Healthcare Improvement Scotland | SMC Advice on new medicines

SMC2480

upadacitinib 15mg prolonged-release tablet (Rinvoq®)

AbbVie Ltd

07 October 2022

The Scottish Medicines Consortium (SMC) has completed its assessment of the above product and, following review by the SMC executive, advises NHS Boards and Area Drug and Therapeutics Committees (ADTCs) on its use in NHSScotland. The advice is summarised as follows:

ADVICE: following a full submission

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

Indication under review: for the treatment of active ankylosing spondylitis (AS) in adult patients who have responded inadequately to conventional therapy.

In a phase III and a phase II/III study, upadacitinib when compared with placebo, significantly improved symptoms of AS in adults with active disease that was inadequately controlled with non-steroidal anti-inflammatory drugs (NSAIDs).

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 adult patients with active ankylosing spondylitis (AS) who have responded inadequately to conventional therapy.[1]

Dosing Information

The recommended dose of upadacitinib is 15mg once daily with or without food, and may be taken at any time of day. Tablets should be swallowed whole and should not be split, crushed, or chewed in order to ensure the entire dose is delivered correctly.

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

Treatment with upadacitinib should be initiated and supervised by physicians experienced in the diagnosis and treatment of conditions for which upadacitinib is indicated. Please see the summary of product characteristics (SPC) for further information, including advice on interactions and dose: initiation, interruption, adjustment, and discontinuation.[1]

Product availability date

01 January 2021

Summary of evidence on comparative efficacy

Upadacitinib is a selective and reversible inhibitor of Janus Kinase (JAK) enzymes; through inhibition of these enzymes, there is a reduction in the transmission of cytokine and growth factor signals that are involved in a broad range of cellular processes which include inflammatory responses, haematopoiesis and immune surveillance.[1]

Evidence for the indication under review comes from the phase II/III SELECT-AXIS 1 study and the phase III SELECT-AXIS 2, study 1. These were both multicentre, randomised, double-blind studies which included adult patients (≥ 18 years of age) with a clinical diagnosis of AS based on central reading of radiographs of the sacroiliac joints and fulfilling the modified New York Criteria for AS. Patients had active AS disease defined as a Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) score of ≥4 and a patient's assessment of total back pain score of ≥4; these patients also had an inadequate response to ≥2 NSAIDs over at least four weeks, or had an intolerance to or contraindication to NSAIDs as defined by the investigator. Concomitant oral corticosteroids (≤10mg prednisolone or equivalent) or NSAIDs were permitted provided patients were on a stable dose for at least 14 days prior to the baseline visit. Concomitant conventional synthetic disease modifying antirheumatic drugs (csDMARDs), including methotrexate, leflunomide, sulfasalazine, and hydroxychloroquine (and in SELECT-AXIS 2, study 1 apremilast and chloroquine also), were permitted provided patients were on a stable dose for at least 28 days prior to the baseline visit.

Patients with previous exposure to JAK inhibitors were excluded.[2-5] In SELECT-AXIS 1, all eligible patients had no prior exposure to bDMARDs and were considered bDMARD naïve.[2-4] However, in SELECT-AXIS 2, study 1, all eligible patients had an inadequate response to one or two bDMARDs; this was defined as discontinuation of a bDMARD, including tumour necrosis factor-alpha (TNF-alpha) and interleukin-17A (IL-17A) inhibitors, due to a lack of efficacy after ≥12 weeks of this treatment at an adequate dose, based on the investigators' assessment, or an intolerance to bDMARDs (regardless of treatment duration). If a patient had previous exposure to two bDMARDs, an intolerance to one and a lack of efficacy to the other, were permitted; however a patient could not have a lack of efficacy with two bDMARDs. Prior exposure to two bDMARDs were allowed for up to 30% of patients in the study population.[5]

In each study, patients were randomised equally to receive oral upadacitinib 15mg or placebo once daily during the 14-week double-blind treatment period (period 1). After completion of period 1, patients were eligible to enter a 90-week open-label extension period (period 2) where they all received oral upadacitinib 15mg once daily. Randomisation was stratified by screening concentrations of high-sensitivity C-reactive protein (hsCRP) and geographical region; additionally in SELECT-AXIS 2, study 1 randomisation was also stratified by class of prior bDMARD use (one TNF-alpha inhibitor, one IL-17A inhibitor, or two bDMARDs).[2-5]

Patients who did not achieve an Assessment of SpondyloArthritis international Society 20 (ASAS20) response or better at two consecutive study visits were permitted to have rescue therapy from week 16 onwards (SELECT-AXIS 1) and week 24 onwards (SELECT-AXIS 2, study 1).[2-6] In SELECT-AXIS 1, rescue therapy included the option of adding or modifying doses of: NSAIDs, paracetamol, low potency opioids (tramadol or a combination of paracetamol and codeine or hydrocodone), and after week 20, modifying a dose of methotrexate or sulfasalazine; the rescue therapy allowed in SELECT-AXIS 2, study 1 was submitted by the company but remains confidential.[2-6] From week 24 onwards, study drug treatment was discontinued if patients did not achieve an ASAS20 response or better at two consecutive study visits.[2-5]

The primary outcome in both SELECT-AXIS 1 and SELECT-AXIS 2, study 1 was the ASAS40 response at week 14. The ASAS is a composite outcome measure consisting of four domains which all have a numerical rating score of 0 to 10: the patient's global assessment of disease activity, the patient's assessment of total back pain, the Bath Ankylosing Spondylitis Functional Index (BASFI), and inflammation (defined as the mean of BASDAI questions on the severity and duration of morning stiffness). An ASAS40 response was defined as at least a 40% improvement, and an absolute improvement of ≥2 units, from baseline in at least three of the four domains, with no worsening observed in the remaining domain. In both studies, efficacy analyses were conducted on the Full Analysis Set (FAS) which consisted of all randomised patients who received at least one dose of the study drug. The multiplicity-controlled primary and secondary outcomes were tested sequentially; testing began with the primary outcome and continued as long as the higher-ranked outcome was significant.[2-5]

In both studies, upadacitinib was associated with a statistically significant improvement in ASAS40 response at 14 weeks compared with placebo. In SELECT-AXIS 1, this was supported by statistically significant improvements in the following multiplicity-controlled secondary outcomes:

Ankylosing Spondylitis Disease Activity Score based on CRP (ASDAS [CRP]), SPondyloArthritis Research Consortium of Canada (SPARCC) Magnetic Resonance Imaging (MRI) spine score, 50% improvement from baseline in BASDAI (BASDAI50), ASAS partial remission, and change from baseline in BASFI;[2, 3] in SELECT-AXIS 2, study 1 statistically significant improvements in all multiplicity-controlled secondary outcomes were met at week 14.[5] The results are detailed in Table 1.

Table 1: Results of primary and selected secondary outcomes at week 14 for the SELECT-AXIS 1 study and SELECT-AXIS 2, study 1. [2, 3, 5]

	SELECT-AXIS 1 Study		**SELECT-AXIS 2, study 1**	
	Upadacitinib (n=93)	**Placebo (n=94)**	**Upadacitinib (n=211)**	**Placebo (n=209)**
Primary outcome: ASAS40 response[a]				
Response, %	52%	26%	45%	18%
Difference for upadacitinib versus placebo (95% CI)	26% (13 to 40), p<0.001		26% (18 to 35), p<0.001	
Selected secondary outcomes:				
Change from baseline in ASDAS (CRP)[b]	-1.45[c] [n=84]	-0.54 [n=84]	-1.52[c]	-0.49
Change from baseline in SPARCC MRI spine score[b]	-6.93[c] [n=68]	-0.22 [n=60]	-3.95[c] [n=181]	-0.04 [n=186]
BASDAI50 response[a], %	45%[d]	23%	43%[c]	17%
Change from baseline in ASQoL[b]	-4.20 [n=88]	-2.67 [n=88]	-5.10[c] [n=210]	-2.03 [n=208]
ASAS partial remission response[a], %	19%[c]	1.1%	18%[c]	4.3%
Change from baseline in BASFI[b]	-2.29[c] [n=86]	-1.30 [n=86]	-2.26[c]	-1.09
Change from baseline in linear BASMI[b]	-0.37 [n=89]	-0.14 [n=89]	-0.48[c] [n=205]	-0.16 [n=201]
Change from baseline in MASES[b]	-2.25 [n=50]	-1.41 [n=51]	-2.60[c] [n=148]	-1.10 [n=162]
Change from baseline in WPAI[b]	-18.11 [n=55]	-12.60 [n=53]	NA	NA
Change from baseline in ASAS HI[b]	-2.75 [n=88]	-1.38 [n=88]	-2.93[c]	-1.07 [n=208]
ASAS20 response[a], %	65%	40%	65%[c]	38%

AS: ankylosing spondylitis; ASAS: Assessment of Spondyloarthritis International Society; ASDAS: Ankylosing Spondylitis Disease Activity Score; ASQoL: Ankylosing Spondylitis Quality of Life; BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; BASFI: Bath Ankylosing Spondylitis Functional Index; BASMI: Bath Ankylosing Spondylitis Metrology Index; CI: confidence interval; CRP: C-reactive protein; HI: Health Index; MASES: Maastricht

Ankylosing Spondylitis Enthesitis Score; MRI: magnetic resonance imaging; NA: not assessed; SPARCC: SPondyloArthritis Research Consortium of Canada; WPAI: work productivity and activity impairment.

Note that for some continuous endpoints that the 'n' number is smaller than the number of subjects included in the Full Analysis Set (FAS) and have been noted below. The submitting company confirmed to a regulatory authority that all subjects included in the FAS was also included in the analyses of ranked key secondary continuous endpoints and that the lower 'n' numbers represent the number of subjects with change from baseline measurements at Week 14. Where applicable, these lower 'n' numbers have been presented above in square brackets.[2]

[a]Results for binary outcomes like this were based on non-responder imputation (NRI) analysis.
[b]Results for continuous outcomes like this were based on a mixed-effect model for repeated measures (MMRM) with the least squares mean change from baseline reported.
[c]Statistically significant with a p-value ≤0.001 for upadacitinib versus placebo when adjusted for multiplicity.
[d]Statistically significant with a p-value of 0.002 for upadacitinib versus placebo when adjusted for multiplicity.

For the upadacitinib group, an improvement in ASAS40 response rates were observed from week 2 and week 4 in the SELECT-AXIS 1 study and the SELECT-AXIS 2, study 1, respectively.[2-5] In SELECT-AXIS 1, the upadacitinib group showed sustained ASAS40 response rates that continued to improve over time up to week 64. Patients treated with placebo who switched to upadacitinib after week 14 also showed a similar response in terms of speed of onset and the magnitude of improvement in ASAS40 responses.[2, 4] There was also an overall improvement, though with varying magnitudes and with fluctuations at different time points, for other secondary outcomes that assessed disease activity (ASDAS [CRP], BASDAI50), and function (BASFI). The open-label extension phase (period 2) is still ongoing in SELECT-AXIS 2, study 1 and long-term efficacy data are not yet available.[5]

In the SELECT-AXIS 2, study 1, post-hoc subgroup analyses for the primary outcome were generally consistent with the FAS and favoured upadacitinib; this included subgroups based on the number and type of previous bDMARD exposure. An ASAS40 response was achieved at week 14 for those treated with upadacitinib versus placebo in: 46% versus 20% of those who had a lack of efficacy or an intolerance to one bDMARD previously (n=365), 36% versus 4.0% of those who had a lack of efficacy to one bDMARD and an intolerance to another bDMARDs (n=54), 47% versus 22% of those who had previous exposure to ≥ one TNF-alpha inhibitor (n=345), and 37% versus 4.0% of those who had previous exposure to ≥ one IL-17A inhibitor (n=55).[5]

In SELECT-AXIS 1, Health Related Quality of Life (HRQoL) was assessed using the Ankylosing Spondylitis Quality of life (ASQoL), Work Productivity and Activity Impairment (WPAI), and the ASAS Health Index (ASAS HI) Questionnaires; in SELECT-AXIS 2, study 1 only ASQoL and ASAS HI were used to assess HRQoL. Changes from baseline to week 14 of these outcome measures, which are presented in Table 1, were greater in the upadacitinib group compared with the placebo group but were not statistically significant except for the changes in ASQoL and ASAS HI in SELECT-AXIS 2, study 1.[2, 3, 5] Additional long-term HRQoL data from the SELECT-AXIS 1 study up to week 64 showed greater, though statistically insignificant, sustained improvements in the upadacitinib group compared with the placebo group.[4]

The submitting company presented Bayesian network meta-analyses (NMA) which compared upadacitinib with TNF-alpha inhibitors (adalimumab, certolizumab pegol, etanercept, golimumab,

and infliximab) and IL-17A inhibitors (ixekizumab and secukinumab). The NMA included 26 studies that were conducted in patients with active AS who had an inadequate response to conventional therapy (that is NSAIDs and physiotherapy). Comparisons were made for the following outcomes: ASAS40, BASDAI50, change from baseline in BASDAI (BASDAI CFB), and change from baseline in BASFI (BASFI CFB). The submitting company concluded that the NMA revealed few significant differences between upadacitinib and all relevant comparators for all outcomes, and demonstrated that upadacitinib had comparable efficacy to most TNF-alpha inhibitors and IL-17A inhibitors for the treatment of active AS. The results of the NMA informed the submitting company's decision to perform a cost-minimisation analysis for the economic evaluation.

Summary of evidence on comparative safety

In the SELECT-AXIS 1 study during the 14-week double-blind treatment phase (period 1), any treatment-emergent adverse event (AE) was reported by 62% (58/93) of patients in the upadacitinib group and 55% (52/94) of patients in the placebo group, and these were considered treatment-related in 29% and 18% respectively. In the upadacitinib and placebo groups respectively, 1.1% in both groups reported a serious AE, and patients discontinuing therapy due to an AE was 2.2% versus 3.2%.[2, 3] In the SELECT-AXIS 2, study 1 during the 14-week double-blind treatment phase (period 1), any treatment-emergent AE was reported by 41% (86/211) of patients in the upadacitinib group and 37% (77/209) of patients in the placebo groups. In the upadacitinib and placebo groups respectively, 2.8% versus 0.5% reported a serious AE, and patients discontinuing therapy due to an AE was 0% versus 1.4%.[5] Long-term safety data from SELECT-AXIS 1, which consists of the double-blind phase (period 1) and the open-label phase (where all patients in the placebo group switched to received upadacitinib treatment) up to week 64 (period 2), showed that 618 AEs (260.1 events per 100 patient-years) were reported in 182 patients (237.6 patient-years) who received upadacitinib. Among these 182 patients, 7 severe AEs (2.9 events per 100 patient-years), 14 serious AEs (5.9 events per 100 patient-years) and 15 AEs (6.3 events per 100 patient-years) leading to discontinuation were reported.[2, 4]

In SELECT-AXIS 1, the most frequently reported treatment-emergent AEs of any grade, with an incidence >5% in either treatment group, during the 14-week double-blind treatment phase (period 1) in the upadacitinib and placebo groups respectively were: increased creatinine phosphokinase (8.6% and 2.1%), diarrhoea (5.4% and 5.3%), nasopharyngitis (5.4% and 4.2%), headache (5.4% and 2.1%), nausea (1.1% and 5.3%).[2, 3] In SELECT-AXIS 1, when including the open-label phase up to week 64 (period 2), the most frequently reported treatment-emergent AEs with an incidence >5 events per 100 patient-years in the all-upadacitinib population (n=182; total of 237.6 patient-years) were: nasopharyngitis (15.6 events per 100 patient-years), increased creatinine phosphokinase (11.8 events per 100 patient-years), upper respiratory tract infection (10.9 events per 100 patient-years), hepatic disorder (10.1 events per 100 patient-years), headache (6.7 events per 100 patient-years) and uveitis (5.5 events per 100 patient-years).[2, 4]

In SELECT-AXIS 2, study 1, AEs of special interest, during the 14-week double-blind treatment phase (period 1) in the upadacitinib and placebo groups respectively, included: COVID-19 (5.7% versus 2.9%), hepatic disorder (2.8% and 1.0%), and neutropenia (2.8% versus 1.0%).[5]

A regulatory authority noted that the extent of upadacitinib exposure in the SELECT-AXIS 1 study is limited, with 182 patients having received at least one dose of upadacitinib and 160 out of the 182 patients had exposure to upadacitinib for ≥ 12 months. However, this was considered acceptable since the long-term safety profile of upadacitinib for patients with AS is similar to that for rheumatoid arthritis and psoriatic arthritis.[2] See the SPC for more detailed safety information.[1]

Summary of clinical effectiveness issues

Axial spondyloarthritis (axSpA) encompasses a spectrum of disease manifestations which include non-radiographic and radiographic axSpA. Radiographic axSpA, also known as AS, requires the presence of defined structural changes of the sacroiliac joints on plain conventional radiographs to confirm its diagnosis, as per the 1984 modified New York criteria.[2] AS is a progressive, irreversible arthritic condition that is characterised by chronic inflammation of the spine and sacroiliac joint; the resulting back pain and stiffness can negatively impact the quality of life and social functioning. AS can ultimately lead to total spinal ankyloses and disability, and can also affect the peripheral joints and cause extra-articular manifestations such as enthesitis, anterior uveitis, psoriasis, and inflammatory bowel disease.[2, 7] The onset of symptoms typically occurs between the ages of 17 to 35 and 90-95% of patients are first diagnosed before the age of 45.[9, 10] The 2017 National Institute of Clinical Excellence (NICE) and British Society of Rheumatology (BSR) guidelines recommend physiotherapy and NSAIDs as first-line treatment options for active AS that is symptomatic. TNF-alpha inhibitors (such as adalimumab, certolizumab pegol, etanercept, golimumab, and infliximab) are recommended for patients with severe active AS who have become intolerant to, or whose disease has responded inadequately to, NSAIDs. Patients who fail to achieve an adequate response with a first biologic therapy should be offered the option to switch to a second biologic, which can be either an alternative TNF-alpha inhibitor or an IL-17A inhibitor such as secukinumab and ixekizumab.[11-13]

Compared with placebo, upadacitinib 15mg once daily increased the proportion of patients achieving an ASAS40 response at week 14 by 26% in SELECT-AXIS 1 and SELECT-AXIS 2, study 1. These results were statistically significant and demonstrate clinical efficacy in patients who are bDMARD-naïve (SELECT-AXIS 1) and had a lack of efficacy to one bDMARD (SELECT-AXIS 2, study 1). Secondary outcomes that included measures of disease activity (ASDAS [CRP], ASAS partial remission, BASDAI50), function (BASFI), and MRI outcomes (SPARCC MRI spine) were also statistically significant in both studies; in SELECT-AXIS 2, study 1, spinal mobility (BASMI) was also significantly improved. The efficacy of upadacitinib continually improved and was generally maintained up to week 64 in SELECT-AXIS 1 (bDMARD naïve patients); long-term data from SELECT-AXIS 2, study 1 (in patients with a lack of efficacy to one bDMARD) is awaited.[2-5]

There were some limitations with the evidence presented. In SELECT-AXIS 1, the long-term efficacy analyses (week 14 to 64), which carried out no statistical significance testing, were performed

using an 'as observed' (AO) approach which implied that data was included regardless of whether a patient was still on randomised treatment or not, and that patients without an evaluation on a scheduled visit were excluded from the AO analysis for that visit. Data from this AO analysis showed that 85% (67/79) of patients initially randomised to upadacitinib had an ASAS40 response at week 64; however an alternative analysis using the number of observed and imputed non-responders together resulted in a lower estimate of 72% (67/93), suggesting that the long-term efficacy may have been overestimated. These results raise uncertainty about the precise magnitude of the long-term efficacy but a regulatory authority concluded that there is sufficient evidence to suggest continued benefit beyond the week 14 period.[2, 4] However, since the long-term data from SELECT-AXIS 2, study 1 are awaited, there are no long-term data from patients who have previously failed to respond to a bDMARD; therefore, there is no estimate of the magnitude of long-term treatment effect in the group of patients who will most likely receive upadacitinib in clinical practice.

In SELECT-AXIS 2, study 1 a patient was defined as having an inadequate response to bDMARDs, due to a lack of efficacy or an intolerance, based on the sole discretion of the study investigators; this could have affected the patient selection process and the magnitude of treatment responses.[5] However, there is not an established definition as to what constitutes an inadequate response to bDMARD treatment at present, with various guidelines outlining different criteria and timelines for assessing this.[11-13] It was noted that 87% of the study population had received one previous bDMARD meaning there is very limited data in patients who have received two prior bDMARDs. In addition to the results for the total population in SELECT-AXIS 2, study 1, post-hoc subgroup analyses for the primary outcome indicated consistent benefits that favoured upadacitinib irrespective of the number (one or two) and type (TNF-alpha or IL-17A inhibitors) of previous bDMARDs used. However, this study was not powered to detect differences between subgroups and the sample size is limited, therefore results should be interpreted with caution. Additionally, for those who had two previous bDMARDs, patients could only have lack of efficacy for one; therefore, there are no data for patients who have had a lack of efficacy to two bDMARDs.[5]

In SELECT-AXIS 1, it was noted that 11% (20/187) of the total study population were entered into the study despite having a lower disease activity than what was required for the inclusion criterion, that is they had a BASDAI and patient's assessment of back pain score of <4. However, this was similar across the two groups (9 patients in the placebo group and 11 in the upadacitinib group) and this issue was addressed by an additional analysis which excluded these 20 patients; the results of this analysis were consistent with the primary analysis and showed that 56% of patients in the upadacitinib group versus 28% in the placebo group achieved an ASAS40 at week 14.[2, 3]

Patients were allowed to continue their prior treatments in both studies, and in SELECT-AXIS 1 there were some slight imbalances between the two groups during the placebo-controlled period (period 1). In SELECT-AXIS 2, study 1 the proportions of patients taking concomitant: NSAIDs, csDMARDs, and oral corticosteroids were more balanced in the upadacitinib and placebo groups respectively. However, neither study analysed the impact or efficacy of combinations of

concomitant treatments, which may differ from clinical practice in Scotland and could affect the generalisability of the results.[2, 3, 5]

Both studies were placebo-controlled, and therefore there is no direct evidence comparing upadacitinib with alternative treatments that would be used in patients with AS who fail conventional therapy. The Bayesian NMA had a number of limitations, including clinical and methodological differences between the studies: considerable differences in the prior treatments (for example approximately half of the included studies were conducted in bDMARD naïve patients) and concomitant treatments (for example there were wide ranges in the proportion of patients who used concomitant: csDMARDs [16% to 60%], sulfasalazine [14% to 54%], methotrexate [6.2% to 21%], and corticosteroids [3.9% to 18%]). The comparators used in the NMA are generally reflective of Scottish practice. Separate analyses were not presented for patients who had no prior exposure to bDMARDs (bDMARD naïve) and for those who had an inadequate response to at least one bDMARD (bDMARD-IR); therefore, the relative efficacy of upadacitinib in each subpopulation is uncertain. The indirect comparison did not assess safety or HRQoL outcomes. In summary, the conclusion that upadacitinib has comparable efficacy to most TNF-alpha inhibitors and IL-17A inhibitors for the treatment of active AS is plausible in spite of these limitations.

Clinical experts consulted by SMC considered that upadacitinib fills an unmet need for patients with severe AS who fail treatment with a TNF-alpha inhibitor and an IL-17A inhibitor, and they consider upadacitinib to be a therapeutic advancement since it has a different mode of action to current alternative treatments. They indicated that its place in therapy is likely to be following an inadequate response or intolerance to TNF-alpha inhibitors and/or IL-17A inhibitors, or when these treatments are contraindicated.

Summary of comparative health economic evidence

The company submitted a cost-minimisation analysis of upadacitinib within its full marketing authorisation. Comparisons were provided against TNF-alpha inhibitors (adalimumab, certolizumab pegol, etanercept, golimumab and infliximab) and the IL-17A inhibitor, secukinumab. Tofacitinib was not included as a comparator since the timing of SMC advice precludes it from being considered in this submission. The general consensus amongst SMC clinical experts was a likely displacement of TNF-alpha inhibitors and IL-17A inhibitors, including secukinumab, through the introduction of upadacitinib at some point along the treatment pathway. One expert noted upadacitinib would likely displace tofacitinib, following initial treatments of TNF-alpha inhibitors and IL-17A inhibitors.

The results of the Bayesian NMA were used to support the use of a cost-minimisation analysis. The submitting company concluded that upadacitinib demonstrated comparable clinical efficacy compared to all relevant comparators in patients with AS who responded inadequately to conventional therapy. The outcomes considered were ASAS40, BASDAI50, change from baseline in BASDAI and change from baseline in BASFI. The NMA did not include safety outcomes.

Upadacitinib, TNF-alpha inhibitors, and secukinumab were assumed to have consistent adverse event profiles. This assumption was established through comparative upadacitinib and secukinumab adverse event profiles from clinical data and SMC 1159/16.[3, 15, 16]

Due to the expected comparable efficacy of each treatment from the NMA results, an assumed 11% annual rate of discontinuation was applied to each. There was supporting evidence for the use of this figure for the comparator treatments.[17] However, as post-year 1 annual discontinuation rates for upadacitinib were unavailable from the clinical data,[3, 15] these were also assumed to be 11%.

The cost-minimisation analysis included medicine acquisition, administration, and monitoring costs. As all treatments were assumed to have consistent adverse event profiles, no adverse event costs were included. Resource use for monitoring was assumed equal across all treatments based on the NMA results. Total and incremental costs were presented for each year over the five-year time horizon. Annual medicine acquisition costs were the main driver of costs.

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 in place for secukinumab and certolizumab pegol and these were included in the results used for decision-making by using estimates of the comparator PAS price. SMC is unable to present the results provided by the company which used an estimate of the PAS price for secukinumab and certolizumab pegol due to commercial confidentiality and competition law issues.

As such, base case results are presented in Table 2 at list prices for all medicines.

Table 2: Base case analysis (list prices)

	Year 1	Year 2	Year 3	Year 4	Year 5	Total
Total undiscounted costs per patient per year						
Upadacitinib (15 mg)	£10,774	£9,237	£8,221	£7,317	£6,512	£42,061
Adalimumab (40mg/0.8ml)	£8,664	£7,325	£6,519	£5,802	£5,164	£33,475
Certolizumab Pegol (200mg/1ml)	£10,753	£8,230	£7,325	£6,519	£5,802	£38,628
Etanercept (25mg/0.5ml)	£9,764	£8,230	£7,325	£6,519	£5,802	£37,640
Golimumab (50mg/0.5ml)	£9,527	£8,084	£7,195	£6,403	£5,699	£36,908
Infliximab (100mg)	£17,677	£13,101	£11,660	£10,378	£9,236	£62,053
Secukinumab (150mg/1ml)	£10,199	£6,513	£5,797	£5,159	£4,592	£32,260
Incremental undiscounted costs per patient per year (A)						
Adalimumab (40mg/0.8ml)	£2,110	£1,912	£1,702	£1,515	£1,348	£8,586
Certolizumab Pegol (200mg/1ml)	£22	£1,007	£896	£798	£710	£3,432
Etanercept (25mg/0.5ml)	£1,010	£1,007	£896	£798	£710	£4,420
Golimumab (50mg/0.5ml)	£1,247	£1,153	£1,026	£913	£813	£5,153

Infliximab (100mg)	**-£6,903**	**-£3,864**	**-£3,439**	**-£3,061**	**-£2,724**	**-£19,992**
Secukinumab (150mg/1ml)	£575	£2,724	£2,424	£2,158	£1,920	£9,801
Notes **A: A negative value represents a cost-saving for upadacitinib**						

The submitting company provided three scenario analyses. Two scenarios considered different fixed annual rates of discontinuation of 6.57% and 11.84% for all treatments. A third considered different discontinuation rates for upadacitinib and secukinumab taken from pivotal trial data. The base case conclusions were insensitive in these scenarios.

The base case and sensitivity analysis results were not discounted at 3.5%. However, conclusions were insensitive when a 3.5% discount rate was applied.

Dose quantities used in the analysis for the comparators were conservative and secukinumab 150mg/1ml and 300mg/2ml doses were investigated in further sensitivity analysis. Results of this analysis at list prices are in presented in Table 3.

Table 3: Sensitivity analysis of 300mg/2ml dose of secukinumab (list prices)

		Incremental undiscounted costs per patient per year (A)					
		Year 1	**Year 2**	**Year 3**	**Year 4**	**Year 5**	**Total**
Proportion of patients receiving 150mg/1ml secukinumab (remainder receiving 300mg/2ml secukinumab)	0%	-£8,866	-£3,509	-£3,123	-£2,780	-£2,474	-£20,753
	10%	-£7,922	-£2,886	-£2,569	-£2,286	-£2,035	-£17,698
	20%	-£6,978	-£2,263	-£2,014	-£1,792	-£1,595	-£14,642
	30%	-£6,034	-£1,639	-£1,459	-£1,299	-£1,156	-£11,587
	40%	-£5,090	-£1,016	-£904	-£805	-£716	-£8,531
	50%	-£4,146	-£393	-£350	-£311	-£277	-£5,476
	60%	-£3,202	£231	£205	£183	£163	-£2,421
	70%	-£2,257	£854	£760	£676	£602	£635
	80%	-£1,313	£1,477	£1,315	£1,170	£1,041	£3,690
	90%	-£369	£2,101	£1,869	£1,664	£1,481	£6,746
	100%	£575	£2,724	£2,424	£2,158	£1,920	£9,801
Notes **A: A negative value represents a cost-saving for upadacitinib**							

Key limitations of the analysis were:

- The conclusions of the NMA were subject to limitations which increased uncertainty in the comparative efficacy of upadacitinib and the comparators. Firstly, the NMA results were initially not presented separately based on prior biologic treatment, only for the combined population of biologic-naïve (bDMARD naïve) and biologic experienced (bDMARD inadequate response). Although this analysis was later provided, results in the biologic experienced subpopulation were not available for TNF-alpha inhibitors and secukinumab. Therefore, the relative efficacy of upadacitinib in each subpopulation was uncertain. Secondly, unlicensed doses or treatment regimens were included for secukinumab and golimumab. Thirdly, the credible intervals around some of the outcomes were wide. Finally, as outcomes were assessed at 12 to 16 weeks, longer-term comparable efficacy was uncertain.

- Although adverse event clinical data supported the comparable adverse event profiles of upadacitinib and secukinumab,[3, 15, 16] these data were only available between 14 to 16 weeks and were drawn from both biologic-naïve and biologic experienced populations. In addition, there were limited published data to facilitate a robust comparison of the adverse event rates between TNF-alpha inhibitors and upadacitinib. Safety outcomes were also not included in the NMA. This created potential uncertainty in the assumption of consistent adverse event profiles of all treatments and the omission of adverse event costs.
- The discontinuation rate data for upadacitinib were only available for one year.[3, 15] Although the year 1 data did suggest a comparable annual discontinuation rate to the 11% used in the base case, uncertainty remained when assuming this for each year across the five-year time horizon given the limited data. However, conclusions in the base case were insensitive under variation of upadacitinib annual discontinuation rates.

Despite these limitations, 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 Group.

- We received a patient group submission from the National Axial Spondyloarthritis Society (NASS), which is a registered charity.

- NASS has received 34% pharmaceutical company funding in the past two years, including from the submitting company.

- Ankylosing spondylitis is an inflammatory condition of the spine which often produces pain, stiffness, deformity and disability throughout adult life. It is a chronic progressive disease and is characterised by periods of fluctuating intensity, leading to slowly increasing spinal and peripheral joint damage. Pain and fatigue affect people's ability to carry on with everyday life. Many have to stop working and there are resulting effects on mental health.

- Whilst the corner stones of treatment are anti-inflammatory medication and exercise, there are those who cannot tolerate non-steroidal anti-inflammatories (NSAIDs) and 20% of people do not respond to the biologic drugs currently available.

- Upadacitinib, as a new medicine targeting a different enzyme could provide an alternative treatment to enable some people with ankylosing spondylitis to exercise more easily and to live a fuller life. As an oral tablet it may be easier to use and store for people than some current injectable treatments that need refrigeration.

Additional information: guidelines and protocols

The British Society of Rheumatology (BSR) and the British Health Professionals in Rheumatology (BHPR) published the "BSR and BHPR guideline for the treatment of axial spondyloarthritis (including ankylosing spondylitis) with biologics" in 2017.[11] The guidance predates the availability of upadacitinib, therefore no specific recommendations are made; however the guidance makes the following relevant recommendations:

- Patients should be considered for anti-TNF therapy if they have active axial spondyloarthritis (axSpA). Active disease is defined as a BASDAI and spinal pain visual analogue scale (VAS) score ≥4 despite standard therapy.
- Extra-articular manifestations and patient choice should be considered when selecting an anti-TNF agent. In the absence of head-to-head studies, systematic reviews have shown no statistical difference in efficacy between infliximab, golimumab, etanercept and adalimumab in the treatment of AS (certolizumab data were not included in these comparative reviews, but its efficacy has been established in clinical trials). However, not all biologics are licensed for or effective in the treatment of extra-articular disease, so treatment choice should take into account comorbidities and the preferred route and frequency of administration.
- Initial efficacy response should be assessed following 3 to 6 months of therapy and responders should then be reassessed every 6 months.
- Response is defined as a reduction in the BASDAI and spinal pain VAS of ≥2 units from baseline.
- In the absence of an initial clinical response by 6 months, or failure to maintain response at two consecutive assessments, withdrawal of that anti-TNF agent should be considered.
- In the event of anti-TNF failure due to inefficacy or adverse events, an alternative anti-TNF agent should be offered if clinically appropriate.

The National Institute for Health and Care Excellence (NICE) "Spondyloarthritis in over 16s: diagnosis and management (NG65)" was updated in 2017.[12] The guidance recommends the use of adalimumab, certolizumab pegol, etanercept, golimumab and infliximab, within their marketing authorisations, as options for treating severe active AS in adults whose disease has responded inadequately to, or who cannot tolerate, NSAIDs. The guideline also advises that the choice of treatment should be made after discussion between the clinician and the patient and recommends that if more than one treatment is suitable, the least expensive (taking into account administration costs and patient access schemes) should be chosen. The guidance recommends that people who cannot tolerate, or whose disease has not responded to, treatment with the first TNF-alpha inhibitor, or whose disease has stopped responding after an initial response, be treated with another TNF-alpha inhibitor.

The Assessment of SpondyloArthritis international Society (ASAS) in collaboration with the European League Against Rheumatism (EULAR) published guidance in 2006 (ASAS-EULAR) which was last updated in 2016.[13] The guideline predates the availability of upadacitinib and therefore

no specific recommendations are made, however the guidance makes the following relevant recommendations:

- Patients suffering from pain and stiffness should use an NSAID as first-line treatment up to the maximum dose, taking risks and benefits into account. For patients who respond well to NSAIDs continuous use is preferred if symptomatic otherwise.
- Patients with purely axial disease should normally not be treated with csDMARDs; sulfasalazine may be considered in patients with peripheral arthritis.
- bDMARDs should be considered in patients with persistently high disease activity despite conventional treatments; current practice is to start with TNF-alpha inhibitor therapy.
- If TNF-alpha inhibitor therapy fails, switching to another TNF-alpha inhibitor or an anti-IL-17 therapy should be considered.

Additional information: comparators

Adalimumab, certolizumab pegol, etanercept, golimumab, infliximab,secukinumab.

Additional information: list price of medicine under review

Medicine	Dose Regimen	Cost per year (£)
Upadacitinib	15mg once daily (oral)	10,478.

Costs from BNF online on 04 August 2022. Costs do not take patient access schemes into consideration.

Additional information: budget impact

The submitting company estimated there would be 3,426 patients eligible for treatment with upadacitinib in year 1 and 4,007 patients in year 5.

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.**

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This assessment is based on data submitted by the applicant company up to and including 16 September 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:*https://www.scottishmedicines.org.uk/about-us/policies-publications/

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.