

Upadacitinib for treating severe rheumatoid arthritis

Technology appraisal guidance

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www.nice.org.uk/guidance/ta665

Your responsibility

The recommendations in this guidance represent the view of NICE, arrived at after careful consideration of the evidence available. When exercising their judgement, health professionals are expected to take this guidance fully into account, alongside the individual needs, preferences and values of their patients. The application of the recommendations in this guidance is at the discretion of health professionals and their individual patients and do not override the responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or their carer or guardian.

All problems (adverse events) related to a medicine or medical device used for treatment or in a procedure should be reported to the Medicines and Healthcare products Regulatory Agency using the [Yellow Card Scheme](#).

Commissioners and/or providers have a responsibility to provide the funding required to enable the guidance to be applied when individual health professionals and their patients wish to use it, in accordance with the NHS Constitution. They should do so in light of their duties to have due regard to the need to eliminate unlawful discrimination, to advance equality of opportunity and to reduce health inequalities.

Commissioners and providers have a responsibility to promote an environmentally sustainable health and care system and should [assess and reduce the environmental impact of implementing NICE recommendations](#) wherever possible.

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1 Recommendations

This guidance only includes recommendations for treating severe rheumatoid arthritis.

The scope for this technology appraisal also included moderate rheumatoid arthritis. This is covered by [NICE technology appraisal guidance on upadacitinib for treating moderate rheumatoid arthritis](#).

- 1.1 Upadacitinib, with methotrexate, is recommended as an option for treating active rheumatoid arthritis in adults whose disease has responded inadequately to intensive therapy with a combination of conventional disease-modifying antirheumatic drugs (DMARDs), only if:
 - disease is severe (a disease activity score [DAS28] of more than 5.1) and
 - the company provides upadacitinib according to the [commercial arrangement](#).
- 1.2 Upadacitinib, with methotrexate, is recommended as an option for treating active rheumatoid arthritis in adults whose disease has responded inadequately to or who cannot have other DMARDs, including at least 1 biological DMARD, only if:
 - disease is severe (a DAS28 of more than 5.1) and
 - they cannot have rituximab and
 - the company provides upadacitinib according to the commercial arrangement.
- 1.3 Upadacitinib, with methotrexate, is recommended as an option for treating active rheumatoid arthritis in adults whose disease has responded inadequately to rituximab and at least 1 biological DMARD, only if:
 - disease is severe (a DAS28 of more than 5.1) and
 - the company provides upadacitinib according to the commercial arrangement.

- 1.4 Upadacitinib can be used as monotherapy for people who cannot take methotrexate because it is contraindicated or because of intolerance, when the criteria in sections 1.1, 1.2 or 1.3 are met.
- 1.5 Continue treatment only if there is a moderate response measured using European League Against Rheumatism (EULAR) criteria at 6 months after starting therapy. After an initial response within 6 months, stop treatment if at least a moderate EULAR response is not maintained.
- 1.6 When using the DAS28, healthcare professionals should take into account any physical, psychological, sensory or learning disabilities, or communication difficulties that could affect the responses to the DAS28 and make any adjustments they consider appropriate.
- 1.7 These recommendations are not intended to affect treatment with upadacitinib that was started in the NHS before this guidance was published. People having treatment outside these recommendations may continue without change to the funding arrangements in place for them before this guidance was published, until they and their NHS clinician consider it appropriate to stop.

Why the committee made these recommendations

Clinical trials show that upadacitinib with methotrexate or conventional DMARDs is more effective than methotrexate or conventional DMARDs for treating moderate to severe active rheumatoid arthritis that has not responded adequately to conventional DMARDs. The trials also show that for moderate to severe active rheumatoid arthritis that has not responded adequately to conventional DMARDs, upadacitinib with methotrexate is more effective than adalimumab with methotrexate or placebo with methotrexate.

Because there are no trials comparing upadacitinib with the full range of biological DMARDs, the company did an indirect comparison. This shows that upadacitinib with conventional DMARDs (including methotrexate) or on its own works as well as the biological DMARDs that NICE has already recommended.

Based on the health-related benefits and costs compared with conventional and biological DMARDs, upadacitinib alone, or with methotrexate, is recommended only for severe active rheumatoid arthritis, in line with recommendations in NICE's technology appraisal guidance

on:

- sarilumab for moderate to severe rheumatoid arthritis
- tofacitinib for moderate to severe rheumatoid arthritis
- baricitinib for moderate to severe rheumatoid arthritis
- certolizumab pegol for treating rheumatoid arthritis after inadequate response to a TNF-alpha inhibitor
- adalimumab, etanercept, infliximab, certolizumab pegol, golimumab, tocilizumab and abatacept for rheumatoid arthritis not previously treated with DMARDs or after conventional DMARDs only have failed
- tocilizumab for the treatment of rheumatoid arthritis
- golimumab for the treatment of rheumatoid arthritis after the failure of previous disease-modifying anti-rheumatic drugs
- adalimumab, etanercept, infliximab, rituximab and abatacept for the treatment of rheumatoid arthritis after the failure of a TNF inhibitor.

2 Information about upadacitinib

Marketing authorisation

- 2.1 Upadacitinib (Rinvoq, AbbVie) is indicated 'for the treatment of moderate to severe active rheumatoid arthritis in adult patients who have responded inadequately to, or who are intolerant to, 1 or more disease-modifying antirheumatic drugs (DMARDs)'. Upadacitinib may be used as monotherapy or with methotrexate.

Dosage in the marketing authorisation

- 2.2 The dosage schedule is available in the [summary of product characteristics](#).

Price

- 2.3 The list price for upadacitinib is £805.56 per 28-day pack (company submission). The average cost for each patient per year is estimated at £10,508, based on the list price. The company has a [commercial arrangement](#). This makes upadacitinib available to the NHS with a discount. The size of the discount is commercial in confidence. It is the company's responsibility to let relevant NHS organisations know details of the discount.

3 Committee discussion

The [appraisal committee](#) considered evidence submitted by AbbVie, a review of this submission by the evidence review group (ERG), and the technical report developed through engagement with stakeholders. See the [committee papers](#) for full details of the evidence.

The appraisal committee was aware that several issues were resolved during the technical engagement stage, and agreed that:

- the ERG's modelling of severe rheumatoid arthritis treatment sequences was acceptable for decision making
- the ERG's application of the network meta-analysis results was acceptable for decision making.

After technical engagement, there were a number of outstanding uncertainties in the analyses (see technical report, pages 13 to 14). The committee took these into account in its decision making.

Treatments for rheumatoid arthritis

A range of treatment options is important in rheumatoid arthritis and upadacitinib is an additional option

- 3.1 The patient expert explained that rheumatoid arthritis is a lifetime condition that can severely reduce quality of life. The clinical experts stated that conventional disease-modifying antirheumatic drugs (DMARDs) such as methotrexate are inadequate for many people with active rheumatoid arthritis. The expert also added that for a significant proportion of people who are eligible for treatment with biological DMARDs, their disease inadequately responds to these treatments. Both the clinical and patient experts said it would be helpful to have new treatments for various points in the treatment pathway. The committee concluded that a range of treatment options was important in rheumatoid arthritis and that upadacitinib would be a welcome additional

option.

There is NICE technology appraisal guidance for different points in the rheumatoid arthritis treatment pathway

3.2 NICE technology appraisal guidance currently recommends the following DMARDs for severe rheumatoid arthritis:

- [tofacitinib](#)
- [baricitinib](#)
- [adalimumab, etanercept, infliximab, certolizumab pegol, golimumab, and abatacept](#)
- [sarilumab](#)
- [tocilizumab](#).

Of these, adalimumab, certolizumab pegol, etanercept, golimumab and infliximab are tumour necrosis factor (TNF)-alpha inhibitors. Tofacitinib and baricitinib are Janus kinase inhibitors, and sarilumab and tocilizumab are interleukin-6 (IL-6) inhibitors. The biological and targeted synthetic DMARDs (adalimumab, etanercept, infliximab, certolizumab pegol, golimumab, abatacept, sarilumab, tofacitinib, baricitinib and tocilizumab) are recommended with methotrexate, in people with severe rheumatoid arthritis that has not responded to intensive treatment with combinations of conventional DMARDs. Disease severity is assessed using the disease activity score (DAS28). A DAS28 of more than 5.1 indicates severe disease (between 3.2 and 5.1 indicates moderate disease, between 2.6 and 3.2 indicates mild disease and 2.6 or less indicates disease remission). For people who have severe disease that has not responded to intensive treatment with conventional DMARDs but who cannot take methotrexate, the guidance recommends that adalimumab, baricitinib, certolizumab pegol, etanercept, tofacitinib, sarilumab or tocilizumab may be used as monotherapy. It recommends treatment should start with the least expensive drug (taking into account administration costs, dose needed and product price per dose) and should only be continued according to European League Against Rheumatism (EULAR) response at 6 months. For people with severe rheumatoid arthritis who have already had at least 1 TNF-

alpha inhibitor that has not worked, [NICE technology appraisal guidance on adalimumab, etanercept, infliximab, rituximab and abatacept](#) and [golimumab](#) recommend the biological DMARD rituximab with methotrexate for treating severe active rheumatoid arthritis. But, if rituximab is contraindicated or withdrawn because of an adverse event, NICE technology appraisal guidance recommends abatacept, adalimumab, etanercept, infliximab, golimumab, tocilizumab, certolizumab pegol, baricitinib, tofacitinib or sarilumab with methotrexate. If methotrexate is contraindicated or withdrawn because of an adverse event, NICE's guidance recommends adalimumab, etanercept, tocilizumab, certolizumab pegol, baricitinib, tofacitinib or sarilumab as monotherapy. NICE technology appraisal guidance also recommends tocilizumab with methotrexate when neither TNF-alpha inhibitors nor rituximab have worked.

There are 4 different points in the severe disease treatment pathway when upadacitinib might be used

3.3 Upadacitinib's marketing authorisation and the company's submission covers its use at 4 points in the treatment pathway, specifically in adults with:

- Severe, active rheumatoid arthritis ('severe disease') that has not responded adequately to 2 or more conventional DMARDs. The comparators at this position included abatacept, adalimumab, baricitinib, certolizumab pegol, etanercept, golimumab, infliximab, sarilumab, tocilizumab and tofacitinib, all with methotrexate. If methotrexate was not tolerated or contraindicated, the comparators included adalimumab, baricitinib, certolizumab pegol, etanercept, golimumab, sarilumab, tocilizumab and tofacitinib, each used alone.
- Severe disease that has not responded adequately to 1 or more biological DMARD, if rituximab is not a treatment option. The comparators at this position included abatacept, adalimumab, baricitinib, certolizumab pegol, etanercept, golimumab, infliximab, sarilumab, tocilizumab and tofacitinib, all with methotrexate. If methotrexate was not tolerated or contraindicated, the comparators included adalimumab, baricitinib, certolizumab pegol, etanercept, golimumab, sarilumab, tocilizumab and tofacitinib, each used alone.
- Severe disease that has not responded adequately to 1 or more biological DMARD, when rituximab is a treatment option. The comparator in this position

was rituximab with methotrexate.

- Severe disease that has not responded adequately to rituximab and 1 or more biological DMARD. The comparators in this position were sarilumab and tocilizumab, both with methotrexate.

The committee also noted that the marketing authorisation includes the use of upadacitinib alone or with methotrexate.

Clinical effectiveness

The clinical trials are acceptable for decision making but do not include all relevant comparators

3.4 The company's clinical evidence came from 4 randomised controlled trials. The trials included people with moderate to severe rheumatoid arthritis (see [section 3.2](#)). The trials were:

- SELECT-COMPARE, a phase 3 trial which included people whose disease responded inadequately to methotrexate. Upadacitinib was given with methotrexate and the comparator was adalimumab with methotrexate or placebo with methotrexate.
- SELECT-NEXT, a phase 3 trial which included people whose disease responded inadequately to at least 1 conventional DMARD. Upadacitinib was given with conventional DMARDs and the comparator was placebo with conventional DMARDs.
- SELECT-MONOTHERAPY, a phase 3 trial which included people whose disease responded inadequately to methotrexate. Upadacitinib was given as a monotherapy and the comparator was methotrexate.
- SELECT-BEYOND, a phase 3 trial which included people whose disease responded inadequately to biological DMARDs. Upadacitinib was given with conventional DMARDs and the comparator was conventional DMARDs and placebo.

The committee concluded that the trials were relevant and acceptable for

decision making but did not include all relevant comparators (see [section 3.3](#)).

The trials show upadacitinib is more clinically effective than adalimumab, conventional DMARDs (including methotrexate) or placebo for moderate to severe disease that has responded inadequately to conventional DMARDs

3.5 In SELECT-COMPARE, upadacitinib with methotrexate showed a statistically significant improvement in American College of Rheumatology response (ACR20) at 12 weeks compared with adalimumab with methotrexate or placebo with methotrexate (upadacitinib 71%, adalimumab 63%, $p \leq 0.050$; placebo 36%, $p \leq 0.001$). In SELECT-NEXT, upadacitinib with conventional DMARDs showed a statistically significant improvement in ACR20 at 12 weeks compared with placebo with conventional DMARDs (upadacitinib 64%, placebo 36%, $p \leq 0.001$). In SELECT-MONOTHERAPY, upadacitinib alone showed a statistically significant improvement in ACR20 at 12 weeks compared with methotrexate alone (upadacitinib 68%, methotrexate 41%, $p \leq 0.001$). The committee also noted that the ERG and company considered that the safety profile for upadacitinib was similar to other biological DMARDs. The committee concluded that upadacitinib with methotrexate was more clinically effective than adalimumab, placebo with methotrexate or placebo with conventional DMARDs. Also, upadacitinib alone was more clinically effective than methotrexate for moderate to severe rheumatoid arthritis that had responded inadequately to conventional DMARDs.

The trials show upadacitinib is more clinically effective than placebo for moderate to severe rheumatoid arthritis that has responded inadequately to biological DMARDs

3.6 In SELECT-BEYOND, upadacitinib with conventional DMARDs showed a statistically significant improvement in ACR20 at 12 weeks compared with placebo with conventional DMARDs (upadacitinib 65%, placebo 28%, $p \leq 0.001$). The committee concluded that upadacitinib with conventional DMARDs was more clinically effective than placebo with conventional DMARDs for moderate to severe rheumatoid arthritis that

had responded inadequately to biological DMARDs.

Indirect comparison

Network meta-analyses show that upadacitinib with conventional DMARDs or alone works as well as biological DMARDs

3.7 Other than the direct comparison with adalimumab, there was no other comparative trial evidence of upadacitinib compared with biological DMARDs. To compare with other biological DMARDs, the company did a network meta-analysis. It did separate analyses for people whose disease responded inadequately to either conventional or biological DMARDs. It also changed ACR responses to EULAR responses to inform treatment-effectiveness estimates used in the economic model. The company used 12- to 14-week data from the clinical trials to estimate EULAR response at week 24. For those whose disease responded inadequately to conventional DMARDs, the network meta-analyses at week 24 showed that:

- Upadacitinib with conventional DMARDs gave better EULAR response rates than conventional DMARDs alone.
- Upadacitinib with conventional DMARDs gave similar EULAR response rates to biological DMARDs with conventional DMARDs.
- Upadacitinib alone gave better EULAR response rates than conventional DMARDs alone.
- Upadacitinib alone gave similar EULAR response rates to biological DMARDs alone.

For those whose disease responded inadequately to biological DMARDs, the company's network meta-analyses at week 24 showed:

- Upadacitinib with conventional DMARDs gave similar EULAR response rates to biological DMARDs with conventional DMARDs.
- Upadacitinib alone gave similar EULAR response rates to biological DMARDs alone.

The committee noted several limitations of the network meta-analyses:

- They relied on EULAR responses that had been mapped from ACR.
- They assumed that the same treatment effect applied regardless of the position in the treatment pathway. This did not reflect clinical practice because treatments used later in the treatment pathway are likely to have a lower response rate.
- They contained a mixed population and some results were applied to populations who would not have the treatment in clinical practice. For example, evidence from trials using methotrexate and rituximab may be applied to people for whom these treatments are not suitable. However, the committee recognised that, given the limitations of the available data, network meta-analyses stratified by line of treatment may not be possible.

The network meta-analyses showed upadacitinib with conventional DMARDs or alone works as well as other biological DMARDs, but the analyses were limited. The committee concluded that for severe disease, there was limited direct trial evidence. Therefore it accepted the network meta-analyses for decision making.

Economic model inputs and assumptions

The company and ERG's mapping algorithm to link HAQ and pain scores are plausible methods to estimate utility values

- 3.8 In the company's base case, health-related quality-of-life data were calculated using a mapping function to work out a person's pain score from their Stanford Health Assessment Questionnaire (HAQ) score. HAQ is 1 component of the ACR criteria and scores physical disability and pain from 0 (least disability) to 3 (most severe disability). The mapping function used SELECT trial data, to estimate EQ-5D values. The ERG noted that [NICE's technology appraisal guidance on adalimumab, etanercept, infliximab, certolizumab pegol, golimumab, tocilizumab and abatacept for rheumatoid arthritis not previously treated with DMARDs or after conventional DMARDs only have failed](#) (from now on referred to as

TA375) used data from the National Databank for Rheumatic Diseases dataset to map from HAQ-to-pain score. The ERG explained that while the company's approach may be acceptable, the ERG preferred the mapping based on the National Databank for Rheumatic Diseases dataset. This was because the dataset contained over 100,000 observations. After consultation, the company suggested that the mapping based on the National Databank for Rheumatic Diseases dataset gave some counter-intuitive results. This was because some of the lowest functionality was associated with reduced pain. The company confirmed that this was not seen in its preferred method based on mapping using the clinical trials. The committee was aware that the choice of mapping did not have a large effect on severe disease because health-related quality of life was similar across the different comparators. It noted that the company's method led to lower cost-effectiveness estimates compared with conventional DMARDs. The committee concluded that both the company and ERG approaches were plausible, but noted that the ERG's approach was used in TA375 and was based on a much larger dataset.

Economic model validation

The company's model is reasonably consistent with the model used in TA375

3.9 The company based its model on the model developed by the assessment group for TA375. The company provided a validation analysis comparing the outputs of its model with those from the model used in TA375 for several treatment sequences. The ERG suggested that the results of this analysis appeared to show that the company's model overestimated quality-adjusted life year (QALY) gains for biological DMARDs compared with conventional DMARDs. It explained that this primarily impacts the cost-effectiveness analysis for moderate disease, when upadacitinib is compared with conventional DMARDs. At the committee meeting, the company advised that it had found errors in the ERG's validation analysis and that its own model produced similar results to the model from TA375. After consultation, the company submitted further validation results that included corrections of 4 errors. The ERG

noted that after consultation, the company's results reasonably aligned with TA375. The committee concluded that the company's model was reasonably consistent with the model used in TA375.

Cost-effectiveness results

In severe disease, upadacitinib with methotrexate is cost effective after conventional DMARDs

3.10 The ERG did analyses for people with severe disease whose disease had responded inadequately to conventional DMARDs. The clinical- and cost-effectiveness estimates for upadacitinib compared with conventional DMARDs were similar to what was previously seen in other technology appraisals for rheumatoid arthritis. Upadacitinib dominated (that is, it was cheaper and more effective than the comparator) or gave an incremental cost-effectiveness ratio (ICER) under £30,000 per QALY gained when confidential comparator discounts were applied. The committee concluded that it could recommend upadacitinib with methotrexate as a cost-effective use of NHS resources for people with severe rheumatoid arthritis whose disease had responded inadequately to conventional DMARDs. This was in line with TA375.

In severe disease, upadacitinib with methotrexate is not cost effective after biological DMARDs if rituximab is a treatment option

3.11 The ERG did an analysis for people with severe disease that has responded inadequately to biological DMARDs when rituximab is a treatment option. In this, upadacitinib with conventional DMARDs was dominated by rituximab with conventional DMARDs (that is, upadacitinib was more expensive and less effective). The committee concluded that upadacitinib with conventional DMARDs was not a cost-effective use of NHS resources for people with severe rheumatoid arthritis whose disease had responded inadequately to biological DMARDs if rituximab was a treatment option. Therefore, it was not recommended at this position in the pathway.

In severe disease, upadacitinib with methotrexate is cost effective after rituximab and other biological DMARDs

3.12 The ERG did analyses for people with severe disease that had not responded adequately to rituximab and other biological DMARDs. In this, the cost-effectiveness estimates for intravenous or subcutaneous tocilizumab with methotrexate compared with upadacitinib with methotrexate were over £100,000 per QALY gained. Sarilumab with methotrexate was dominated by upadacitinib with methotrexate (that is, upadacitinib was less expensive and more effective). The committee therefore recommended upadacitinib with conventional DMARDs for people with severe rheumatoid arthritis whose disease has not responded adequately to rituximab and other biological DMARDs.

In severe disease, upadacitinib monotherapy is cost effective after conventional DMARDs if methotrexate is not suitable

3.13 The marketing authorisation for upadacitinib includes its use as a monotherapy. The committee noted that the clinical- and cost-effectiveness results for upadacitinib monotherapy were similar to those for upadacitinib with methotrexate. It was aware that the available evidence for upadacitinib monotherapy was from people whose disease responded inadequately to methotrexate. The clinical expert explained that methotrexate is not tolerated by some patients or it is contraindicated. In line with TA375, the committee agreed that the minority of people with severe active rheumatoid arthritis who could not tolerate methotrexate should not be treated differently from other people with severe disease, as far as possible. The committee agreed that upadacitinib monotherapy was cost effective for severe active rheumatoid arthritis after conventional DMARDs if methotrexate was not suitable.

Other factors

Healthcare professionals should consider any disabilities or communication difficulties when using the DAS28 measure

- 3.14 A potential equality issue was raised during the scoping process, about people with rheumatoid arthritis who have difficulty communicating. For these people, it may be more difficult to assess outcomes when using the DAS28 measure. The committee concluded that healthcare professionals should consider any physical, psychological, sensory or learning disabilities, or communication difficulties that could affect the responses to the DAS28 and make any adjustments they consider appropriate.

The benefits of upadacitinib can be captured in the cost-effectiveness analysis

- 3.15 Upadacitinib, like other targeted synthetic DMARDs, is taken orally. This is valued by patients. The committee noted that there are also other treatments with a similar mechanism of action available for rheumatoid arthritis. Therefore the committee concluded that all the benefits of upadacitinib can be captured in the model.

4 Implementation

- 4.1 Section 7(6) of the National Institute for Health and Care Excellence (Constitution and Functions) and the Health and Social Care Information Centre (Functions) Regulations 2013 requires clinical commissioning groups, NHS England and, with respect to their public health functions, local authorities to comply with the recommendations in this appraisal within 3 months of its date of publication.
- 4.2 The Welsh ministers have issued directions to the NHS in Wales on implementing NICE technology appraisal guidance. When a NICE technology appraisal recommends the use of a drug or treatment, or other technology, the NHS in Wales must usually provide funding and resources for it within 2 months of the first publication of the final appraisal document.
- 4.3 When NICE recommends a treatment 'as an option', the NHS must make sure it is available within the period set out in the paragraphs above. This means that, if a patient has rheumatoid arthritis and the doctor responsible for their care thinks that upadacitinib is the right treatment, it should be available for use, in line with NICE's recommendations.

5 Appraisal committee members and NICE project team

Appraisal committee members

The 4 technology appraisal committees are standing advisory committees of NICE. This topic was considered by [committee D](#).

Committee members are asked to declare any interests in the technology to be appraised. If it is considered there is a conflict of interest, the member is excluded from participating further in that appraisal.

The [minutes of each appraisal committee meeting](#), which include the names of the members who attended and their declarations of interests, are posted on the NICE website.

NICE project team

Each technology appraisal is assigned to a team consisting of 1 or more health technology analysts (who act as technical leads for the appraisal), a technical adviser and a project manager.

Alan Moore and Abitha Senthinathan

Technical leads

Jamie Elvidge and Richard Diaz

Technical advisers

Gemma Barnacle and Gavin Kenny

Project managers

Update information

December 2020: Recommendation 1.4 updated to clarify when upadacitinib can be used as monotherapy.

Minor changes since publication

January 2022: Link to NICE Pathway removed.

November 2021: We added a link to the technology appraisal guidance on upadacitinib for treating moderate rheumatoid arthritis.

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