

upadacitinib 15mg prolonged-release tablet (Rinvoq®)

AbbVie Ltd

15 January 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

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

Indication under review: for the treatment of moderate to severe active rheumatoid arthritis (RA) in adult patients who have responded inadequately to, or who are intolerant to one or more disease-modifying anti-rheumatic drugs (DMARDs). Upadacitinib may be used as monotherapy or in combination with methotrexate.

SMC restriction: in patients with severe disease (a disease activity score [DAS28] greater than 5.1) that has not responded to intensive therapy with a combination of conventional DMARDs and in patients with severe disease inadequately controlled by a TNF antagonist in whom rituximab is not appropriate.

Upadacitinib (with or without methotrexate) compared with placebo, significantly improved signs and symptoms of RA in patients with an inadequate response to conventional DMARDs and in patients with an inadequate response to biological DMARDs. Upadacitinib was non-inferior to a biologic DMARD in patients who had an inadequate response to methotrexate.

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 active RA in adult patients who have responded inadequately to, or who are intolerant to one or more DMARDs. Upadacitinib may be used as monotherapy or in combination with methotrexate.¹

Dosing Information

The recommended dose of upadacitinib is 15mg once daily.

Upadacitinib is to be taken orally once daily with or without food and may be taken at any time of the day. Tablets should be swallowed whole and should not be split, crushed, or chewed.

Treatment should not be initiated in patients with an absolute lymphocyte count (ALC) that is <500 cells/mm³, an absolute neutrophil count (ANC) that is <1,000 cells/mm³ or who have haemoglobin (Hb) levels that are <8 g/dL.

Treatment should be interrupted if a patient develops a serious infection until the infection is controlled. Interruption of dosing may be needed for management of laboratory abnormalities.

Treatment with upadacitinib should be initiated and supervised by physicians experienced in the diagnosis and treatment of rheumatoid arthritis.

Refer to Summary of product characteristics (SPC) for further detail.¹

Product availability date

December 2019

Summary of evidence on comparative efficacy

Upadacitinib selectively and reversibly inhibits janus kinase (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.¹

The submitting company has requested that SMC considers upadacitinib when positioned for use in adult patients with moderate to severe rheumatoid arthritis who have responded inadequately to, or who are intolerant to two or more DMARDs. The submitting company suggests that upadacitinib will be used in four populations:

- Moderate active RA that has not responded adequately to therapy with two or more conventional DMARDs (cDMARDs);
- Severe active RA that has not responded adequately to therapy with two or more cDMARDs;
- Severe active RA that has not responded adequately to therapy with advanced therapies (for patients with rituximab intolerance/contraindication);

- Severe active RA that has not responded adequately to advanced therapies and who are eligible for rituximab. ‘Advanced therapies’ include biological DMARDs (bDMARDs), and targeted synthetic DMARDs (tsDMARDs), such as JAK inhibitors.

Four randomised, double-blind, phase III studies (SELECT-COMPARE, SELECT-NEXT, SELECT-MONOTHERAPY, SELECT-BEYOND) recruited adult patients with a diagnosis of RA for ≥ 3 months in accordance with the 2010 American College of Rheumatology (ACR)/European League Against Rheumatism (EULAR) classification criteria. Patients were required to have ≥ 6 swollen joints, ≥ 6 tender joints, and high-sensitivity C-reactive protein (CRP) level ≥ 5 mg/L (SELECT-COMPARE) and CRP ≥ 3 mg/L (SELECT-MONOTHERAPY, SELECT-BEYOND, SELECT-NEXT) at screening. In SELECT-COMPARE patients were required to have had an inadequate response to methotrexate treatment, and either ≥ 3 bone erosions on x-ray or ≥ 1 bone erosion and a positive rheumatoid factor (RF) or ≥ 1 bone erosion and a positive anti-cyclic citrullinated peptide (aCCP) autoantibody. In SELECT-NEXT patients were required to be on a stable dose of cDMARD and have previously failed at least one cDMARD. In SELECT-MONOTHERAPY patients were required to have had an inadequate response to methotrexate but be able to tolerate a methotrexate dose of at least 10mg/week. In SELECT-BEYOND patients were required to be on a stable cDMARD dose and to have previously failed at least one bDMARD.²⁻⁵

In SELECT-COMPARE patients were randomised in a 2:2:1 ratio to receive upadacitinib 15mg orally once daily (n= 651), placebo (n= 651), or adalimumab subcutaneously 40mg every other week (n= 327), all in conjunction with a stable background dose of methotrexate.^{5, 6} In SELECT-NEXT patients were randomised equally to upadacitinib 30mg orally once daily (n= 219), upadacitinib 15mg once daily (n= 221), or placebo (n= 221). Patients were permitted to continue up to two concomitant background cDMARDs at stable doses, with the exception of the combination of methotrexate and leflunomide.^{4, 6} In SELECT-MONOTHERAPY patients were randomised equally to upadacitinib 30mg orally once daily (n= 215), upadacitinib 15mg orally once daily (n= 217), or methotrexate (n= 216). All cDMARDs other than methotrexate must have been discontinued within the protocol-specified washout period.^{3, 6} In SELECT-BEYOND patients were randomised equally to upadacitinib 30mg orally once daily (n= 165), upadacitinib 15mg orally once daily (n= 165), or placebo (n= 169). Patients were permitted to continue up to two concomitant background cDMARDs at stable doses, with the exception of the combination of methotrexate and leflunomide. The control groups of all studies were switched to upadacitinib 15mg or 30mg once daily after the initial 12/14 weeks. Upadacitinib 30mg is an unlicensed dose and will not be discussed further.^{2, 6}

The primary outcome for SELECT-COMPARE was the proportion of patients who achieved clinical remission based on a Disease Activity Score (DAS) in 28 joints using CRP level (DAS28-CRP) of < 2.6 at week 12. The primary outcome for SELECT-NEXT, SELECT-MONOTHERAPY, and SELECT-BEYOND was the proportion of patients who achieved low disease activity (LDA) based on DAS28-CRP of ≤ 3.2 at week 12 (week 14 in SELECT-MONOTHERAPY). Key ranked secondary outcomes were controlled for type I statistical error using graphic multiple testing procedures (hierarchical testing strategy for SELECT-COMPARE), with no formal testing of outcomes after the first non-significant outcome. Efficacy outcomes were assessed in all randomised patients who received at least one dose of study drug.⁶

In all four phase III studies, the primary outcomes as well as all key (alpha-controlled) secondary outcomes achieved statistical significance in favour of upadacitinib over placebo or (in SELECT-MONOTHERAPY) methotrexate. In SELECT-COMPARE, upadacitinib was found to be non-inferior to adalimumab for the outcome LDA DAS28-CRP ≤ 3.2 at Week 12. Details of the results are presented in Table 1. Subgroup analyses of the primary outcome were broadly supportive of treatment with upadacitinib compared with placebo across all studies.⁶

Table 1: Response and remission in key studies: SELECT-MONOTHERAPY, SELECT-NEXT, SELECT-COMPARE, and SELECT-BEYOND.¹

Week	SELECT-MONOTHERAPY		SELECT-NEXT*		SELECT-COMPARE**			SELECT-BEYOND*	
	MTX (n=216)	UPA 15mg (n=217)	PBO (n=221)	UPA 15mg (n=221)	PBO (n=651)	UPA 15mg (n=651)	ADA 40mg (n=327)	PBO (n=169)	UPA 15mg (n=164)
LDA DAS28-CRP ≤ 3.2 (% of patients)									
12 ^a or 14 ^b	19	45 ^c	17	48 ^c	14	45 ^c	29	14	43 ^c
26	-	-	-	-	18	55	39	-	-
48	-	-	-	-	-	50	35	-	-
CR DAS28-CRP < 2.6 (% of patients)									
12 ^a or 14 ^b	8	28 ^c	10	31 ^c	6	29 ^c	18	9	29
26	-	-	-	-	9	41	27	-	-
48	-	-	-	-	-	38	28	-	-
ACR20 (% of patients)									
12 ^a or 14 ^b	41	68 ^e	36	64 ^c	36	71 ^c	63	28	65 ^c
26	-	-	-	-	36	67	57	-	-
48	-	-	-	-	-	65	54	-	-
ACR50 (% of patients)									
12 ^a or 14 ^b	15	42	15	38	15	45	29	12	34
26	-	-	-	-	21	54	42	-	-
48	-	-	-	-	-	49	40	-	-
ACR70 (% of patients)									
12 ^a or 14 ^b	3	23	6	21	5	25	13	7	12
26	-	-	-	-	10	35	23	-	-
48	-	-	-	-	-	36	23	-	-
LDA CDAI ≤ 10 (% of patients)									
12 ^a or 14 ^b	25	35	19	40 ^c	16	40	30	14	32
26	-	-	-	-	22	53	38	-	-
48	-	-	-	-	-	47	34	-	-

Descriptive p-values not presented. ACR20 (or 50 or 70) = American College of Rheumatology $\geq 20\%$ (or $\geq 50\%$ or $\geq 70\%$) improvement; ADA = adalimumab; CDAI = Clinical Disease Activity Index; CR = Clinical Remission; CRP = C-Reactive Protein, DAS28 = Disease Activity Score 28 joints; IR = inadequate responder; LDA = Low Disease Activity; MTX = methotrexate; PBO = placebo; UPA= upadacitinib

* Patients in SELECT-NEXT and SELECT-BEYOND received stable background doses of conventional DMARD(s)

** Patients in SELECT-COMPARE received stable background doses of methotrexate.

^a SELECT-NEXT, SELECT-EARLY, SELECT-COMPARE, SELECT-BEYOND

^b SELECT-MONOTHERAPY

^c $p \leq 0.001$ upadacitinib versus placebo or methotrexate

Health Related Quality of Life (HRQoL) was assessed using three instruments: Health Assessment Questionnaire Disability Index (HAQ-DI), 36-Item Short Form Health Survey physical component summary (SF-36 PCS), and Functional Assessment of Chronic Illness Therapy Fatigue scale (FACIT-F). Across all studies, patients taking upadacitinib 15mg compared with placebo reported greater quality of life improvements, including reduction in fatigue.^{1, 6} See Table 2 for details.

Table 2: Physical function and quality of life outcomes in key studies: SELECT-MONOTHERAPY, SELECT-NEXT, SELECT-COMPARE, and SELECT-BEYOND.¹⁻⁵

Study	SELECT-MONOTHERAPY		SELECT-NEXT		SELECT-COMPARE			SELECT-BEYOND	
	MTX (n=216)	UPA 15mg (n=216)	PBO (n=220)	UPA 15mg (n=216)	PBO (n=648)	UPA 15mg (n=644)	ADA 40mg (n=324)	PBO (n=165)	UPA 15mg (n=163)
least squares mean change from baseline HAQ-DI									
Week 12 ^a or 14 ^b	-0.3	-0.7 ^c	-0.3	-0.6 ^c	-0.3	-0.6 ^c	-0.5	-0.2	-0.4 ^c
Week 26	-	-	-	-	-0.3	-0.7	-0.6	-	-
least squares mean change from baseline SF-36 PCS									
N	195	200	207	209	616	616	-	145	156
Week 12 ^a or 14 ^b	4.3	8.3 ^c	3.0	7.6 ^c	3.6	7.9 ^c	6.3	2.4	5.8
Week 26	-	-	-	-	4.5	9.5	7.8	-	-
least squares mean change from baseline FACIT-F									
N	-	-	207	207	613	612	-	-	-
Week 12	-	-	3.0	7.9 ^c	4.8	9.0 ^c	7.4	-	-
Week 26	-	-	-	-	5.5	9.7	8.2	-	-

Descriptive p-values not presented. ADA = adalimumab; FACIT-F = Functional Assessment of Chronic Illness Therapy Fatigue scale; HAQ-DI = Health Assessment Questionnaire Disability Index; IR = inadequate responder; MTX = methotrexate; PBO = placebo; SF-36 PCS = 36-Item Short Form Health Survey physical component summary; UPA = upadacitinib

^a SELECT-NEXT, SELECT-COMPARE, SELECT-BEYOND

^b SELECT-MONOTHERAPY

^c p<0.001 upadacitinib vs placebo or methotrexate

SELECT-CHOICE is an ongoing double-blind, phase III, controlled study that randomised patients with RA on stable doses of cDMARDs, who have had an inadequate response or intolerance to bDMARDs, to receive oral upadacitinib 15mg once daily (n=303) or intravenous abatacept on day 1, week 2, 4, 8, 12, 16 and 20 (n=309). The primary outcome was the change from baseline in DAS28-CRP (range, 0 to 9.4, with higher scores indicating more disease activity) at week 12, assessed for non-inferiority. Key secondary outcomes at week 12 were the superiority of upadacitinib over abatacept in the change from baseline in the DAS28-CRP and the percentage of patients having clinical remission, defined as a DAS28-CRP of less than 2.6. In patients with RA refractory to bDMARDs, upadacitinib was superior to abatacept in the change from baseline in the DAS28-CRP; difference = -0.52 points; 95% confidence interval (CI): -0.69 to -0.35; p<0.001 for both non-inferiority and superiority.⁷ The study will continue to evaluate longer-term secondary outcomes and is expected to complete in June 2022.

SELECT-SUNRISE was a multicentre, phase IIb/III, double-blind, dose-ranging study conducted in Japan, in which patients with active RA and an inadequate response to cDMARDs were randomised to receive upadacitinib 7.5, 15 or 30mg once daily or matching placebo for 12-weeks. The primary outcome was ACR20 response at week 12 using non-responder imputation. Of the 197 patients enrolled into the study, 49 patients received upadacitinib 15mg and 49 patients received placebo. At week 12, 84% of the upadacitinib group achieved the primary outcome of ACR20 response compared with 43% in the placebo group ($p < 0.001$). The safety profile was consistent with other upadacitinib RA studies.⁸

Two Bayesian network meta-analyses (NMAs) were conducted in patients with moderate to severe RA to compare upadacitinib against a number of relevant comparators: abatacept, adalimumab, baricitinib, certolizumab pegol, etanercept, golimumab, infliximab, rituximab, sarilumab, tocilizumab, tofacitinib, and intensive cDMARDs. One analysis was conducted in patients who had an inadequate response to cDMARDs and included 55 studies. The other analysis was conducted in patients who had an inadequate response to bDMARDs and included 12 studies. In the base case, the reported outcomes were ACR response and EULAR response at three and six months in the cDMARD inadequate response NMA and at three and six months in the bDMARD inadequate response NMA. In the cDMARD inadequate response NMA, it was estimated that upadacitinib (monotherapy or in combination with cDMARD) has a greater probability of achieving an ACR20, ACR50, and ACR70 response in comparison with placebo and with cDMARDs. In the bDMARD inadequate response NMA, it was estimated that upadacitinib combination therapy was likely to have a greater probability of achieving an ACR20, ACR50, and ACR70 response in comparison with cDMARDs. EULAR responses were “mapped” based on ACR data, the results of which were felt to be broadly similar by the submitting company.

Summary of evidence on comparative safety

Overall, in the clinical study programme, the frequency of adverse events (AEs) during the first 3 months was 50% when upadacitinib was given in monotherapy (compared with 48% for methotrexate), and 56% when given in combination with other cDMARDs (versus 48% for placebo plus cDMARD, and 48% for adalimumab plus methotrexate). The frequency of serious AEs was 3.0% for upadacitinib monotherapy (versus 2.3% for methotrexate) and 3.4% when given in combination with other cDMARDs (versus 1.8% for placebo plus cDMARDs and 2.4% for adalimumab plus methotrexate). Of the total number of patients who received at least one dose of upadacitinib in either a phase II or phase III study, 67% (2,972/4,443) had exposure to upadacitinib for at least 48 weeks.⁶

In SELECT-COMPARE, safety data were available for upadacitinib versus adalimumab up to week 26, both in combination with methotrexate. In the upadacitinib ($n=650$) and adalimumab ($n=327$) groups respectively, 64% versus 60% reported any AE; 3.7% versus 4.3% reported a serious AE; 3.5% versus 6.1% reported an AE leading to discontinuation of study drug; 35% versus 29% reported infection; 1.8% versus 1.5% reported serious infection; 6.6% versus 3.7% reported

hepatic disorder; 0.3% versus 0% reported gastrointestinal perforation; 0% versus 0.3% reported malignancy; 0.3% versus 0.9% reported venous thromboembolism.⁶

In the placebo-controlled upadacitinib 15mg analysis set (n= 2,077; upadacitinib = 1,035; placebo = 1,042), which included data from SELECT-NEXT, SELECT-COMPARE, and SELECT-BEYOND, the most common AEs identified as adverse drug reactions by the investigators were: upper respiratory tract infection (14% upadacitinib versus 9.5% placebo), nausea (3.5% versus 2.2%), blood creatine phosphokinase (CPK) increased (2.5% versus 0.9%), cough (2.2% versus 1.0%), neutropenia (1.8% versus 0.2%), pyrexia (1.2% versus 0%), hypercholesterolemia (1.1% versus 0.2%), herpes zoster (0.7% versus 0.2%), pneumonia (0.5% versus 0.3%), herpes simplex (0.8% versus 0.5%), and oral candidiasis (0.4% versus <0.1%).⁶

There are several important uncertainties concerning the safety profile of upadacitinib relating to malignancies, major adverse cardiovascular events, venous thromboembolic events and effects on multiple laboratory parameters. Longer-term safety data are awaited. A safety concern shared by all immunomodulatory therapies is infection, which the European Medicines Agency (EMA) consider to be manageable. When compared with adalimumab, upadacitinib (both in combination with methotrexate) was associated with a higher, albeit small difference in number of AEs for most AEs.⁶

Summary of clinical effectiveness issues

Rheumatoid arthritis is a common progressive autoimmune disease affecting approximately 1% of the population and is characterised by joint inflammation and swelling. Women are affected more frequently than men. It is not curable and a significant number of patients experience pain, stiffness, destruction of joints, decline in function and premature mortality.⁶

Scottish Intercollegiate Guidelines Network (SIGN) guidance recommends that all patients with moderate to severe disease activity should receive DMARDs, adjusted to achieve remission or a low disease activity score. Treatment is typically initiated with a cDMARD, most commonly methotrexate.⁹ For patients with severe disease not adequately controlled by cDMARDs Healthcare Improvement Scotland (HIS) has endorsed National Institute for Health and Care Excellence (NICE) technology appraisal (TA) 375 which recommends the following bDMARDs (in combination with methotrexate) as treatment options: adalimumab, etanercept, infliximab, certolizumab pegol, golimumab, tocilizumab and abatacept. Adalimumab, etanercept, certolizumab pegol and tocilizumab can also be used as monotherapy for people who cannot take methotrexate. For patients with severe disease not adequately controlled by cDMARDs and a tumour necrosis factor (TNF) antagonist, HIS has endorsed NICE TA195, which recommends rituximab and, for rituximab-ineligible patients, the following bDMARDs (in combination with methotrexate) as treatment options: adalimumab, etanercept, infliximab and abatacept. More recently JAK inhibitors (baricitinib and tofacitinib) and the humanised anti-interleukin-6 (IL-6) receptor antibody, sarilumab, have been made available to patients in Scotland; baricitinib (SMC 1265/17), tofacitinib (SMC 1298/18), and sarilumab (1314/18) can be used in patients with severe

disease that has not responded to intensive therapy with a combination of cDMARDs and additionally in patients with severe disease inadequately controlled by a TNF antagonist who are ineligible to receive rituximab.

The submitting company has requested that SMC considers upadacitinib when positioned for use in adult patients with moderate to severe RA who have responded inadequately to, or who are intolerant to two or more DMARDs. In the four main phase III studies, the primary outcomes as well as all key secondary outcomes achieved statistical significance in favour of upadacitinib over placebo (with a background of conventional DMARD in both groups) or over methotrexate in the monotherapy study. In SELECT-COMPARE, upadacitinib was found to be non-inferior to adalimumab (and superior to adalimumab when evaluated as a secondary outcome). The selection of primary outcome and key secondary outcomes across studies was appropriate and in accordance with EMA guidelines. Overall, the EMA concluded that upadacitinib has a clinically relevant effect in inducing remission or low disease activity in patients with active rheumatoid arthritis both as second and third line treatment, relevant to the licensed indication and proposed positioning.

An interim analysis from SELECT-CHOICE also suggests non-inferiority of upadacitinib to abatacept (and superior to abatacept when evaluated as a secondary outcome). For many of the efficacy outcomes, a treatment effect with upadacitinib was observed in the first or second week, indicating rapid onset of effect, and treatment effect appears to be maintained up to one year and beyond.^{6, 7}

There are important limitations to the evidence presented that should be considered. The design of SELECT-MONOTHERAPY, as a means to demonstrate upadacitinib monotherapy efficacy and safety in the population with an inadequate response to methotrexate, was flawed as the comparator group (methotrexate monotherapy) were by definition being undertreated. In order to gain approval in this setting, the EMA requested indirect treatment comparisons of upadacitinib monotherapy versus upadacitinib plus methotrexate which the company completed and which were considered adequate by the EMA. There is a lack of direct evidence comparing upadacitinib monotherapy with upadacitinib plus methotrexate, most notably in regards to radiographic progression and long-term outcomes.⁶ In SELECT-BEYOND, the EMA noted that “investigator’s best choice” would have been a more suitable comparator group than placebo to evaluate the efficacy of upadacitinib in the third-line setting. In all the studies evaluated, rescue therapies were offered to patients after the double-blind period of each study (at week 12 or 14), and therefore not all patients remained on their randomised treatment for the entire study duration. The short placebo-controlled periods are justified from an ethical point of view to limit the time patients with active disease receive placebo; for example, in SELECT-COMPARE rescue therapy was initiated between weeks 14 and 26 in 19%, 24%, and 47% of patients in the upadacitinib, adalimumab, and placebo groups respectively. Finally, no data are available for the use of upadacitinib in patients who have previously been treated with other JAK inhibitors.⁵

There is a lack of long-term efficacy and safety data for treatment with upadacitinib. At present, data are available up to week 60 for SELECT-NEXT and SELECT-BEYOND, and up to week 48 for

SELECT-COMPARE and SELECT-MONOTHERAPY. Long-term data are particularly important to further characterise the risk of long latency, low frequency AEs associated with upadacitinib, including malignancies, major adverse cardiovascular events, and venous thromboembolic events. The safety profile of upadacitinib could be considered a limitation of the treatment; compared with adalimumab, most AEs occurred more frequently for upadacitinib (both in combination with methotrexate) although the differences were small,⁶ when compared with abatacept, upadacitinib was associated with a higher incidence of serious AEs.⁷

Although there are some direct data comparing upadacitinib with relevant comparators, there remains a lack of direct comparative evidence for a number of other relevant treatments. The indirect treatment comparisons had limitations: the population included in the analyses (moderate to severe RA) did not match the populations in the requested positioning, which relates to patients with either moderate disease (scenario 1) or severe disease, however data were not available for subgroups in certain studies. Consequently, there is clinical heterogeneity in the treatments and posology included in the networks, which introduces uncertainty into the analyses; the analyses did not assess patient reported outcomes (HAQ-DI) or safety, which may be clinically relevant considering that direct evidence to date suggests the safety profile of upadacitinib was generally comparable with adalimumab and less favourable compared to abatacept; the bDMARD IR NMA did not include adalimumab, etanercept, and infliximab however this may have been challenging due to the lack of evidence. In the results of the NMA, treatments were ranked by effectiveness and not by SUCRA (Surface Under the Cumulative RANking) scores, probability best, or mean rank, which are preferable. Despite the limitations, the conclusions made by the company, that upadacitinib was superior to cDMARDs and non-inferior to bDMARDs and tsDMARDs, seem reasonable.

Clinical experts consulted by SMC considered that upadacitinib would serve as an alternative to other JAK inhibitors in this setting.

Summary of comparative health economic evidence

The company submitted a cost-utility analysis for the comparison of upadacitinib versus conventional DMARDs and best supportive care in moderate patients with rheumatoid arthritis after two or more conventional DMARDs. Additionally, the company presented a cost-minimisation analysis for the comparison of upadacitinib versus a range of advanced therapies as first or second line therapy. The biologic therapies included were abatacept, adalimumab, baricitinib, certolizumab, etanercept, golimumab, infliximab, rituximab, sarilumab, tocilizumab and tofacitinib. All analyses were presented for sub-groups of patients depending on eligibility of treatment with methotrexate.

The time horizon for the cost-utility analysis was 45 years and 5 years in the cost-minimisation analysis. A discrete event simulation (DES) model was used which simulates the experiences of individual patients based on their characteristics without the need for health states. Patients with

moderate disease were modelled to receive several lines of subsequent therapies and are allowed to progress to severe disease.

In the moderate patient group, individual patients were modelled to receive treatment with upadacitinib or cDMARD up until month 6 at which point their response (no response, moderate, and good) was assessed based on EULAR response criteria as observed in the relevant upadacitinib studies as the base case, with scenario analysis provided using the results from the NMA. Patients with moderate and good response were assumed to remain on treatment until discontinuation due to loss of response or adverse events based on long-term observational data from the British Society for Rheumatology Biologics Register (BSRBR), extrapolated using separate parametric distributions for the moderate and good responders using the generalized gamma distribution. Patients who have lost response were assumed to receive next line of treatment. Methotrexate ineligible patients were only assumed to receive best supportive care following discontinuation until they progressed to severe disease. Patients on best supportive care were assumed to have no response. The efficacy of downstream therapies were based on network meta-analyses consistent with the clinical case but a 5% treatment waning effect has also been assumed.

Patients were modelled to transition to severe disease based on the long-term progression of their DAS28 score. Patients who transition to severe disease were assumed to receive adalimumab as first line, rituximab as second line and sarilumab as third line (all monotherapy or in combination with methotrexate). The progression in DAS28 score was modelled as a function of health assessment questionnaire (HAQ) score using repeated measures linear mixed effect model with data from the upadacitinib trials. The rate of initial decrease in HAQ score at 6 months for moderate and good responders were as observed in the BSRBR and was applied linearly. Patients on treatment with cDMARDs and best supportive care (BSC) were assumed to experience a gradual increase in their score based on a latent class growth model whereas for patients on biologic treatments, it was assumed to remain constant while on treatment. This approach was justified using data for 3 years from the BSRBR showing that patients treated with biologic therapies generally maintained their HAQ score past the six-month assessment of response while on treatment. No progression in HAQ was assumed for patients on cDMARDs after 15 years. Upon treatment discontinuation the HAQ score was assumed to revert back to pre-treatment values for both comparators.

Mortality was modelled using UK life tables segregated by age and sex. Disease specific mortality was also applied.

Utility values were modelled by mapping HAQ from the relevant upadacitinib trials to EQ-5D scores using a 3-step algorithm as described in Hernandez et al (2014)¹³. This involved estimating pain visual analogue scale (VAS), assigning patients to each of the 4 latent classes depending on HAQ and pain VAS scores and applying weights from published sources to estimate utility values. Utility decrements associated with adverse events in first-line treatments were also included based on medicine class (JAK inhibitor, bDMARDs, cDMARDs).

Apart from medicine acquisition and administration costs, the model also included costs of disease monitoring, treatments of adverse events and annual hospitalisation costs. The latter were modelled as a linear function of HAQ score based on an analysis using the Norfolk Arthritis Register (NOAR) database.

The cost-minimisation model compared medicine acquisition and administration costs associated with conventional and biologic DMARDs and JAK inhibitors in RA patients with severe disease. Additionally, the model included monitoring and costs associated with the treatment of serious adverse events. Treatment discontinuation rates as observed in the BSRBR were applied at 6 and 12 months and annually thereafter. Only 30% of patients were assumed to be still on treatment by year 5.

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 for upadacitinib.

The base case results with the PAS for the moderate disease population are presented in tables 3, 4 and 5 below.

Table 3 Base case results: moderate population: upadacitinib plus methotrexate

Technologies	Total LYG	ICER (£/QALY)
Base case: Upadacitinib trial data, moderate population		
Methotrexate	15.254	Reference
Upadacitinib + methotrexate	15.254	23,481
Scenario analysis: NMA effectiveness data		
Methotrexate	15.24	
Upadacitinib+ methotrexate	15.24	23,098
Abbreviations LYG: Life Year Gained, QALY: Quality Adjusted Life Year; ICER: incremental cost-effectiveness ratio		

Table 4 Base case results: moderate population: upadacitinib monotherapy

Technologies	Total LYG	ICER (£/QALY)
Base case: Upadacitinib trial data, moderate population		
Methotrexate	15.254	Reference
Upadacitinib	15.254	24,772
Scenario analysis: NMA effectiveness data		
Methotrexate	15.24	Reference
Upadacitinib	15.24	23,743
Abbreviations LYG: Life Year Gained, QALY: Quality Adjusted Life Year; ICER: incremental cost-effectiveness ratio		

Table 5: Base case results: moderate population: upadacitinib monotherapy vs best supportive care

Technologies	Total LYG	ICER (£/QALY)
Base case: Upadacitinib trial data, moderate population		
BSC	15.254	Reference
Upadacitinib	15.254	12,686
Scenario analysis: NMA effectiveness data		
BSC	15.24	
Upadacitinib	15.24	16,353
Abbreviations LYG: Life Year Gained, QALY: Quality Adjusted Life Year; ICER: incremental cost-effectiveness ratio; BSC: best supportive care		

Selected scenario analyses are presented in table 6. The only increase of the ICERs is associated with the mapping algorithm of HAQ to pain VAS scores.

Table 6: Selected scenario analyses

Scenario	ICER (vs upadacitinib + methotrexate)	ICER (vs upadacitinib)
1: Same efficacy of cDMARD/methotrexate as placebo	16,013	16,000
2: Double transition to severe RA	18,929	19,640
3: Use NMA results for efficacy parameter for both first line cDMARD and upadacitinib	20,688	20,341
4: Use HAQ to VAS pain score mapping algorithm used in NICE TA375 ¹⁴	27,343	28,607
5: Use cDMARD-IR NMA as basis of efficacy for all relevant comparators in the treatment sequence	19,590	20,232
6: Scenarios 1+4 combined	18,787	18,772
Abbreviations: cDMARD, conventional disease-modifying antirheumatic drugs; RA, rheumatoid arthritis; NMA, network meta-analysis; HAQ, health assessment questionnaire; VAS, visual analogue scale; IR, inadequate responder		

The base case results for the cost-minimisation analysis in the severe disease population are shown in table 7 and 8. PAS discounts are in place for certolizumab, tocilizumab, golimumab, baracitinib, tofacitinib and sarilumab and these were included in the results used for decision-making by SMC by using estimates of the comparator PAS prices.

The results presented do not take account of the PAS for certolizumab, tocilizumab, golimumab, baracitinib, tofacitinib and sarilumab or the PAS for upadacitinib but these were considered in the results used for decision-making at SMC. SMC is unable to present the results provided by the company which used estimates of the PAS prices for these medicines due to commercial confidentiality and competition law issues.

Table 7: Base case results: severe population (cost-minimisation) list price (5 years); methotrexate eligible

Comparator	For upadacitinib monotherapy	For upadacitinib plus methotrexate
Upadacitinib monotherapy	-	-
Upadacitinib plus methotrexate	-	-
Infliximab plus methotrexate	£3,629	£3,674
Adalimumab plus methotrexate	£6,245	£6,290
Etanercept plus methotrexate	£4,728	£4,773
Golimumab plus methotrexate	£3,362	£3,407
Tofacitinib plus methotrexate	£3,949	£ 3,993
Certolizumab plus methotrexate	£4,977	£5,022
Baracitinib plus methotrexate	-£45	-£0
Tocilizumab IV plus methotrexate	-£6,112	-£6,067
Tocilizumab SC plus methotrexate	-£4,160	-£4,115
Abatacept IV plus methotrexate	-£9,711	-£9,666
Sarilumab plus methotrexate	-£3,987	-£3,942
Abatacept SC plus methotrexate	-£14,409	-£14,364
Rituximab plus methotrexate*	£14,237	£14,281

Abbreviations: IV, intravenous; SC, subcutaneous;
*As second line advanced therapy

Table 8: Base case results: severe population (cost-minimisation) list price (5 years); methotrexate ineligible

Comparator	Incremental costs: for upadacitinib monotherapy
Upadacitinib	-
Etancercept	£4,773
Adalimumab	£6,290
Tofacitinib	£3,993
Certolizumab	£5,022
Baracitinib	£0
Sarilumab	-£3,942
Tocilizumab IV	-£6,067
Tocilizumab SC	-£4,115

Abbreviations: IV, intravenous; SC, subcutaneous;

The main limitations associated with the analyses were:

- There is a lack of direct comparative data for the comparison of upadacitinib and the majority of other biologic therapies in patients with severe RA. Similar efficacy has been assumed in the economic evaluation based on a network meta-analysis in patients segregated based on class of previous treatments rather than severity of disease and with several relative comparators missing from the analysis. A cost minimisation analysis may have been especially inappropriate for the comparison with rituximab; however, results using a cost-utility analysis were provided. This showed that upadacitinib plus methotrexate was cheaper but less effective than rituximab plus methotrexate in severe disease (south-west quadrant ICER of £67,558). As a monotherapy, the results showed that upadacitinib dominated rituximab plus methotrexate in severe disease (cheaper, more effective); however, there are concerns that the data used in this analysis relate to biologic DMARD-naïve patients which would not be appropriate given the position as a second line therapy in severe disease. The NMA is associated with other limitations and uncertainties as discussed in the clinical case.
- There are uncertainties with the long-term progression of disease in the cost-utility analysis in moderate disease patients. Patients have been assumed to progress to severe disease based on a linear extrapolation of their DAS28 score which has been modelled as a function of patients' long-term HAQ score for which the modelling is also associated with uncertainties due to lack of longer term data given the chronic nature of the disease.
- There are uncertainties in modelling long-term utility data. The incremental cost-effectiveness ratio increases when the modelling of pain VAS approach is consistent with that seen in previous submissions for other RA treatments as shown in table 6, scenario 4.
- Cost-utility model efficacy in the moderate patient group has been obtained from the relevant subgroups of the four upadacitinib trials as the base case. This differs from modelling approaches in previous submissions for other RA treatments in moderate disease where efficacy data from network meta-analyses were used. The company has provided an explanation of why this approach was taken and the cost-effectiveness ratios in the relevant scenarios are consistent with the base case results using the direct trial data as shown in the scenario analyses using the NMA shown in tables 3-5 above. It is likely that similar ICERs resulted (despite lower effectiveness for upadacitinib in the NMA) due to assumptions around subsequent treatments and their impact on costs in the upadacitinib arm.

Despite limitations, the economic case was considered demonstrated in patients with severe disease (a disease activity score [DAS28] greater than 5.1) that has not responded to intensive therapy with a combination of conventional DMARDs and in patients with severe disease inadequately controlled by a TNF antagonist in whom rituximab is not appropriate.

Given the limitations with the analysis in patients with moderate disease, the economic case has not been demonstrated for this population.

*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 Rheumatoid Arthritis Society (NRAS), which is a registered charity.
- NRAS has received 9% pharmaceutical company funding in the past two years, including from the submitting company.
- RA is an incurable, painful disease. Physical and emotional well-being, relationships, and sexuality are all impacted by the condition. As three out of four people are of working age when diagnosed, many worry about losing their job because of their condition. Watching loved-ones suffer from severe pain and fatigue can be very distressing.
- Response to treatment varies considerably and patients may require multiple therapies before they find one that works for them.
- Upadacitinib would provide an additional treatment option and as another member of a relatively new class of medicines (JAK inhibitors), is to be welcomed. It can also be used in different places in the current treatment pathway and, as an oral therapy, would likely be preferred by patients over treatments that are injected or require an infusion. As RA affects all areas of life, a medicine that works for those patients who have not responded to or have been unable to take other medicines could also help their partners, family and carers. However, due to the heterogeneity of the condition it is likely it will be successful for a proportion of patients, but not everyone.

Additional information: guidelines and protocols

The Scottish Intercollegiate Guidelines Network (SIGN) published guideline 123 Management of early rheumatoid arthritis in February 2011. All patients with moderate to severe disease activity should receive treatment with DMARDs, adjusted with the aim of achieving remission or a low disease activity score (DAS)/28-joint disease activity score (DAS28). Use of TNF antagonists for the treatment of severe, active and progressive rheumatoid arthritis in adults not previously treated with methotrexate or other DMARDs is not recommended.¹⁰

The National Institute for Health and Care Excellence (NICE) published guideline NG100 in July 2018 (updated in October 2020), which refers to Multiple Technology Appraisal (MTA) advice for the use of biologics (TA375 and TA195). In patients that have had inadequate response to cDMARDs, the following treatments have been recommended (with restrictions): sarilumab,

adalimumab, etanercept, infliximab, certolizumab pegol, golimumab, tocilizumab, abatacept, tofacitinib, and baricitinib. In patients with inadequate response or intolerance to biological DMARDs, and rituximab is suitable, NICE recommend rituximab plus methotrexate. When rituximab is not suitable, the following treatments are available: sarilumab, adalimumab, etanercept, infliximab, abatacept, golimumab, certolizumab pegol, tocilizumab, tofacitinib, and baricitinib.¹¹

EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2019 update makes the following recommendations: Phase I: methotrexate first-line (or alternative cDMARD if methotrexate contraindicated); Phase II: poor prognostic factors present = methotrexate plus bDMARD or JAK inhibitor. Poor prognostic factors absent = change to or add a second cDMARD; Phase III: change the bDMARD or JAK inhibitor.¹²

Additional information: comparators

Methotrexate, leflunomide, sulfasalazine, hydroxychloroquine, baricitinib, tofacitinib, adalimumab, certolizumab, etanercept, golimumab, infliximab, sarilumab, tocilizumab, abatacept and rituximab.

Additional information: list price of medicine under review

Medicine	Dose Regimen	Cost per year (£)
upadacitinib	15mg orally once daily	£10,472

Costs from BNF online on 31 October 2020. Costs do not take patient access schemes into consideration.

Additional information: budget impact

Severe RA population

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.

*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 11 December 2020.

**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.