NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Appraisal consultation document

Upadacitinib for treating moderate to severe rheumatoid arthritis

The Department of Health and Social Care has asked the National Institute for Health and Care Excellence (NICE) to produce guidance on using upadacitinib in the NHS in England. The appraisal committee has considered the evidence submitted by the company and the views of non-company consultees and commentators, clinical experts and patient experts.

This document has been prepared for consultation with the consultees. It summarises the evidence and views that have been considered, and sets out the recommendations made by the committee. NICE invites comments from the consultees and commentators for this appraisal and the public. This document should be read along with the evidence (see the committee papers).

The appraisal committee is interested in receiving comments on the following:

- Has all of the relevant evidence been taken into account?
- Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?
- Are the recommendations sound and a suitable basis for guidance to the NHS?
- Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?

Issue date: January 2020

Note that this document is not NICE's final guidance on this technology. The recommendations in section 1 may change after consultation.

After consultation:

- The appraisal committee will meet again to consider the evidence, this appraisal consultation document and comments from the consultees.
- At that meeting, the committee will also consider comments made by people who are not consultees.
- After considering these comments, the committee will prepare the final appraisal document.
- Subject to any appeal by consultees, the final appraisal document may be used as the basis for NICE's guidance on using upadacitinib in the NHS in England.

For further details, see NICE's guide to the processes of technology appraisal.

The key dates for this appraisal are:

Closing date for comments: 21 February 2020

Second appraisal committee meeting: TBC

Details of membership of the appraisal committee are given in section 6.

1 Recommendations

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 with the discount agreed in the patient access scheme.

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 with the discount agreed in the patient access scheme.

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 with the discount agreed in the patient access scheme.

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 and 1.2 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, withdraw 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 upadacitinib with methotrexate or conventional DMARDs to be 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 treating 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 with methotrexate or upadacitinib on its own is

recommended only for severe active rheumatoid arthritis, in line with previous recommendations in NICE technology appraisal guidance on:

- sarilumab
- tofacitinib
- baricitinib
- certolizumab pegol (after a TNF-alpha inhibitor)
- adalimumab, etanercept, infliximab, certolizumab pegol, golimumab, tocilizumab and abatacept (after conventional DMARDs)
- tocilizumab
- golimumab (after DMARDs)
- adalimumab, etanercept, infliximab, rituximab and abatacept (after a TNF-alpha inhibitor).

For moderate active rheumatoid arthritis, the cost-effectiveness modelling is not robust. Also, the cost-effectiveness estimates for upadacitinib are likely to be higher than what NICE considers a cost-effective use of NHS resources. Therefore, upadacitinib with methotrexate or upadacitinib on its own is not recommended for moderate active rheumatoid arthritis.

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, one 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 recommended dose is 15 mg once daily orally. Treatment should not be started in patients with an absolute lymphocyte count that is less than 500 cells/mm^3, an absolute neutrophil count that is less than

1,000 cells/mm^3 or who have haemoglobin (Hb) levels that are less than 8 g/dL. Treatment should be interrupted if a patient develops a serious infection, until the infection is controlled.

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 (simple discount patient access scheme). 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 (section 6) 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 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 these points in the rheumatoid arthritis treatment pathway

3.2 NICE currently recommends the following biological 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. All of these biological DMARDs 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, sarliumab 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 recommends 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. See the NICE pathway on drug treatments for rheumatoid arthritis.

There are 6 different points in the treatment pathway when upadacitinib might be used

3.3 Upadacitinib's marketing authorisation and the company's submission covers its use at 6 points in the treatment pathway, specifically in adults with:

- Moderate, active rheumatoid arthritis ('moderate disease') that has not responded adequately to 1 conventional disease-modifying antirheumatic drug (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 3.9).
- 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 sarliumab 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, as defined in 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 conventional DMARDs. 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 clinical 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≤0.050), placebo 36% (p≤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≤0.001). In SELECT-MONOTHERAPY, upadacitinib alone showed a statistically significant improvement in ACR20 at 12 weeks compared with methotrexate alone (upadacitinib 68%, MTX 41%, p≤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≤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. The company did separate analyses for patients whose disease responded inadequately to either conventional or biological DMARDs. The company 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 concluded that, although there was limited direct trial evidence, upadacitinib with conventional DMARDs or alone works as well as other biological DMARDs.

Positioning of upadacitinib in the treatment pathway

In moderate disease, the preferred position of upadacitinib is after 2 or more conventional DMARDs

3.8 The company presented results for upadacitinib at 2 places in the moderate rheumatoid arthritis treatment pathway (see section 3.3). A clinical expert statement explained that it was more likely that upadacitinib would be used after 2 conventional DMARDs. Also, EULAR guidelines state that 2 conventional DMARD treatments should be given before considering a biological DMARD. The clinical expert explained that EULAR guidelines also recommend considering a biological DMARD treatment after 1 conventional DMARD treatment in people who have a poor prognosis. The ERG explained that the company's network meta-analysis did not include separate results for people with a poor prognosis. Analyses done by the ERG showed that positioning upadacitinib after 1 conventional DMARD was likely to have a cost-effectiveness estimate much higher than £30,000 per quality-adjusted life year (QALY) gained, compared with positioning it after 2 or more conventional DMARDs. The committee concluded that, of the 2 potential positions for moderate disease, it was more appropriate to consider upadacitinib after treatment with 2 or more conventional DMARDs. It also concluded that upadacitinib with methotrexate was preferred to upadacitinib alone when methotrexate was tolerated, based on the cost-effectiveness estimates. The committee noted that these conclusions were in line with previous NICE technology appraisal guidance for rheumatoid arthritis.

The appropriate comparator for moderate disease after 2 conventional DMARDs is best supportive care, which is unlikely to give an EULAR response

3.9 In the company and ERG analysis, after 2 conventional DMARDs, there were 2 potential comparators: further conventional DMARD treatment and best supportive care. The clinical expert explained that at this position, further treatment with conventional DMARDs was not expected to give a response. Despite this, continued treatment was usually given, and corticosteroids were also a treatment option. The committee heard from the company that the definition of best supportive care after 2 conventional DMARDs included some continued conventional DMARD treatment, particularly methotrexate. The committee concluded that after 2 conventional DMARDs, previously-used conventional DMARDs with optional corticosteroids would constitute best supportive care. This was the most appropriate comparator to upadacitinib because it reflected clinical practice. The committee also concluded that best supportive care was unlikely to give an EULAR response.

Treatment sequences of different lengths may bias the cost-effectiveness estimates

3.10 In the company's analyses, the upadacitinib model arm had a longer overall treatment sequence length than the control arm. The ERG advised that having unequal sequence lengths means at some point, an active treatment in the longer sequence is at the same position as best supportive care in the shorter sequence. The relative effectiveness of the active treatment at this point may be overestimated if best supportive care has no response rate (see section 3.9). The ERG was concerned that this would bias the model in favour of the longer sequence (that is, upadacitinib). The clinical expert advised that in practice, any DMARD treatment would be expected to have a lower response rate the later it is used in the treatment pathway, compared with if it was used earlier. This was not captured in the network meta-analysis, which assumes a constant effect of each treatment regardless of its pathway position. So, the ERG explained it was likely that the model overestimated the response rate of

treatments at later lines in the pathway. This means the cost-effectiveness model is further biased in favour of the arm with the longest treatment sequence (upadacitinib). The committee concluded that unequal treatment lengths may bias cost-effectiveness results.

Best supportive care response rate

It is not appropriate to model both a 0% response rate for best supportive care and the full response rate from the clinical evidence for upadacitinib

3.11 After 2 or more conventional DMARDs, the company's base case compared upadacitinib with best supportive care. In this analysis, best supportive care was assumed to give no EULAR response (0% response rate). The ERG explained that the control arms of the upadacitinib trials, including placebo controls, showed notable response rates. This is consistent with the placebo arms of other trials in rheumatoid arthritis. The ERG advised that some proportion of the upadacitinib response seen in the clinical trials would be caused by the same placebo effect seen in the control arms. The ERG therefore preferred to apply the placebo response from the network meta-analysis to best supportive care when it was compared with upadacitinib. The committee recalled that the clinical expert would not expect best supportive care to give a treatment response at this position. However, it agreed that the placebo effect will be present in the upadacitinib response rates. Therefore, comparing this with a 0% response rate would overestimate the effectiveness of upadacitinib relative to best supportive care. The committee concluded that it was not appropriate to apply a 0% response rate for best supportive care while also applying the full, observed response rate for upadacitinib. It also agreed that this also applies when best supportive care was at the same position as any active treatment in comparative treatment sequences (see section 3.10).

The company's 'net treatment effect' analysis may be appropriate to model effectiveness of upadacitinib relative to best supportive care, but not the relative costs

3.12 In its response to technical engagement, the company provided a scenario analysis which estimated the 'net treatment effect' of upadacitinib relative to the trial control arms. This decreased the upadacitinib response rate to reflect that some of the overall response could be because of a trial or placebo effect. In this analysis, the company used the resulting, lower response rate for the upadacitinib model arm, compared with a 0% response rate for the best supportive care arm. The ERG explained that reducing the response rate for upadacitinib may underestimate the treatment cost in the model, compared with what would be expected in clinical practice. This was because fewer people were assumed to have their disease respond to upadacitinib, and incur the costs of ongoing upadacitinib treatment. In practice, there would still be a proportion of the upadacitinib response rate attributable to the placebo effect. The committee concluded that this analysis may be the most appropriate way to model the clinical effectiveness of upadacitinib relative to a 0% response rate for best supportive care. However, this approach may underestimate both the ongoing treatment costs associated with upadacitinib that would happen in practice and the cost-effectiveness estimates for upadacitinib.

The company's approach for modelling the long-term health assessment questionnaire (HAQ) of people whose disease responded to placebo is acceptable

3.13 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 trajectory as those whose disease responded to biological DMARDs. The ERG explained that the upadacitinib response rate was likely to include a relatively large part caused by a placebo effect. This was also present in the trial control arms, and so it may be inappropriate to make different assumptions about long-term HAQ trajectories in the

model. 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 HAQ trajectory as those whose disease responded to conventional DMARDs. The clinical and patient experts advised that natural recovery from symptoms happened rarely in clinical practice, and this was not usually sustained for a long time. So, the committee agreed that applying a HAQ trajectory associated with biological DMARD treatment was likely to be an overly optimistic assumption about best supportive care. It concluded that it was more appropriate to assume that people whose disease responded to best supportive care had the same, decreasing long-term HAQ trajectory as people whose disease responded to conventional DMARDs. This was consistent with previous NICE technology appraisals in rheumatoid arthritis.

Economic model inputs and assumptions

The model underestimates how many patients' disease progresses from moderate to severe, making its results less robust

3.14 The company's model included the possibility of treatment for moderate disease progressing to treatment for severe disease. This progression was not modelled in previous NICE technology appraisal guidance on adalimumab, etanercept, infliximab, certolizumab pegol, golimumab, tocilizumab and abatacept for rheumatoid arthritis. However, the committee agreed that the progression reflects what happens in clinical practice and noted that it had been modelled in the previous NICE technology appraisal on sarilumab. This transition was modelled by estimating the relationship between DAS28, which defines disease severity, and HAQ from the SELECT trials. The ERG noted that the company did not apply the intercept term from its estimate relationship, and that applying the intercept term results in no patients' disease progressing from moderate to severe in the model. In response to technical engagement, the company provided an analysis showing that

7% of people with moderate disease have their disease progress to severe after 2 years in the model. The ERG advised that this estimate was for patients who have not had treatment, and that a more accurate estimation including patients who have had treatment was 1% to 3%. The ERG explained that this figure was significantly lower than the figure predicted by the UK Early Rheumatoid Arthritis Network database (19%). The committee agreed that the model appeared to underestimate the number of patients with moderate disease whose disease progressed to severe, and who had the associated biological treatments rather than carry on having best supportive care. The committee concluded that this substantially reduces the robustness of the cost-effectiveness estimates of upadacitinib for treating moderate disease.

The mapping algorithm to link HAQ and pain scores that was used in the previous NICE technology appraisal should be used to estimate utilities

3.15 In the company's base case, health-related quality of life data was calculated using a mapping function to work out a person's pain score from their HAQ score. This used SELECT trial data, to estimate EQ-5D values. The ERG noted that a previous NICE technology appraisal (adalimumab, etanercept, infliximab, certolizumab pegol, golimumab, tocilizumab and abatacept for rheumatoid arthritis not previously treated with DMARDs or after conventional DMARDs only have failed) 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. The committee agreed with the ERG's preferred approach. It concluded that the company's approach may be valid, but it preferred to use utilities calculated using the HAQ-to-pain mapping function used in the previous NICE technology appraisal, which was based on a much larger dataset.

Economic model validation

It is uncertain how closely the company's model is consistent with the model used in the previous technology appraisal

3.16 The company based its model on the model developed by the assessment group for the NICE technology appraisal on adalimumab, etanercept, infliximab, certolizumab pegol, golimumab, tocilizumab and abatacept. The company provided a validation analysis comparing the outputs of its model with those from the model used in the previous NICE technology appraisal 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 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 the previous technology appraisal. The committee concluded that it was uncertain how closely the company's model was consistent with the model used in the previous technology appraisal.

Cost-effectiveness results

In moderate disease the cost-effectiveness estimates are not robust, but upadacitinib is unlikely to be cost effective

3.17 The committee evaluated the cost effectiveness of upadacitinib for moderate disease based on the following conclusions:

- The most appropriate position for upadacitinib in the moderate rheumatoid arthritis treatment pathway is after 2 conventional DMARDs (see section 3.8).
- Best supportive care is the relevant comparator at this point in the treatment pathway (see section 3.9).

- It is not appropriate to assume there is a 0% response rate for best supportive care while also applying the full, observed response rate for upadacitinib (see section 3.11).
- The company's 'net treatment effect' scenario may be an appropriate way of modelling relative effectiveness, but it is likely to underestimate upadacitinib treatment costs (see section 3.12).
- It is appropriate to assume a differential long-term HAQ trajectory for people who respond to best supportive care and people who respond to biological DMARDs (see section 3.13).
- It is appropriate to use the mapping algorithm accepted in the NICE technology appraisal on adalimumab, etanercept, infliximab, certolizumab pegol, golimumab, tocilizumab and abatacept for rheumatoid arthritis (see section 3.15).

In these scenarios the cost-effectiveness estimates, including the confidential discounts for comparator and subsequent treatments, resulted in incremental cost-effectiveness ratios (ICERs) above £20,000 per QALY gained for the company's 'net treatment effect' approach compared with best supportive care. The ICER for the company's HAQ trajectory scenario was above £30,000 per QALY gained compared with best supportive care. The exact ICERs are confidential and cannot be reported here. The company's model appeared to underestimate the number of patients with moderate disease whose disease would progress to be treated as severe disease (see section 3.14). It also considered that the company's 'net treatment effect' scenario likely underestimated treatment costs (see section 3.12). It agreed that these issues added a large amount of uncertainty to the cost-effectiveness results for upadacitinib in moderate disease, and that the true cost-effectiveness estimate was likely to be higher than those reported. The committee concluded that it had not seen robust cost-effectiveness estimates for upadacitinib in people with moderate disease. However, it also concluded that upadacitinib was not likely to be cost-effective use of NHS resources for treating moderate disease, and did not recommend it in this group.

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

3.18 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 with conventional DMARDs were similar to what was previously seen for rheumatoid arthritis. This was upadacitinib either dominating (that is, it was cheaper and more effective than the comparator) or giving an ICER over £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 the NICE technology appraisal guidance on adalimumab, etanercept, infliximab, certolizumab pegol, golimumab, tocilizumab and abatacept.

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

3.19 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

3.20 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

3.21 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. The clinical expert explained that methotrexate is not tolerated by some patients or it is contraindicated. In previous NICE guidance on rheumatoid arthritis, Janus kinase (JAK) inhibitors have been recommended as monotherapies when methotrexate is not suitable. 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

3.22 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

3.23 Upadacitinib, like several other biological 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 Proposed date for review of guidance

5.1 NICE proposes that the guidance on this technology is considered for review by the guidance executive 3 years after publication of the guidance. NICE welcomes comment on this proposed date. The guidance executive will decide whether the technology should be reviewed based

on information gathered by NICE, and in consultation with consultees and commentators.

Gary McVeigh
Chair, appraisal committee
January 2020

6 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
Technical lead

Jamie Elvidge
Technical adviser

Gemma Barnacle
Project manager

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