

Upadacitinib for treating moderate rheumatoid arthritis

Technology appraisal guidance

Published: 10 November 2021

www.nice.org.uk/guidance/ta744

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.

Contents

1 Recommendations	4
2 Information about upadacitinib	6
Marketing authorisation indication	6
Dosage in the marketing authorisation	6
Price.....	6
3 Committee discussion	7
Treatments for rheumatoid arthritis	7
Clinical effectiveness	9
Modelling progression from moderate to severe rheumatoid arthritis	13
Utility values	17
Economic model validation.....	18
Cost-effectiveness results	19
Other factors	22
4 Implementation.....	23
5 Appraisal committee members and NICE project team	24
Appraisal committee members	24
NICE project team	24

1 Recommendations

This guidance only includes recommendations for treating moderate rheumatoid arthritis.

The scope for this technology appraisal also included severe rheumatoid arthritis. This is covered by [NICE technology appraisal guidance on upadacitinib for treating severe 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 2 or more conventional disease-modifying antirheumatic drugs (DMARDs), only if:
 - disease is moderate (a disease activity score [DAS28] of 3.2 to 5.1) and
 - the company provides upadacitinib according to the [commercial arrangement](#).
- 1.2 Upadacitinib can be used as monotherapy when methotrexate is contraindicated or if people cannot tolerate it, when the criteria in section 1.1 are met.
- 1.3 If more than 1 treatment is suitable, start treatment with the least expensive drug (taking into account administration costs, dose needed and product price per dose). This may vary because of differences in how the drugs are used and treatment schedules.
- 1.4 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.
- 1.5 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 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 trial evidence suggests that upadacitinib plus conventional DMARDs (including methotrexate) is more effective than placebo plus conventional DMARDs for treating moderate disease that has not responded well enough to conventional DMARDs. Evidence also suggests that upadacitinib alone is more effective than methotrexate for the same population.

Using methods accepted in [NICE technology appraisal guidance 375](#) and [NICE technology appraisal guidance 715](#), the cost-effectiveness estimate was within what NICE normally considers an acceptable use of NHS resources, although these methods may have to be reconsidered in future appraisals. So upadacitinib, alone or with methotrexate, is recommended for people with moderate rheumatoid arthritis whose disease has responded inadequately to intensive therapy with 2 or more conventional DMARDs.

2 Information about upadacitinib

Marketing authorisation indication

- 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 in combination with methotrexate.

Dosage in the marketing authorisation

- 2.2 The dosage schedule is available in [upadacitinib's 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), NICE's technical report, and responses from 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.

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. A range of biological and targeted synthetic DMARDs are available for moderate rheumatoid arthritis (see [NICE technology appraisal guidance on filgotinib \[TA676\]](#), and [NICE's technology appraisal guidance on adalimumab, etanercept, infliximab and abatacept \[TA715\]](#)). But these were not recommended at the time of the committee's discussion, so these treatments were not considered comparators. At the first committee meeting, patient experts explained that people with moderate disease that has not responded adequately to conventional DMARDs had few effective treatment options. The committee concluded that it is important for people with moderate rheumatoid arthritis to have a range of treatment options.

There are 2 different points in the moderate disease treatment

pathway when upadacitinib might be used

3.2 Disease severity is assessed using the disease activity score (DAS28). A DAS28 above 5.1 indicates severe disease and a DAS28 between 3.2 to 5.1 indicates moderate disease. Upadacitinib's marketing authorisation and the company's evidence submission covers its use at 2 points in the treatment pathway, specifically in adults with:

- Moderate disease that has not responded adequately to 1 conventional DMARD. The comparator at this position was conventional DMARDs.
- Moderate disease that has not responded adequately to 2 or more conventional DMARDs. At this position there were 2 potential comparators, conventional DMARDs or best supportive care (see [section 3.3](#) and [section 3.4](#)).

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

The preferred position for upadacitinib is after 2 or more conventional DMARDs

3.3 The company presented results for upadacitinib at 2 positions in the moderate rheumatoid arthritis treatment pathway (see [section 3.2](#)). A clinical expert stated that it was more likely that upadacitinib would be used after 2 conventional DMARDs. Also, the European League Against Rheumatism (EULAR) guidelines state that 2 conventional DMARDs should be tried before considering a biological DMARD. But the guidelines recommend considering a biological DMARD after 1 conventional DMARD when poor prognostic factors are present. These include the presence of rheumatoid factor, antibodies against cyclic citrullinated peptide, high disease activity and early joint damage. The ERG explained that the company's network meta-analysis did not give separate results for people with a poor prognosis. Analyses done by the ERG showed that positioning upadacitinib after 1 conventional DMARD was more likely to lead to a cost-effectiveness estimate much higher than £30,000 per quality-adjusted life year (QALY) gained than positioning it after 2 or more conventional DMARDs. The committee

concluded that the most appropriate position for upadacitinib was after treatment with 2 or more conventional DMARDs. It also concluded that, if methotrexate was tolerated, upadacitinib plus methotrexate was preferred to upadacitinib alone. The committee noted that these conclusions were in line with previous NICE technology appraisals for rheumatoid arthritis.

The appropriate comparator after 2 conventional DMARDs is best supportive care, which is unlikely to give a EULAR response

3.4 In the company and ERG analysis, after 2 conventional DMARDs, there were 2 potential comparators: further conventional DMARD treatment or best supportive care. The clinical expert explained that at this position, further treatment with conventional DMARDs was not expected to give a EULAR response. Despite this, patients are usually offered continued treatment with a combination of conventional DMARDs that have not been used previously, and corticosteroids are also a treatment option. The clinical expert also highlighted that after disease progression with methotrexate, it is unlikely to be used again except as part of combination therapy. The company explained that best supportive care after 2 conventional DMARDs included some continued conventional DMARDs, particularly methotrexate. The committee concluded that after 2 conventional DMARDs, best supportive care is the conventional DMARDs that had been used before, with optional corticosteroids. This was the most appropriate comparator in this group because it reflects clinical practice. The committee also concluded that best supportive care is unlikely to give a response measured using EULAR criteria but noted this was difficult to account for (see [section 3.8](#)).

Clinical effectiveness

Subgroup analyses of the moderate population in SELECT-NEXT and SELECT-MONOTHERAPY trials are most relevant for decision making, but may not reflect clinical practice

3.5 The company's clinical evidence came from 4 phase 3 randomised controlled trials. The trials included people with moderate to severe

rheumatoid arthritis (defined in [section 3.2](#)). The trials were:

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

The committee considered the subgroup analyses of people with moderate disease. It noted that SELECT-NEXT was most relevant for the population who could tolerate methotrexate, because it included people who had an inadequate response to at least 1 conventional DMARD. It also included a higher proportion of people who were taking 2 conventional DMARDs at baseline than SELECT-COMPARE (the exact data is confidential and cannot be reported here). The only trial that included a treatment effect for upadacitinib alone was SELECT-MONOTHERAPY. But it only included people who had had an inadequate response to methotrexate. The committee considered that it was reasonable to use the clinical-effectiveness data from this trial, even though it did not reflect the population of people who could not tolerate methotrexate. The committee concluded that SELECT-NEXT and SELECT-MONOTHERAPY were acceptable for decision making but may not reflect clinical practice.

Upadacitinib is more effective than conventional DMARDs for moderate disease

3.6 In the full population of SELECT-NEXT, upadacitinib with conventional DMARDs showed a statistically significant improvement in American

College of Rheumatology response (ACR20) at 12 weeks, compared with placebo plus conventional DMARDs (upadacitinib 64%, placebo 36%, $p < 0.001$). In SELECT-MONOTHERAPY, upadacitinib alone showed a statistically significant improvement in ACR20 at 12 weeks compared with methotrexate alone (upadacitinib 68%, methotrexate 41%, $p < 0.001$). Similar results were seen for the moderate subgroups in both trials (exact data is confidential and cannot be reported here). The ERG and company considered that upadacitinib's safety profile is similar to that of other biological DMARDs. The committee concluded that upadacitinib plus conventional DMARDs (including methotrexate) is more clinically effective than placebo plus conventional DMARDs (including methotrexate) for moderate disease. Also, it concluded that upadacitinib alone was more clinically effective than methotrexate alone for moderate rheumatoid arthritis that has responded inadequately to conventional DMARDs.

Direct head-to-head trial data is most appropriate to model efficacy of upadacitinib

3.7 A network meta-analysis was used for decision making for people with severe disease in [NICE's technology appraisal guidance of upadacitinib for treating severe rheumatoid arthritis](#). However, the ERG explained that for moderate disease, it may be more appropriate to use the SELECT trials because:

- the trials measured EULAR responses for all relevant comparators for moderate disease (with placebo plus conventional DMARDs used as a proxy for best supportive care, see [section 3.8](#) and [section 3.9](#))
- the company's method for estimating the placebo effect in the network meta-analysis was uncertain and the ERG could not fully assess its reliability
- using direct head-to-head evidence is in line with [NICE's guide to the methods of technology appraisal](#).

The committee concluded that direct head-to-head trial data was more appropriate to model efficacy of upadacitinib than the network meta-analysis results for moderate disease.

Using the placebo arms of the SELECT trials to model the efficacy of best supportive care has limitations but is acceptable

3.8 The ERG modelled the efficacy of best supportive care based on the response rates seen in the placebo plus conventional DMARDs arm of the SELECT-NEXT trial (the SELECT-MONOTHERAPY trial was used to model cost effectiveness for people who could not tolerate methotrexate; see [section 3.5](#)). Best supportive care was the committee's preferred comparator and was not expected to give a EULAR response in clinical practice. However, the committee noted that a considerable response rate was seen in the placebo arms of the SELECT trials, as well as in other clinical trials in rheumatoid arthritis. It noted that this response could have been caused by several factors, including a placebo effect, disease resolving naturally over time, regression to the mean, response bias and variation in symptoms. Some of these factors might have also contributed to the response to upadacitinib in the SELECT trials. Therefore, the committee agreed it would not be appropriate to assume full clinical efficacy for upadacitinib while assuming no response to best supportive care. The ERG provided analyses that used SELECT-NEXT response rates for upadacitinib plus methotrexate and for placebo plus conventional DMARDs (a proxy for best supportive care) because it retained the relative treatment effect seen in the clinical evidence. In line with clinical expert opinion, the committee stated that it preferred to compare upadacitinib (with or without methotrexate) with methotrexate plus placebo (best supportive care) using data from the SELECT trials. After this, patients in both treatment arms would have conventional DMARDs with or without corticosteroids and no EULAR response would be expected in clinical practice. The committee concluded that the ERG's analyses had limitations because the trials did not fully reflect what is expected to happen in clinical practice, but were acceptable.

Using estimates from the TA375 network meta-analysis to model the efficacy of best supportive care also has limitations but is acceptable

3.9 The committee was aware that since this appraisal began, TA715 had published. This was a partial review of [NICE technology appraisal](#)

guidance 375 (TA375). In TA375, the efficacy of methotrexate from a network meta-analysis was used to estimate the efficacy of best supportive care in the comparator arm of the model. In TA715, the committee agreed that because no new evidence was being considered in that appraisal, there was no strong reason to deviate from the assumptions in TA375. In its response to the second consultation, the company considered that applying the efficacy estimate from TA375 was the most consistent and transparent approach and there was no robust justification to change it. The committee noted that the treatment sequence in TA375 included methotrexate monotherapy before best supportive care. This was not consistent with clinical expert advice that methotrexate would only be used as part of combination therapy. It also noted that the network meta-analysis in TA375 showed a moderate or good EULAR response in a significant number of patients on methotrexate, but clinical advice was that a EULAR response would not be expected at this point in the treatment pathway. The committee concluded that using estimates from the TA375 network meta-analysis had limitations but may be acceptable. It agreed to consider this analysis as well as the analysis using the placebo arm of the SELECT trials (see section 3.8) in its decision making.

Modelling progression from moderate to severe rheumatoid arthritis

Assuming 19% of people have disease progression after 2 years is appropriate

3.10 The company's model included treatment for moderate disease that had progressed to severe disease. This was consistent with recent NICE technology appraisals on treating rheumatoid arthritis. The company modelled progression by estimating the relationship between the DAS28 and health assessment questionnaire (HAQ) results from the clinical evidence. HAQ is 1 component of the ACR20 response criteria. It scores physical disability and pain from 0 (least disability) to 3 (most severe disability). The ERG noted that the company's original model did not apply this estimated relationship. After the first consultation, the company submitted 2 scenario analyses assuming that 11% and 19% of

people with moderate disease have disease progression to severe disease after 2 years. The ERG explained that this was in line with the figure predicted by the UK Early Rheumatoid Arthritis Network database (19%). The committee noted that in the company's scenario analyses, most people's disease progressed to severe after 12 years, which produced lower cost-effectiveness estimates for upadacitinib. The clinical expert estimated that in clinical practice around 30% of people with moderate disease were likely to have disease progression to severe disease by 12 years. However, at the second consultation, consultees explained that rheumatoid arthritis disease activity tends to be fairly stable over time and that analysis of the Early Rheumatoid Arthritis Study did not provide any evidence that a larger number of patients (than 19%) would have an increased DAS28 score over a longer period of time. The committee was aware that this estimate may no longer be correct because of the introduction of biologic DMARDs recommended in TA715 and TA676 but noted that in this analysis varying the rate of progression did not have a large impact on the cost-effectiveness results. It concluded that it was appropriate to assume that 19% of people with moderate disease have disease progression to severe disease after 2 years.

Including an effect of methotrexate after upadacitinib for moderate rheumatoid arthritis is debatable

- 3.11 The committee considered the treatment sequences for the populations with moderate disease and whether it was appropriate to include a clinical effect for methotrexate after upadacitinib, and before best supportive care (which had no efficacy). The committee was aware that the original ERG report criticised this approach for allowing the upadacitinib arm of the model to count the placebo effect twice, while the comparator arm only counted it once. In the second consultation, the company noted that for moderate disease, TA375 assumed that methotrexate would be given after biological treatment and that this was associated with a response. The same assumption was used in TA715, and a similar assumption was made in [NICE's technology appraisal guidance on baricitinib, tofacitinib and sarilumab](#), which did not make positive recommendations for moderate rheumatoid arthritis. A clinical expert considered that methotrexate would not be used as monotherapy

again when it had already been used earlier in the pathway. They explained that methotrexate would be continued only as part of combination treatment. The committee considered it debatable whether methotrexate monotherapy would be used at this point in the treatment pathway or what size of response would be expected, if any. On balance, the committee agreed that although it was debatable, it would consider analyses that included an effect of methotrexate after upadacitinib in its decision making.

Alternative treatment sequences after progression from moderate to severe disease are plausible

- 3.12 The committee understood that using upadacitinib to treat moderate disease could change the treatment pathway for severe disease. The ERG explored 3 alternative treatment sequences for severe disease: scenario 1, scenario 2 and a preferred scenario. These included people who could and could not tolerate methotrexate. For people who could tolerate methotrexate, all treatments were taken in combination with methotrexate. Table 1 describes the treatment options in each scenario at first, second and third line for severe disease. The ERG's clinical expert explained that for people whose disease progresses to severe, adalimumab would generally be used first because it is the cheapest biological DMARD. If there was an inadequate response, rituximab is likely to be used next, even for people who cannot tolerate methotrexate. The ERG's clinical expert explained that in the first scenario analysis, people who have had upadacitinib could have abatacept instead of sarilumab because it works in a different way to upadacitinib. The ERG's second scenario explored using upadacitinib instead of sarilumab because people tend to prefer oral treatments to subcutaneous injections. The clinical expert agreed that abatacept, sarilumab and upadacitinib could be used as third-line treatment options. Fourth-line treatment was best supportive care in all the scenarios. The clinical expert clarified that the decision to use a particular treatment would depend on several factors including infection risk, liver function and cost of treatment. Given the multiple factors used to decide the appropriate treatment, the committee agreed that it was difficult to know with certainty if upadacitinib should be included in the treatment sequences for severe disease in the comparator arm before it had been used in

routine clinical practice. It agreed that sequences in both arms should reflect clinical practice. Sequences for both arms may include different treatment options depending on what patients have previously received at an earlier disease stage. The committee understood that TA375 and the summary of product characteristics for rituximab recommend it only in combination with methotrexate. It was concerned that the ERG's analyses may not reflect treatment sequences for people who cannot tolerate methotrexate, because rituximab is not licensed as a monotherapy. It understood that this was a small population and may reflect clinical practice but noted that treatment sequences may vary in the NHS in England. The committee concluded that the ERG's alternative treatment sequences for severe disease were plausible.

Table 1 Treatment sequences for people whose disease progresses from moderate to severe in the ERG's model

Scenario	Treatment arm	First-line treatment for severe disease	Second-line treatment for severe disease	Third-line treatment for severe disease
Preferred	Upadacitinib	Adalimumab	Rituximab	Sarilumab
Preferred	Best supportive care	Adalimumab	Rituximab	Sarilumab
Scenario 1	Upadacitinib	Adalimumab	Rituximab	Abatacept (subcutaneous)
Scenario 1	Best supportive care	Adalimumab	Rituximab	Sarilumab
Scenario 2	Upadacitinib	Adalimumab	Rituximab	Sarilumab
Scenario 2	Best supportive care	Adalimumab	Rituximab	Upadacitinib

Utility values

The company's and the ERG's mapping algorithms are plausible methods for estimating utility values

3.13 In the company's base-case analysis, health-related quality of life data was calculated using a mapping function to work out a person's pain score from their HAQ score. The mapping algorithm used data from the SELECT trials to estimate EQ-5D values. The ERG noted that TA375 used data from the National Databank for Rheumatic Diseases dataset to map pain scores from HAQ scores. It explained that the company's approach may be acceptable, but it preferred mapping based on the National Databank for Rheumatic Diseases dataset. This was because the dataset contained over 100,000 observations. After the first consultation, the company suggested that mapping based on the National Databank for Rheumatic Diseases dataset produced some counterintuitive results. Some of the lowest functionality was associated with a reduction in pain. The company noted that this did not happen using its preferred method of mapping using data from the clinical trials. The committee noted that the choice of mapping did not have a large effect on the cost-effectiveness estimates for severe disease, because health-related quality of life was similar across the different comparators. But it noted that for moderate disease, the company's method gave lower cost-effectiveness estimates for upadacitinib compared with best supportive care. The committee concluded that both mapping approaches were plausible, but noted that the ERG's approach was used in TA375 and was based on a much larger dataset.

The company's approach to modelling long-term health assessment questionnaire results is acceptable

3.14 In the ERG's preferred base-case analysis, people whose disease responded to best supportive care were assumed to have the same long-term HAQ results as those whose disease responded to biological DMARDs. The ERG explained that a large amount of the upadacitinib response was likely to have been caused by a placebo effect. This was also present in the trial control arms, so it may be inappropriate to make

different assumptions about long-term HAQ results in the model. The clinical and patient experts advised that natural recovery from symptoms is rare, and it would not be sustained for a long time. The committee agreed that applying the long-term HAQ results associated with biological DMARDs to best supportive care was likely to be an overly optimistic assumption. In response to technical engagement, the company provided an alternative scenario analysis. In this, people whose disease responded to best supportive care were assumed to have the same long-term HAQ results as those whose disease responded to conventional DMARDs. The committee concluded that it was appropriate to assume that people whose disease responded to best supportive care had the same decreasing long-term HAQ results as people whose disease responded to conventional DMARDs. This was consistent with previous NICE technology appraisals in rheumatoid arthritis.

Economic model validation

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

3.15 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 QALY gains for biological DMARDs compared with conventional DMARDs. It explained that this mostly affects 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 TA375 model. After the first consultation, the company submitted further validation results that included corrections of 4 errors. The ERG noted that after consultation the company's results were reasonably aligned with TA375. The committee concluded that the company's model is reasonably consistent with the model used in TA375, which was considered acceptable for decision making.

Cost-effectiveness results

Upadacitinib with methotrexate is cost effective after 2 conventional DMARDs

3.16 The committee evaluated the cost effectiveness of upadacitinib for moderate disease considering the following conclusions:

- The most appropriate position for upadacitinib in the moderate rheumatoid arthritis treatment pathway is after 2 or more conventional DMARDs (see [section 3.3](#)).
- Best supportive care is the relevant comparator at this point in the treatment pathway (see [section 3.4](#)).
- Subgroup analyses including only the moderate population from SELECT-NEXT and SELECT-MONOTHERAPY are appropriate to model the efficacy of upadacitinib (see [section 3.5](#)). Using the placebo arm of the SELECT trials or the methotrexate estimate from the TA375 network meta-analysis is acceptable to model the efficacy of best supportive care (see [section 3.8](#) and [section 3.9](#)). After this, all people had further best supportive care with no efficacy until their disease had progressed to severe.
- Although debatable, analyses that include a treatment effect for methotrexate or best supportive care after upadacitinib should be considered (see [section 3.11](#)).
- It is appropriate to assume that 19% of people with moderate disease have disease progression to severe disease after 2 years (see [section 3.10](#)).
- The ERG's alternative treatment sequences for severe disease were plausible but uncertain, particularly for the population who cannot tolerate methotrexate (see [section 3.12](#)).
- The company's and the ERG's mapping algorithms that link HAQ and pain scores are plausible methods for estimating utility values (see [section 3.13](#)).
- It is appropriate to assume that long-term HAQ results after response to best supportive care are different than after response to biological DMARDs (see [section 3.14](#)).

The ERG included the confidential discounts for the comparators and subsequent treatments in its analyses. Because of these confidential discounts, the exact incremental cost-effectiveness ratios (ICERs) cannot be reported here. When including methotrexate after upadacitinib in the treatment sequence and the TA375 network meta-analysis estimate, the ICER was between £20,000 and £30,000 per QALY gained, compared with best supportive care. The committee also considered scenarios using alternative treatments and using the SELECT trials placebo results. These gave ICERs above £30,000 per QALY gained compared with best supportive care. The committee considered the benefits and risks of routinely commissioning upadacitinib for the NHS. It acknowledged that although several treatment options (such as filgotinib, adalimumab, etanercept and infliximab) were now available, it was important for people with moderate rheumatoid arthritis to have a range of treatment options (see [section 3.1](#)). It agreed that patients, carers and healthcare professionals would need to consider the advantages and disadvantages of each technology. If more than 1 treatment is suitable, the committee considered that choosing the least expensive treatment would be important, especially for technologies with reasonably similar mechanisms of action. It agreed that choosing the least expensive option would be an appropriate way to manage financial risk to the NHS. The committee considered that using methods accepted in TA375 and TA715, the cost-effectiveness estimate was in the range that NICE normally considers an acceptable use of NHS resources. However, it noted that these methods may have to be reconsidered in future appraisals (see [section 3.18](#)). The committee concluded that it could recommend upadacitinib with methotrexate as a cost-effective use of NHS resources for people with moderate rheumatoid arthritis whose disease has responded inadequately to intensive therapy with 2 or more conventional DMARDs. In line with previous NICE guidance for rheumatoid arthritis, the committee also concluded that treatment should continue only if there is a moderate response measured using the EULAR criteria at 6 months after starting therapy.

Upadacitinib monotherapy's cost effectiveness is more uncertain but it is likely to be a reasonable use of NHS resources if methotrexate is unsuitable

3.17 The committee noted that the cost-effectiveness estimates for

upadacitinib monotherapy would be higher than for upadacitinib plus methotrexate, because methotrexate could not be included in the treatment sequence. This would have the most impact when removing methotrexate from the treatment sequence from its position after upadacitinib in moderate disease (see [section 3.11](#)). However, the committee noted that this population is much smaller than the population who can have methotrexate. In line with previous appraisals for rheumatoid arthritis, it agreed that the small number of people who could not tolerate methotrexate should not be disadvantaged compared with other people with moderate disease, as far as possible. Therefore, the committee recommended upadacitinib monotherapy when methotrexate is contraindicated or if people cannot tolerate it.

Cost-effectiveness modelling assumptions for future rheumatoid arthritis technologies may need to be reconsidered

3.18 The committee noted that the treatment pathway for moderate rheumatoid arthritis was now substantially different from the assumptions used in TA715 and TA676. Committees considering technologies for rheumatoid arthritis in the future may need to reconsider cost-effectiveness modelling assumptions in the following areas:

- The sequence of treatments available for moderate and severe disease in both the intervention and comparator arms so that it truly reflects current NHS practice.
- The treatment effect for methotrexate or best supportive care for moderate disease.
- Estimates of the proportion of people with moderate disease who have disease progression to severe disease.

Other factors

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

- 3.19 During the scoping process a potential equality issue was raised 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 appropriate adjustments.

The benefits of upadacitinib were captured in the cost-effectiveness analysis

- 3.20 Upadacitinib, like several other biological DMARDs, is taken orally. This is valued by patients. The committee noted that there are other oral treatments with a similar mechanism of action available for rheumatoid arthritis. It concluded that all the benefits of upadacitinib were captured in the model.

4 Implementation

- 4.1 Section 7 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 moderate 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.

Abitha Senthinathan and Alan Moore

Technical leads

Richard Diaz, Jamie Elvidge and Alex Filby

Technical advisers

Gavin Kenny and Gemma Barnacle

Project managers

ISBN: 978-1-4731-4331-9