant outcome in the hierarchy. In all three studies, the co-primary and all secondary outcomes were significantly improved with both upadacitinib dose groups compared with placebo ($p<0.001$). Details are presented in Table 1.[2,3,4]

**Table 1: Results for the co-primary and selected secondary outcomes in placebo-controlled studies (Measure Up 1, Measure Up 2 and AD Up).**[1-4,6]

| | **Measure Up 1** | | | **Measure Up 2** | | | **AD Up (+TCS)** | | |
|---|---|---|---|---|---|---|---|---|---|
| | UPA 15 | UPA 30 | PBO | UPA 15 | UPA 30 | PBO | UPA 15 | UPA 30 | PBO |
| Number of patients | 281 | 285 | 281 | 276 | 282 | 278 | 300 | 297 | 304 |
| **Co-primary outcomes at week 16** | | | | | | | | | |
| EASI 75 | 70% | 80% | 16% | 60% | 73% | 13% | 65% | 77% | 26% |
| Adj diff vs placebo (95% CI) | 53% (46 to 60) | 63% (57 to 70) | - | 47% (40 to 54) | 60% (53 to 66) | - | 38% (31 to 45) | 51% (44 to 57) | - |
| vIGA-AD 0/1 | 48% | 62% | 8.4% | 39% | 52% | 4.7% | 40% | 59% | 11% |
| Adj diff vs placebo (95% CI) | 40% (33 to 46) | 54% (47 to 60) | - | 34% (28 to 40) | 47% (41 to 54) | - | 28% (22 to 35) | 48% (41 to 54) | - |

| Secondary outcomes at week 16 | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| WP NRS ≥4 improvement* | 52% (143/274) | 60% (168/280) | 12% (32/272) | 42% (113/270) | 60% (167/280) | 9.1% (25/274) | 52% (149/288) | 64% (186/291) | 15% (44/294) |
| EASI 90 | 53% | 66% | 8.1% | 42% | 58% | 5.4% | 43% | 63% | 13% |
| EASI 100 | 17% | 27% | 1.8% | 14% | 19% | 0.7% | 12% | 23% | 1.3% |
| DLQI ≥4 improvement ** | 75% (192/254 | 82% (210/256) | 29% (73/250) | 72% (180/251) | 78% (195/251) | 28% (71/250) | | | |

*WP NRS ≥4 improvement was assessed in patients with score ≥4 at baseline

**DLQI 0/1 was assessed in patients aged ≥16 years with DLQI ≥4 at baseline

UPA 15= upadacitinib 15mg; UPA 30=upadacitinib 30mg; PBO=placebo; TCS=topical corticosteroid; EASI 75=≥75% improvement in Eczema Area and Severity Index; adj diff=adjusted difference; CI=confidence interval; vIGA-AD 0/1= validated Investigator Global Assessment for Atopic Dermatitis score of 0 or 1 ; WP NRS=worst pruritus numerical rating scale; EASI 90=≥90% improvement in Eczema Area and Severity Index; EASI 100=complete improvement in Eczema Area and Severity Index; DLQI=Dermatology Life Quality Index

Early assessment of lesions, using EASI 75 at weeks 2 and 4 and EASI 90 at week 4, and itch, using WP NRS ≥4 improvement at week 1, indicated that the treatment effect had a rapid onset. All assessments of quality of life and patient reported outcomes including the Dermatology Life Quality Index (DLQI), Patient-Oriented Eczema Measure (POEM), Hospital Anxiety and Depression Scale (HADS) and SCORing of Atopic Dermatitis (SCORAD) significantly favoured both upadacitinib groups over placebo.[2-4]

Patients who completed the 16-week studies could enter blinded extensions where patients in the placebo groups were re-randomised equally to receive upadacitinib 15mg or 30mg orally daily for 120 weeks. Interim results are currently available to week 52, which suggest that patients who continued upadacitinib during the blinded extension generally maintained treatment responses to week 52.[2]

In the comparative Heads Up study, eligible patients were randomised equally to receive upadacitinib 30mg orally once daily for 24 weeks plus placebo subcutaneous injections every 2 weeks (n=348) or dupilumab 600mg subcutaneous loading dose and then 300mg by subcutaneous injection every 2 weeks to week 22 plus placebo tablets daily until week24 (n=344).

Randomisation was stratified by disease severity at baseline (vIGA-AD of 3 or 4) and age (<40 or ≥40 to <65 or ≥65 years). All patients also used an emollient twice daily. Rescue medication was permitted at any time the discretion of the investigator.[5]

The primary outcome was the proportion of patients who achieved EASI 75 at week 16 in the ITT population (all randomised patients). A hierarchical statistical testing strategy was applied to the primary and seven ranked secondary outcomes with no formal testing of outcomes after the first non-significant outcome in the hierarchy. Results for primary and ranked secondary outcomes all significantly favoured upadacitinib over dupilumab; details of primary and several secondary outcomes are presented in Table 2. Other than worst pruritus numerical rating scale, no other patient reported or quality of life outcomes were assessed during Heads Up.[5]

**Table 2: Primary and selected secondary outcomes at week 16 in Heads Up study.**[5,7]

| | Upadacitinib 30mg orally once daily (n=348) | Dupilumab 300mg SC every 2 weeks (n=344) | Adjusted difference (95% CI), p-value |
|---|---|---|---|
| **Primary outcome** | | | |
| EASI 75 | 71% | 61% | 10% (2.9 to 17), p=0.006 |
| **Secondary outcomes** | | | |
| % change in WP NRS | (n=258) -67% | (n=251) -49% | -18% p<0.001 |
| EASI 100 | 28% | 7.6% | 20% p<0.001 |
| EASI 90 | 61% | 39% | 22% p<0.001 |
| Improvement in WP NRS ≥4 for patients with WP NRS ≥4 at baseline | (n=340) 55% | (n=336) 36% | 19% p<0.001 |

sc=subcutaneous; CI=confidence interval; EASI 75=≥75% improvement in Eczema Area and Severity Index; WP NRS=worst pruritus numerical rating scale; EASI 100=complete improvement in Eczema Area and Severity Index; EASI 90=≥90% improvement in Eczema Area and Severity Index

The company did not provide direct evidence of efficacy for the proposed positioning in patients in whom the disease has not responded to at least one other conventional systemic immunosuppressant therapy (ciclosporin, methotrexate, azathioprine or mycophenolate mofetil) or conventional systemic therapy is not suitable. Instead, post hoc results for the small number of patients with previous exposure to ciclosporin were provided and used for the network meta-analyses (NMAs). However, approximately 50% of study patients had received previous systemic therapy and pre-specified subgroup analyses from Measure Up 1, Measure Up 2, AD Up and Heads Up suggests that the treatment effect in these patients was consistent with results in the full populations.[2,7]

The submitting company presented separate Bayesian NMAs the licensed populations (adolescents) and the proposed restricted sub-population. The NMA results for the base case of the economics used fixed effects models and were from the all observed populations. The NMA for the adolescent population compared upadacitinib with dupilumab and BSC in adolescent patients who may or may not have received prior systemic treatment, with data from three studies (two based on adolescent subgroups), using EASI 75 at week 16. The results suggest that, as monotherapy, upadacitinib 15mg was superior to placebo and dupilumab. Scenario analyses were also presented using the primary ITT analyses and EASI 50.

The NMA for the restricted sub-population compared upadacitinib with dupilumab and BSC, all in combination with topical corticosteroids, in adult patients who have previously received ciclosporin (as a proxy for prior systemic therapy). The NMA used data from post hoc subgroups from two of the three included studies and compared the outcome, EASI 50 plus an improvement in DLQI of ≥4 points (EASI 50 + DLQI ≥4) at week 16. No separate NMA was presented for adolescent patients who have received at least one previous systemic therapy due to small patient

numbers. The results suggest that in combination with topical corticosteroids, upadacitinib 30mg was superior to dupilumab, with no evidence of a difference for upadacitinib 15mg. Scenario analyses included the primary ITT analyses, additional outcomes (EASI 50 and EASI 75) as well as data from Heads Up.

On request, the company provided the NMA results for these populations using random effects models, which indicated that there was no evidence of a difference between upadacitinib 15mg or 30mg and dupilumab; all credible intervals were wide and included 1.

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

## Summary of evidence on comparative safety

The use of upadacitinib for the treatment of moderate to severe atopic dermatitis was generally well-tolerated. The safety profile of the 15mg dose of upadacitinib in the atopic dermatitis studies was similar to the 15mg dose for other licensed indications. The safety profile of the 30mg dose was similar although a dose-dependent increase in the frequency of most treatment-related adverse events was noted.[2]

In the placebo-controlled studies, the most commonly reported treatment-emergent adverse events (AEs) with upadacitinib 15mg or 30mg were upper respiratory tract infection (25%), acne (15%), herpes simplex (8.4%), headache (6.3%), increased creatine phosphokinase (5.5%), cough (3.2%), folliculitis (3.2%), abdominal pain (2.9%), nausea (2.7%), neutropenia (2.3%), pyrexia (2.1%), and influenza (2.1%).[1]

In Heads Up, a treatment-emergent AE was reported by 78% (270/348) of the upadacitinib group and 67% (230/344) of the dupilumab group and these were considered treatment-related in 49% and 38% respectively. In the upadacitinib and dupilumab groups respectively, patients reporting a severe AE were 8.9% versus 4.4%, patients with a reported serious AE were 4.0% versus 2.0% and patients discontinuing therapy due to an AE was 3.2% versus 1.2%. The most frequently reported treatment-emergent AEs in the upadacitinib group versus the dupilumab group were: acne (18% versus 3.2%), atopic dermatitis (11% versus 9.3%), upper respiratory tract infection (7.5% versus 4.9%), increased blood creatine phosphokinase (7.5% versus 3.2%), nasopharyngitis (6.6% versus 7.8%), folliculitis (6.3% versus 1.2%), urinary tract infection (5.5% versus 4.4%), headache (4.9% versus 6.7%) and conjunctivitis (1.4% versus 10%).[5]

Serious infections, opportunistic infections and the potential risk of malignancy due to its immunomodulatory effect have been identified with upadacitinib and are noted in the special warnings and precautions section of the SPC.[1]

## Summary of clinical effectiveness issues

Atopic dermatitis is a common, chronic, relapsing, inflammatory skin disease characterised by highly pruritic, erythematous, excoriated, and oozing papules and plaques that may become lichenified over time. The main features of the condition are the chronic eczematous rash and debilitating pruritus which can a significant negative impact on quality of life through depression, suicidal ideation, sleep disturbance and consequent fatigues, reduced work productivity and daily activities. The pathogenesis of atopic dermatitis is a complex combination of immune deviation, barrier dysfunction, and environmental risk factors. One third of patients have moderate to severe disease. The treatment of atopic dermatitis in adolescent and adult patients depends on the extent and severity of disease and follows a step-wise approach starting with topical therapy (emollients, progressing to topical corticosteroids and calcineurin inhibitors for sensitive areas). For patients who do not respond to topical therapy, phototherapy or systemic therapies are generally added. Conventional systemic treatments can include azathioprine, methotrexate, mycophenolate mofetil and ciclosporin (which is the only one licensed specifically for the treatment of severe atopic dermatitis when systemic therapy is required).[2,8] At present, there are four other targeted systemic treatments with a marketing authorisation for the treatment of moderate to severe atopic dermatitis in patients who are candidates for systemic therapy: two of these are licensed for use in adult and adolescent patients (dupilumab and abrocitinib) and two only in adult patients (baricitinib and tralokinumab). Only dupilumab (SMC2232 and SMC2011), baricitinib (SMC2337) and tralokinumab (SMC2403) have been reviewed by SMC and have similarly been accepted for restricted use in patients who have had an inadequate response to existing immunosuppressants such as ciclosporin or when these are unsuitable. The submitting company has requested that SMC considers the use of upadacitinib within its full licensed indication and also in this proposed restricted sub-population. Clinical experts consulted by SMC considered that there was an unmet need for further effective treatment options for atopic dermatitis.

The evidence from placebo-controlled studies, Measure Up 1 and 2 (as monotherapy) and AD Up (in combination with topical corticosteroids), found a consistent and highly significant treatment effect which was considered clinically relevant. In all three placebo-controlled studies, the treatment effect was higher at the 30mg than the 15mg dose: EASI 75 at week 16 was 73% to 80% with upadacitinib 30mg and 60% to 70% with upadacitinib 15mg; vIGA-AD 0/1 was 52% to 62% and 39% to 48% in the 30mg and 15mg groups, respectively. However the studies were not designed to compare the upadacitinib doses. There was also a statistically significant difference between upadacitinib and placebo in the adolescent subgroups of the three studies. Although the treatment effect was dose-related, only the upadacitinib 15mg daily dose was licensed for adolescents. Upadacitinib 30mg was also statistically significantly better than the relevant comparator, dupilumab, for the primary and all secondary outcomes in adult patients in Heads Up.[2-5]

The primary analyses in studies used the ITT populations with patients who received rescue medication considered non-responders for categorical outcomes. In the placebo-controlled studies, this led to a notably higher proportion of placebo patients classified as non-responders

due to rescue. In Measure Up 1, this was 47% compared with 11% and 5.6% in the upadacitinib 15mg and 30mg groups respectively, 43% compared with 8.7% and 5.7% respectively in Measure Up 2 and 26% compared with 5.0% and 4.7% respectively in AD Up. This imbalance of higher non-responders in the placebo groups affected the relative treatment difference versus placebo. Sensitivity analyses using observed data, which did not impute those receiving rescue as non-responders, confirmed that the results remained statistically significant but the treatment differences were smaller. In clinical practice, many patients will use systemic therapy in combination with topical corticosteroids which affect the generalisability of the primary analyses results.[1,2]

Other factors which may affect the generalisability of study results to clinical practice include the enrolment of adolescent patients weighing ≥40kg while the SPC recommends a dose of upadacitinib 15mg daily for adolescent patients weighing ≥30kg. The studies only included a small number of patients aged ≥65 years; they were not analysed as a separate subgroup and the upadacitinib dose is also limited to 15mg daily in elderly patients. In clinical practice, upadacitinib may be used after treatment with other targeted therapy but very few patients in the clinical studies had received previous targeted treatment.[1,2,9]

Blinded, controlled evidence is limited to a period of 16 weeks for the placebo-controlled and 24 weeks for the active-controlled studies, which is sort for a chronic condition. The treatment effect of upadacitinib has been shown to be maintained at interim 52-week analyses of blinded but uncontrolled evidence. There is no evidence on duration of remission or response, any rebound effect, time to relapse and efficacy of re-treatment.[2]

Evidence from the four clinical studies supports the licensed indication for upadacitinib. Direct comparative evidence is limited to upadacitinib 30mg versus dupilumab in adult patients only. The company performed NMAs to address the lack of direct versus dupilumab in adolescent patients. The NMA suggested that in adolescent patients, who may or may not have received previous systemic treatment, upadacitinib 15mg was superior to dupilumab. Due to a lack of relevant evidence, there was no indirect comparison of upadacitinib with ciclosporin in adolescent patients, which SMC clinical experts considered a relevant comparator.

There were no direct comparative data versus dupilumab in the proposed restricted positioning and the results of the NMAs suggested that, when used in combination with topical corticosteroids, upadacitinib 30mg was superior to dupilumab but there was no evidence of a difference for upadacitinib 15mg. The validity of the NMA results are limited by the use of small patient numbers from post hoc analyses. The NMA supporting the proposed restricted adult population was wider than a population in whom the disease had an inadequate response to conventional systemic therapy, or such treatment is not suitable and included adult patients who have previously received ciclosporin, regardless of response or suitability. The prior use of ciclosporin, as a proxy for other prior systemic therapy, was considered reasonable by SMC clinical experts. As noted, there was no separate NMA to support the proposed restricted adolescent population. Across the NMAs, scenario analyses did not confirm superiority for all comparisons. Despite evidence of clinical and methodological heterogeneity, fixed effects models were used for the NMAs. Results using random effects models for all comparisons of upadacitinib versus dupilumab suggested no evidence of a difference between treatments and the wide credible

intervals indicated high uncertainty. No safety or health related quality of life outcomes, other than DLQI, were indirectly compared. Due to these limitations, and lack of direct comparative data for upadacitinib 15mg, the company's conclusions are uncertain.

The introduction of the oral JAK inhibitor, upadacitinib, would provide an additional convenient treatment option for adult and adolescent patients with moderate to severe atopic dermatitis who have had an inadequate response to, or in whom conventional systemic therapy is unsuitable. Clinical experts consulted by SMC considered that upadacitinib is a therapeutic advancement offering an additional oral treatment for these patients.

## Summary of comparative health economic evidence

The submitting company presented a cost-utility analysis evaluating upadacitinib within a subpopulation of the licensed indication in patients in whom disease has not responded to at least one other conventional systemic immunosuppressant therapy or where conventional systemic therapy is not suitable (systemic-exposed). Two separate analyses were presented for the upadacitinib 15mg and upadacitinib 30mg doses.

For the systemic-exposed population, patients were assumed to have previously received and had an inadequate response to, or not been suitable for, conventional systemic therapy (ciclosporin, methotrexate, azathioprine or mycophenolate mofetil). Comparisons were provided against dupilumab plus topical corticosteroids and best supportive care (BSC). Clinical expert responses received by SMC suggested that dupilumab (and baricitinib) may be key comparators likely to be displaced. As per SMC process, baricitinib is not considered a relevant comparator as SMC advice on this medicine was published within 6 months prior to receipt of the upadacitinib submission.

A hybrid model consisting of a short-term decision tree (to 52 weeks) followed by a long-term Markov model structure was presented. The 1-year decision tree was designed to capture short-term treatment decisions and represented the probability of treatment response at 16 and 52 weeks. The Markov model was implemented over a lifetime horizon and reflected the long-term course of atopic dermatitis with treatment response health states starting from year 2 onwards. Patients achieving a response at either assessment were assumed to remain on the assigned active treatment, with an annual discontinuation rate applied in year 2 onwards. Upon discontinuation, patients were assumed to revert to transition to the "BSC (non-responders)" health state. Patients entering the model on BSC could enter a separate BSC responder health state, if the criteria for response was met. The risk of death was assumed consistent with the general population. An annual cycle length was implemented in the Markov model and no half-cycle correction was applied, due to the use of weekly decision nodes in the decision tree.

The main source of efficacy data was a pooled analysis of patients enrolled in the three placebo controlled trials - Measure UP 1, Measure UP 2 and AD UP, [2-4] which fed into the NMAs described above. Data from the HEADS UP study versus dupilumab were not used for the base case analysis although were presented as a scenario analysis. An "all-observed" population (uncensored for the use of rescue medication) was used and the composite outcome of EASI50 + DLQI≥4 was the determinant of treatment effect. A treatment waning effect, representing an adjustment for the

placebo effect observed in the clinical studies, was applied for upadacitinib and dupilumab with a reduction from 98% in year 2 to 87% in year 10, with a greater linear decline for BSC from 75% in year 2 to 0% in year 5.

EQ-5D-5L data were collected in the upadacitinib clinical trials and mapped to the UK EQ-5D-3L value set using the van Hout et al crosswalk method.[10] Utility weights included baseline utility, EASI 75 response and EASI 75 non-response. Age adjustment was applied, however adverse event disutilities were not included in the analysis as they were deemed to be generally mild in severity and unlikely to influence the results.

Costs of medicines acquisition and administration, adverse event management, rescue medication, and patient monitoring were included in the analysis. For upadacitinib, the two analyses assumed that one tablet of the respective doses (15 mg and 30mg) were used daily (therefore the cost of one 30mg tablet was applied rather than two 15mg tablets). A stopping rule was applied at weeks 16 and 52, in that patients who did not respond to active treatment were assumed to discontinue. Health state resource use included outpatient, inpatient and day case admissions as well as community care and unplanned A&E attendances. Healthcare use was assumed to be higher for responders versus non-responders.

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 simple discount was offered on the list price. A PAS discount is also in place for dupilumab and this was included in the results used for decision-making by using estimates of the comparator PAS price.

For the comparison with dupilumab the results presented do not take account of the PAS for dupilumab or the PAS for upadacitinib 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.

The base case and scenario analyses using list prices for the dupilumab comparisons and including the upadacitinib PAS versus BSC are summarised below.

**Table 3: Summary of base case results (all observed), at list price versus dupilumab and with upadacitinib PAS versus BSC**

| Response criteria | Upadacitinib dose | Mono/combo | Comparator | ICER (£ per QALY) |
|---|---|---|---|---|
| **Adult systemic-exposed** | | | | |
| EASI 50 + DLQI ≥4 | 15 mg | Combo | Dupilumab | £87,736 (SW Quadrant) |
| EASI 50 + DLQI ≥4 | 15 mg | Combo | BSC | £10,028 |
| EASI 50 + DLQI ≥4 | 30 mg | Combo | Dupilumab | £116,943 |
| EASI 50 + DLQI ≥4 | 30 mg | Combo | BSC | £18,366 |

BSC: Best Supportive Care, COMBO: Combination Therapy, DLQI: Dermatology Life Quality Index, EASI: Eczema Area and Severity Index, ICER: Incremental Cost-effectiveness Ratio, MONO: Monotherapy, QALYs: Quality-adjusted life years, SW Quadrant: South West Quadrant (upadacitinib is less costly but less effective than the comparator),

**Table 4: Scenario analysis vs dupilumab (list price)**

| | Adult systemic-exposed population | |
|---|---|---|
| | **Upadacitinib 15 mg + TCS vs dupilumab + TCS** | **Upadacitinib 30 mg + TCS vs dupilumab + TCS** |
| ***Time horizon*** | | |
| 15 years | £106,543 (SW Quadrant) | £134,890 |
| 30 years | £90,384 (SW Quadrant) | £120,574 |
| ***Alternative response timepoint*** | | |
| Response observed at week 16 for all treatments and BSC | £85,112 (SW Quadrant) | £121,676 |
| ***Analysis using primary dataset*** | | |
| EASI 50 + DLQI ≥4 | £82,531 (SW Quadrant) | £134,287 |
| EASI 75 | £98,770 (SW Quadrant) | £97,796 |
| ***Alternative response definitions:*** | | |
| EASI 75 | £115,404 (SW Quadrant) | £102,065 |
| Systemic-exposed data including data from HEADS UP, using EASI 75 at 16 weeks | Not presented | Not presented |
| ***Base case using monotherapy (all observed)*** | | |
| EASI 50 + DLQI ≥ 4 | Dominant | £96,682 |

DLQI: Dermatology Life Quality Index, EASI: Eczema Area and Severity Index, ICER: Incremental Cost-effectiveness Ratio, SW Quadrant: South West Quadrant (upadacitinib is less costly but less effective than the comparator), TCS: Topical Corticosteroids, dominant: upadacitinib is less costly and more effective than comparator.

**Table 5: Scenario analysis vs BSC as comparator, with PAS applied for upadacitinib**

| | Adult systemic-exposed population | |
|---|---|---|
| | **Upadacitinib 15 mg + TCS vs BSC** | **Upadacitinib 30 mg + TCS vs BSC** |
| ***Time horizon*** | | |
| 15 years | £10,355 | £19,004 |
| 30 years | £10,047 | £18,399 |
| ***Alternative response timepoint*** | | |
| Response observed at week 16 for all treatments and BSC | £10,799 | £18,975 |
| ***Analysis using primary dataset*** | | |
| EASI 50 + DLQI ≥4 | £9,376 | £17,577 |
| EASI 75 | £9,286 | £17,447 |
| ***Alternative response definitions:*** | | |
| EASI 75 | £9,575 | £17,943 |
| Systemic-exposed data including data from HEADS UP, using EASI 75 at 16 weeks | Not presented | Not presented |

| *Base case using monotherapy (all observed)* | | |
|---|---|---|
| EASI 50 + DLQI ≥ 4 | £8,771 | £17,840 |

BSC: Best Supportive Care, DLQI: Dermatology Life Quality Index, EASI: Eczema Area and Severity Index, ICER: Incremental Cost-effectiveness Ratio, SW Quadrant: South West Quadrant (upadacitinib is less costly but less effective than the comparator), TCS: Topical Corticosteroids

The analysis is subject to a number of limitations as described below:

- There is a lack of direct comparative evidence for the comparison with dupilumab in combination with topical corticosteroids. There is substantial uncertainty about the NMA results used in the analysis based on a fixed effects model rather than a random effects model which may better capture the uncertainty in the indirect evidence. Evidence of any difference in effectiveness between upadacitinib 15mg or 30mg and dupilumab or ciclosporin is therefore uncertain.

- There was a lack of direct evidence against other conventional systemic therapies such as ciclosporin to justify the positioning for the systemic eligible population. The NMA presented was highly uncertain, particularly when a random effects model was used.

- The decision tree component of the model was designed to include response timepoints at week 16 and week 52 which matched those of the clinical studies. However, the efficacy timepoint in the base case was applied at week 4 for upadacitinib on account of its rapid onset of action based on evidence that many patients achieved EASI 75 as early as week 1. Despite these observations, it would be preferable to have a consistent response timepoint applied for all treatments and assume that response occurred at 16 weeks to minimise bias. This was explored in the scenario analyses and led to a small increase in ICERs.

- The assumptions around treatment waning are uncertain. It is unclear whether upadacitinib would have a similar waning rate to dupilumab as assumed in the base case, although the company highlighted there was clinical support for the assumptions made. Waning rates for BSC could also be variable and based on the rates applied could affect the results.

- The key effectiveness estimates in the model were week 16 and week 52 response probabilities and both are subject to uncertainty, particularly for comparisons against dupilumab. The key drivers of cost-effectiveness were week 16 response probabilities and conditional discontinuation probabilities (used to inform the week 52 response and annual discontinuation). Scenario analysis was conducted using direct comparative data versus dupilumab from the HEADS UP study which increased the ICER but did not include combination therapy with TCS.

- Results of the economic analysis for 30 mg dosage are based on the costs and administration of the 30 mg tablets and cannot be replicated with administration of 2 x 15 mg tablets. There is a risk of overpaying if prescriber & patient preferences favour the dispensing of 2x15 mg tablets instead of 30 mg tablets. The submitting company claims that the use of 2x15mg tablets goes against the SmPC guidance, however this does not specify that the full dose must be administered as a single tablet.

Despite these limitations, the economic case has been demonstrated in the adult systemic-exposed subpopulation.

## Summary of patient and carer involvement

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

- We received patient group submissions from the National Eczema Society, Eczema Outreach Support and Allergy UK. National Eczema Society and Allergy UK are registered charities and Eczema Outreach Support is a Scottish charitable incorporated organisation.

- National Eczema Society has received 22% pharmaceutical company funding in the past two years, including from the submitting company. Eczema Outreach Support has received 24.7% pharmaceutical company funding in the past two years, including from the submitting company. Allergy UK has received 32% pharmaceutical company funding in the last two years, including from the submitting company.

- Atopic eczema is a chronic dry skin condition. Its major symptom is itchiness, which can be intense and unbearable. The condition affects all aspects of a person's life including sleep, ability to engage in activities and for children the ability to attend school and even make friends. Eczema can be all consuming and can negatively impact the wellbeing and mental health of carers who can feel inadequate to help their child manage this debilitating condition.

- Current treatment options do not work effectively for everyone and some are not eligible to take them. Having an additional different treatment option would be advantageous, especially for young people to reduce the burden and psychological impact of living with eczema over a lifetime.

- The simplicity of taking one tablet daily may increase treatment compliance resulting in controlled eczema and improved quality of life for the whole family. The introduction of upadacitinib would also broaden patient choice and increase the likelihood that people with moderate to severe eczema would find a treatment that is effective for them. Many patients, are likely to prefer an oral medication such as upadacitinib over an injection. In addition the side effects of upadacitinib are generally 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.[9] 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, tralokinumab and upadacatinib.

## Additional information: comparators

Dupilumab, baricitinib, tralokinumab, abrocitinib

## Additional information: list price of medicine under review

| Medicine | Dose Regimen | Cost per year (£) |
|---|---|---|
| Upadacitinib | 15mg or 30mg orally once daily | 10,472 to 20,945 |

*Costs from BNF online on 6 January 2021. Costs do not take patient access schemes into consideration.*

## Additional information: budget impact

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.

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

**References**

1. AbbVie Ltd. Upadacitinib prolonged-release tablets (Rinvoq®) Summary of product characteristics. Electronic Medicines Compendium www.medicines.org.uk/emc/ Last updated 27 August 2021.

2. European Medicines Agency (EMA) European Public Assessment Report. Upadacitinib (Rinvoq®). 24 June 2021, EMEA/H/C/004760/X/0006/G. www.ema.europa.eu

3. Guttman-Yassky E, Teixeira HD, Simpson EL, Papp KA, Pangan AL et al. Once-daily upadacitinib versus placebo in adolescents and adults with moderate-to-severe atopic dermatitis (Measure Up 1 and Measure Up 2): results from two replicate, double-blind, randomised, controlled phase 3 trials. Lancet 2021; 397: 2151–68

4. Reich K, Teixeira HD, de Bruin-Weller M, Bieber T, Soong W et al. Safety and efficacy of upadacitinib in combination with topical corticosteroids in adolescents and adults with moderate-to-severe atopic dermatitis (AD Up): results from a randomised, double-blind, placebo-controlled phase 3 trial. Lancet 2021; 397: 2169–81

5. Blauvelt A, Teixeira HD, Simpson EL, Costanzo A, de Bruin-Weller M et al. Efficacy and safety of upadacitinib vs dupilumab in adults with moderate-to-severe atopic dermatitis. A randomised clinical trial. JAMA Dermatol 2021; 157: 1047–55.

6. Data on file AbbVie Inc. A phase 3 randomized, placebo-controlled, double-blind study to evaluate upadacitinib in combination with topical corticosteroids in adolescent and adult subjects with moderate to severe atopic dermatitis. M16-047 week 16 Clinical Study Report R&D/20/0182.

7. Data on file AbbVie Inc. A phase 3b multicentre, randomized, double-blind, active-controlled study comparing the safety and efficacy of upadacitinib to dupilumab in adult subjects with moderate to severe atopic dermatitis. M16-046 week 16 Clinical Study Report R&D/20/1137.

8. BMJ Best Practice. Eczema. Available at: www.bestpractice.bmj.com. Last updated 20 August 2021.

9. Wollenberg A, Barbarot S, Bieber T, Christen-Zaech S, Deleuran M, *et al.* Consensus-based European guidelines for treatment of atopic eczema (atopic dermatitis) in adults and children: part II. Journal of the European Academy of Dermatology and Venereology 2018; 32: 850-78.

10. van Hout B, Janssen MF, Feng YS, Kohlmann T, Busschbach J, Golicki D, Lloyd A, Scalone L, Kind P, Pickard AS. Interim scoring for the EQ-5D-5L: mapping the EQ-5D-5L to EQ-5D-3L value sets. Value Health. 2012 Jul-Aug;15(5):708-15.

This assessment is based on data submitted by the applicant company up to and including 11 February 2022.

**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.*