Healthcare Improvement Scotland | SMC Advice on new medicines

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SMC2495

upadacitinib 15mg prolonged-release tablets (Rinvoq®)

AbbVie Ltd

04 November 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 Therapeutic Committees (ADTCs) on its use in NHSScotland. The advice is summarised as follows:

ADVICE: following a resubmission

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 adults with moderate disease (a disease activity score [DAS28] of 3.2 to 5.1) when intensive therapy with 2 or more conventional DMARDs has not controlled the disease well enough.

In a phase III randomised, placebo-controlled and active comparator study in patients who had an inadequate response to methotrexate, upadacitinib significantly improved the signs and symptoms of RA compared with placebo.

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.

SMC has issued separate advice for upadacitinib in patients with severe disease (DAS28 greater than 5.1).

Chairman
Scottish Medicines Consortium

Indication

Upadacitinib is indicated 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.

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 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. The JAK family of enzymes contains four members, JAK1, JAK2, JAK3 and TYK2, which work in pairs to phosphorylate and activate signal transducers and activators of transcription. This phosphorylation, in turn, modulates gene expression and cellular function. Upadacitinib preferentially inhibits signalling by JAK1.[2]

The submitting company has requested that SMC considers upadacitinib when positioned for use in adults with moderate active RA that has not responded adequately to 2 or more conventional synthetic DMARDs. SMC has previously accepted upadacitinib for restricted use in patients with severe active RA (a disease activity score [DAS28] greater than 5.1) that has not responded to intensive therapy with a combination of conventional DMARDs (cDMARD) and in patients with severe disease inadequately controlled by a TNF antagonist in whom rituximab is not appropriate (SMC2315).

The key evidence is from a randomised, double-blind, phase III study (SELECT-COMPARE) that recruited adult patients with a diagnosis of RA for ≥3 months as per 2010 American College of Rheumatology (ACR)/European League Against Rheumatism (EULAR) classification criteria. Patients were also required to have ≥6 swollen joints (based on 66 joint counts), ≥6 tender joints (based on 68 joint counts), and high-sensitivity C-reactive protein (CRP) level ≥5mg/L at screening. 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 autoantibody.

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.[3, 4] At weeks 14, 18, and 22, patients without an improvement of ≥20% in the tender joint count and swollen joint count from baseline received rescue therapy, switching from placebo to upadacitinib, upadacitinib to adalimumab, or adalimumab to upadacitinib. All placebo patients at week 26 were switched to upadacitinib regardless of clinical response.[3]

The primary outcome 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. A hierarchical statistical testing strategy was applied in the study with no formal testing of outcomes after the first non-significant outcome in the hierarchy. Therefore the results reported for these outcomes are descriptive only and not inferential (no p-values reported). Upadacitinib was found to be non-inferior to adalimumab for the outcome Low Disease Activity (LDA) DAS28-CRP ≤3.2 at week 12. In addition, the proportion of patients with no radiographic progression at week 26 was 76% in the placebo group and 84% in the upadacitinib 15mg group.[1] The primary and secondary outcomes for SELECT-COMPARE are shown in Table 1.

Table 1. Primary and secondary outcomes in SELECT-COMPARE. [1]

	SELECT-COMPARE		
Week	**Placebo (n=651)**	**Upadacitinib 15mg (n=651)**	**Adalimumab 40mg (n=327)**
CR DAS28-CRP <2.6 (% of patients)			
12	6	29*	18
26	9	41	27
48	-	38	28
LDA DAS28-CRP ≤3.2 (% of patients)			
12	14	45*	29
26	18	55	39
48	-	50	35
ACR20 (% of patients)			
12	36	71*	63
26	36	67	57
48	-	65	54
ACR50 (% of patients)			
12	15	45	29

26	21	54	42
48	-	49	40
ACR70 (% of patients)			
12	5	25	13
26	10	35	23
48	-	36	23
LDA CDAI ≤10 (% of patients)			
12	16	40	30
26	22	53	38
48	-	47	34

Descriptive p-values not presented. ACR20 (or 50 or 70) = American College of Rheumatology ≥20% (or ≥50% or ≥70%) improvement; CDAI = Clinical Disease Activity Index; CR = Clinical Remission; CRP = C-Reactive Protein, DAS28 = Disease Activity Score 28 joints; LDA = Low Disease Activity

* p≤0.001 upadacitinib versus placebo

Health Related Quality of Life was assessed using three instruments: Health Assessment Questionnaire Disability Index, 36-Item Short Form Health Survey physical component summary, and Functional Assessment of Chronic Illness Therapy Fatigue scale. Patients taking upadacitinib 15mg compared with placebo reported greater quality of life improvements, including reduction in fatigue.[1, 4]

Supportive studies included SELECT-NEXT; SELECT-BEYOND; SELECT-MONOTHERAPY and SELECT-CHOICE.

SELECT-NEXT was a multicentre, randomised, double-blind, parallel-group, placebo-controlled, phase III study, which evaluated the efficacy and safety of upadacitinib (15mg or 30mg orally once daily) compared with placebo in 661 patients with moderately to severely active RA who were on a stable dose of cDMARDs and had an inadequate response to at least one cDMARDs. The primary outcome was the proportion of patients with LDA based on DAS28-CRP ≤3.2 at Week 12, which was significantly improved for upadacitinib 15mg compared with placebo (48% versus 17%).[4]

SELECT-BEYOND was a multicentre, randomised, double-blind, parallel-group, placebo-controlled period phase III study, which evaluated the efficacy and safety of upadacitinib (15mg or 30mg orally once daily) compared with placebo in 499 patients with moderately to severely active RA with an inadequate response or intolerance to at least one biologic DMARD (bDMARD). The primary outcome of DAS28-CRP≤3.2 at Week 12 was significantly improved for upadacitinib 15mg compared with placebo (43% versus 14%).[4]

SELECT-MONOTHERAPY was a multicentre, randomised, double-blind, parallel-group controlled, phase III study, which evaluated the efficacy and safety of upadacitinib (15mg or 30mg orally once daily) compared with methotrexate in 648 patients with moderately to severely active RA with inadequate response to methotrexate. The primary outcome of proportion of patients with LDA (based on DAS28-CRP ≤3.2) at Week 14 was significantly improved for upadacitinib 15mg compared with methotrexate (45% versus 19%).[4]

SELECT-CHOICE was a double-blind, phase III, controlled trial 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 (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. Although shown to be more efficacious, upadacitinib was associated with more serious adverse events (AEs) than abatacept.[5]

A Bayesian network meta-analysis (NMA) was 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) in patients who had an inadequate response to cDMARDs and included 55 studies. The reported outcomes were ACR response and EULAR response at three and six months. 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. For the other comparators, the results suggested there was likely to be no difference between upadacitinib and comparators, since the credible intervals overlapped.

Summary of evidence on comparative safety

Overall, in the clinical study programme, the frequency of 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.[4]

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.[3]

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 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.[4]

Summary of clinical effectiveness issues

RA 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.[4]

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.[6, 7] Healthcare Improvement Scotland (HIS) has endorsed National Institute of Health and Care Excellence (NICE) technology appraisal guidance TA715; this recommends adalimumab, etanercept and infliximab in combination with methotrexate as treatment options for patients with moderate active RA (DAS 3.2 to 5.1) not controlled by intensive therapy with 2 or more cDMARDs. Adalimumab and etanercept can also be used as monotherapy if methotrexate is contraindicated or not tolerated.[8]

Upadacitinib has previously been assessed by SMC for the full RA licensed indication and was accepted for restricted use 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 (SMC2315). Following the HIS endorsement of NICE TA715, the company has resubmitted to request that SMC consider upadacitinib in adult patients with moderate RA that has not responded adequately to 2 or more conventional synthetic DMARDs.

The SELECT-COMPARE study included patients on a stable background dose of methotrexate and who had an inadequate response to methotrexate. This study showed upadacitinib was superior to placebo and non-inferior to adalimumab for the outcome of LDA based on DAS28-CRP≤ 3.2; adalimumab is a relevant comparator in the company's proposed positioning. There were a number of supportive clinical studies that showed efficacy of upadacitinib in several treatment lines, including patients with an inadequate response to cDMARDs (SELECT-NEXT) and bDMARDs (SELECT-BEYOND). Evidence from SELECT-CHOICE also suggests non-inferiority of upadacitinib to abatacept. For many of the efficacy outcomes, a treatment effect with upadacitinib was seen as early as week 1 or 2, indicating a rapid onset, and treatment effect appears to be maintained through to one year and beyond.[4, 5]

SELECT-COMPARE included a wider patient population than the company's proposed positioning, since it included patients with moderate and severe active RA and, in addition, patients had an inadequate response to one cDMARD (methotrexate) only. However, the company's proposed positioning is in line with the advice endorsed by HIS for the use of adalimumab, etanercept and infliximab for the treatment of moderate RA.

There is a lack of evidence comparing upadacitinib monotherapy with upadacitinib plus methotrexate, most notably in regards to radiographic progression and long-term outcomes.[4] The

placebo-controlled period was relatively short for a long-term condition; patients in SELECT-COMPARE could receive rescue therapy after week 14 and this was initiated in 19%, 24%, and 47% of patients in the upadacitinib, adalimumab, and placebo groups respectively. Data are available up to 48 weeks in SELECT-COMPARE and longer term data will be 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.

Although there are some direct data comparing upadacitinib with relevant comparators, there remains a lack of head-to-head evidence for various other relevant treatments. The NMA had a number of limitations, including the population being wider than the proposed positioning and clinical heterogeneity in the included studies; however, the company's conclusion on the relative efficacy of upadacitinib versus the comparators seemed reasonable.

Summary of comparative health economic evidence

The company submitted a cost-minimisation analysis comparing upadacitinb (as monotherapy and in combination with MTX) with adalimumab, etanercept and infliximab in adult patients with moderate RA that has not responded adequately to therapy with 2 or more cDMARDs. A simple model was used to estimate the costs of treatment over a 5-year time horizon.

Clinical data to support the assumption of comparable efficacy between upadacitinib and comparators were based on the SELECT-COMPARE[3] study as described above. This showed upadacitinib was non-inferior to adalimumab, which the company assumed could generalise to also support the assumption of comparable efficacy with etanercept and infliximab.

Medicine, administration, monitoring and adverse event costs were included. Medicine costs of upadacitinib and comparators were estimated separately for the response period (first 6 months) and then subsequent annual costs. Administration and monitoring costs were based on values reported in the NICE technology appraisal guidance TA375.[9] Assumptions were included regarding the proportion of patients who remain on treatment each year based on the British Society for Rheumatology Biologics Register[10]. This showed 60% of patients on treatment in year 2 falling to 30% in 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 simple discount was offered on the list price. Results indicate upadacitinib is cost-saving versus all comparators.

Sensitivity analysis using alternative time horizons (2 and 10 years) and discontinuation assumptions were explored but did not alter the conclusions of the analysis.

The main limitation is the lack of direct data comparing upadacitinib with the alternative comparators. Direct evidence is provided versus adalimumab showing comparable efficacy, which is assumed to generalise to the comparisons with etanercept and infliximab. This is a source of uncertainty in the model but is consistent with the approach used in other appraisals in this area.

Despite the lack of direct data to support comparable efficacy with other comparators, the company's assumption that the results versus adalimumab can generalise is reasonable and has been accepted previously by SMC. Therefore, the economic case has been demonstrated.

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 15.5% 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 75% of people are of working age when diagnosed, many worry about losing their job because of their condition. It can be very distressing for a partner of someone with RA to witness their loved-one in severe pain and suffering the debilitating effects of fatigue and so this disease does very much impact on the whole family.
- Response to treatment varies considerably and patients may require multiple therapies before they find one that works for them.
- Upadacitinib is an additional treatment option in a relatively new class of medicines and is to be welcomed. It can also be used in different places in the current treatment pathway and has the potential to save costs due to being an oral therapy. It 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.

Additional information: guidelines and protocols

HIS considered NICE technology appraisal guidance TA715 (October 2021), **adalimumab, etanercept, infliximab and abatacept** for treating moderate rheumatoid arthritis after conventional DMARDs have failed and advised that the recommendations are as valid for Scotland as for England and Wales. This guidance states that:

1.1 Adalimumab, etanercept and infliximab, all with methotrexate, are recommended as options for treating rheumatoid arthritis in adults, only if:

- Intensive therapy with 2 or more conventional disease-modifying antirheumatic drugs (DMARDs) has not controlled the disease well enough and
- disease is moderate (a disease activity score (DAS28) of 3.2 to 5.1)

- the companies provide adalimumab, etanercept and infliximab at the same or lower prices than those agreed with the Commercial Medicines Unit.

1.2 Adalimumab and etanercept can be used as monotherapy when methotrexate is contraindicated or not tolerated, when the criteria in 1.1 are met.

1.3 Continue treatment only if there is a moderate response measured using European League Against Rheumatism (EULAR) criteria at 6 months after starting therapy. If this initial response is not maintained, stop treatment.

1.4 If more than one treatment is suitable, start treatment with the least expensive drug (taking into account administration costs, dose needed and product price per dose). This may need to vary because of differences in how the drugs are used and treatment schedules.

1.5 Take into account any physical, psychological, sensory or learning disabilities, or communication difficulties that could affect the responses to the DAS28 and make any appropriate adjustments.

1.6 Abatacept with methotrexate is not recommended, within its marketing authorisation, for treating moderate active rheumatoid arthritis in adults when 1 or more DMARDs has not controlled the disease well enough.

EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2019 update makes the following recommendations:

- Phase I, in patients who are naive to any DMARD therapy: methotrexate first-line (or alternative cDMARD [including leflunomide, sulfasalazine] if methotrexate contraindicated);
- Phase II, in patients who had an insufficient response (IR) to initial course(s) of cDMARDs: if poor prognostic factors present = methotrexate plus bDMARD (TNF inhibitor: adalimumab, certolizumab, etanercept, golimumab, infliximab; interleukin 6 receptor inhibitors: sarilumab, tocilizumab; costimulation modulator: abatacept; anti-B cell: rituximab) or JAK inhibitor. If poor prognostic factors absent = change to or add a second cDMARD;
- Phase III, in patients who had an IR to a first bDMARD or JAK inhibitor: change the bDMARD or JAK inhibitor. [7]

Additional information: comparators

adalimumab, etanercept, infliximab

Additional information: list price of medicine under review

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

Costs from Dictionary of Medicines and Devices Browser on 24 August 2022. Costs do not take patient access schemes into consideration.

Additional information: budget impact

The company estimated there would be 2,285 patients eligible in year 1 rising to 2,473 patients in year 5, to which confidential uptake rates were applied.

SMC is unable to publish the with PAS budget impact due to commercial in confidence issues. A budget impact template is provided in confidence to NHS health boards to enable them to estimate the predicted budget with the PAS.

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

References

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10. Soliman MM, Ashcroft DM, Watson KD, Lunt M, Symmons DPM, Hyrich KL. Impact of concomitant use of DMARDs on the persistence with anti-TNF therapies in patients with rheumatoid arthritis: results from the British Society for Rheumatology Biologics Register. Annals of the Rheumatic Diseases. 2011;70(4):583-9.

This assessment is based on data submitted by the applicant company up to and including 14 October 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.