

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Final draft guidance

Upadacitinib for treating moderately to severely active ulcerative colitis

1 Recommendations

1.1 Upadacitinib is recommended, within its marketing authorisation, as an option for treating moderately to severely active ulcerative colitis in adults:

- when conventional or biological treatment cannot be tolerated, or
- if the condition has not responded well enough or has stopped responding to these treatments, and
- if the company provides upadacitinib according to the commercial arrangement (see [section 2](#)).

1.2 Choose the most appropriate treatment after discussing the advantages and disadvantages of the treatments available with the person having treatment. If patients and clinicians consider upadacitinib to be one of a range of suitable options, choose the least expensive treatment (taking into account drug administration costs, dose needed and frequency, and product price per dose).

Why the committee made these recommendations

Standard treatments for moderately to severely active ulcerative colitis after conventional treatments are biological treatments (adalimumab, golimumab, infliximab, ustekinumab or vedolizumab) or tofacitinib.

Clinical trial evidence shows that upadacitinib is more effective than placebo for treating moderately to severely active ulcerative colitis. There is no direct evidence comparing upadacitinib with treatments that are offered after conventional treatment.

Indirect comparison suggests that upadacitinib is likely to be as effective as most of them.

The most likely cost-effectiveness estimates for upadacitinib compared with other treatments are within the range NICE normally considers an acceptable use of NHS resources. So, upadacitinib is recommended.

2 Information about upadacitinib

Marketing authorisation indication

- 2.1 Upadacitinib (RINVOQ, AbbVie) is indicated for ‘the treatment of adult patients with moderately to severely active ulcerative colitis who have had an inadequate response, lost response or were intolerant to either conventional therapy or a biological agent’.

Dosage in the marketing authorisation

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

Price

- 2.3 The price per 28-tablet pack is £805.56 for upadacitinib 15 mg and £1,281.54 for upadacitinib 30 mg (all prices excluding VAT; BNF online accessed October 2022). The estimated cost for 6 weeks of induction treatment (45 mg) is £3,131 based on list price (excluding VAT). The estimated cost of maintenance treatment is £10,472 at standard dose (15 mg) or £16,660 at high dose (30 mg) per person per year based on list price (excluding VAT).
- 2.4 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 [evaluation committee](#) considered evidence submitted by AbbVie, a review of this submission by the external assessment group (EAG), and responses from stakeholders. See the [committee papers](#) for full details of the evidence.

Clinical management

Treatment pathway

3.1 Upadacitinib is a type of treatment called a Janus-associated kinase (JAK) inhibitor. It has a marketing authorisation for treating moderately to severely active ulcerative colitis when conventional or biological treatment cannot be tolerated, or if the disease has not responded well enough or stopped responding to treatment. The committee noted that choice of treatment for ulcerative colitis is highly individualised based on a range of factors. The company's submission considered 2 subgroups:

- 'Biologic-naive' – people who have had a conventional treatment and their disease did not respond to it or they could not tolerate it, but they have not had a biological treatment (a tumour necrosis factor [TNF]-alpha inhibitor, vedolizumab or ustekinumab) or tofacitinib (another JAK inhibitor).
- 'Biologic-experienced' – people who have had a conventional or biological treatment or tofacitinib and their disease did not respond to it or they could not tolerate it.

The committee acknowledged there are other non-biologic treatments that have since been recommended for these populations and not considered in this evaluation, and there may be more in the future. The committee understood the treatment subgroup definitions but noted they may need reconsideration in the future to avoid clinical confusion. Patient and clinical experts noted that upadacitinib, as an oral treatment, offers additional benefit over some of the current treatment options because it can be taken at home. Clinical experts noted that some treatments are

started in hospital because they need to be given intravenously. They suggested that upadacitinib is a step-change in managing moderately to severely active ulcerative colitis. They noted that because it performed well, it should not be reserved for after failure of biological treatment. The committee concluded that the company's categorisation based on biological treatment experience was appropriate.

Clinical evidence

Data sources and generalisability

3.2 The clinical-effectiveness evidence for upadacitinib comes from placebo-controlled, double-blind randomised controlled trials:

- Induction treatment: the U-ACHIEVE (n=473) and U-ACCOMPLISH (n=515) trials included people with moderately to severely active ulcerative colitis. They were randomised to have upadacitinib (45 mg once daily) or placebo. The primary outcome was clinical remission, measured using the adapted Mayo score. Secondary outcomes included endoscopic improvement and remission, clinical response (adapted Mayo score), histologic–endoscopic mucosal improvement, mucosal healing, lack of bowel urgency and abdominal pain. All outcomes were measured at 8-weeks follow-up. People whose disease had an inadequate response at week 8 had a further 8 weeks of induction treatment.
- Maintenance treatment: the U-ACHIEVE maintenance trial included 451 people whose disease clinically responded to upadacitinib in the induction trials. People took either upadacitinib (15 mg or 30 mg) or placebo, once daily. The primary outcome was clinical remission (adapted Mayo score) at week 52. Secondary outcomes included endoscopic improvement and remission, maintenance of clinical remission, corticosteroid-free clinical remission, histologic–endoscopic mucosal improvement, mucosal healing, lack of bowel urgency and abdominal pain.

Clinical experts noted that these studies included people whose disease had not responded to therapies currently available in the NHS. The committee concluded that the trials are adequate and generalisable to UK clinical practice.

Clinical effectiveness

3.3 At the end of induction treatment, the rate of remission was statistically significantly higher in the upadacitinib 45 mg group than the placebo group (adjusted treatment difference compared with placebo of 22% and 29% in the 2 studies) for the overall population. Remission rates were consistent in the biologic-naive and biologic-exposed subgroups. At week 52 of the maintenance phase, a statistically significantly greater proportion of people who had upadacitinib were in remission compared with those who had placebo (adjusted treatment difference compared with placebo of 31% [15 mg upadacitinib] and 39% [30 mg upadacitinib]). Remission rates were consistent in the biologic-naive and biologic-exposed subgroups. Clinical experts noted that the trials show upadacitinib will provide clinically meaningful benefits. The committee concluded that upadacitinib is more effective than placebo at inducing and maintaining remission.

Safety profile

3.4 In the induction trials, the most common adverse events with upadacitinib were creatine phosphokinase increase, acne and nasopharyngitis. In the maintenance trial these were nasopharyngitis, worsening of ulcerative colitis and creatine phosphokinase increase. Discontinuation from the trial because of adverse events was more common with placebo than with upadacitinib. There were no deaths in any trial. The committee was aware of the [European Medicine Agency safety committee review of JAK inhibitors for inflammatory disorders](#) (including upadacitinib for ulcerative colitis). This is because a clinical trial of tofacitinib in rheumatoid arthritis showed people with risk of heart disease were more likely to experience a major cardiovascular problem and had a higher risk of developing cancer

with tofacitinib than TNF-alpha inhibitors. The company submitted a summary of the most recent data from a long-term extension study of upadacitinib (U-ACTIVATE). No new safety risks were identified in people who completed maintenance treatment in U-ACHIEVE and continued upadacitinib in the extension study. The committee concluded that based on the evidence presented, upadacitinib has an acceptable safety profile.

Indirect treatment comparison

Company network meta-analyses

3.5 Because there were no head-to-head studies, the company did network meta-analyses of 2 randomised placebo-controlled trials of upadacitinib (U-ACHIEVE induction and maintenance, and U-ACCOMPLISH induction) and 18 trials of comparators. The network meta-analyses for efficacy endpoints assessed clinical remission and clinical response in 2 subgroups:

- For the biologic-naive subgroup, the analysis estimated the relative efficacy of upadacitinib compared with adalimumab, golimumab, infliximab, tofacitinib, ustekinumab and vedolizumab.
- For the biologic-exposed subgroup, the analysis estimated the relative efficacy of upadacitinib compared with adalimumab, tofacitinib, ustekinumab and vedolizumab.

The safety network meta-analysis assessed the rate of serious infection in the overall population during induction treatment with upadacitinib compared with adalimumab, golimumab, infliximab, tofacitinib, ustekinumab and vedolizumab. The EAG noted that the company's network meta-analyses had some unresolvable technical issues with an unclear impact that must be considered when interpreting the results:

- For all networks, the consistency assumption could not be tested formally.

- The results of the network meta-analysis for the maintenance phase were less reliable than those for the induction phase.
- The company and EAG preferred different approaches to generating the network meta-analyses results.

The EAG was not satisfied with alternative approaches it explored and proposed that clinical opinion be sought on the plausibility of the results. The committee noted the wide credible intervals leading to uncertainty in the results. The company stated that its results were supported by evidence from 2 recently published network meta-analyses of treatment for moderate to severe ulcerative colitis (Burr et al. 2022; Lasa et al. 2022). Clinical experts agreed that these published analyses broadly reached the same conclusions as the company's analyses. They noted that the published analyses also included filgotinib and ozanimod, which were recently recommended for treating moderately to severely active ulcerative colitis ([NICE technology appraisal guidance on filgotinib](#) and [ozanimod](#)). The committee noted that filgotinib and ozanimod have not yet been widely used in clinical practice and were not included as comparators in this appraisal. The committee concluded that the results of the company's network meta-analyses are plausible and appropriate for decision making.

Results of network meta-analyses

- 3.6 The company's network meta-analyses suggested that upadacitinib is as effective and sometimes more effective than comparators in the biologic-naive and biologic-exposed subgroups. The company considers the results confidential so they cannot be reported here. The company's safety network analysis suggested that upadacitinib has a low risk of serious infection. The committee concluded that upadacitinib was at least as effective as its comparators, and has a similar low risk of serious infection.

Economic model

Company's modelling approach

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3.7 The company estimated the cost effectiveness of upadacitinib using a model with a hybrid structure (the induction phase was modelled using a decision tree and the maintenance phase was modelled using a Markov structure). The company provided cost-effectiveness estimates for the biologic-naïve and biologic-exposed subgroups. The company's model structure was similar to those used in earlier ulcerative colitis technology appraisals. It included health states defined by remission and response without remission (where people in the model received maintenance treatment with upadacitinib and comparators), active ulcerative colitis (with no drug treatment), and surgery and post-surgery. The company model did not include a second-line biologic therapy health state. The EAG stated that it was not plausible for the company to assume that after having only 1 treatment people would move to an 'active ulcerative colitis' health state (where people had no treatment for the remaining duration of the model). Instead, in clinical practice, people would either be offered surgery within 12 months or other drug treatments. Clinical advisers to the EAG suggested these other medicines may include the treatment which previously gave the best symptom relief, even if the person's disease had not responded to it. The committee noted that the company's approach of not modelling further treatment after first-line treatment exaggerates the differences between treatments over a lifetime. The committee agreed that the company's model did not reflect NHS clinical practice. The committee added that it expects company submissions in future appraisals to reflect more up-to-date practice, recognising there are many treatments available for ulcerative colitis. This should include a structured decision-analytic model for ulcerative colitis that realistically represents what happens in NHS clinical practice. The committee concluded that the company's modelled treatment pathway did not reflect NHS clinical practice.

EAG adjustment of the model

3.8 The EAG preferred to adapt the company's model using an alternative health state, 'on subsequent treatment', after treatment failure in its base case. In this, people have another drug treatment from the available

options (the comparators). The committee noted that this alternative approach led to different costs and quality-adjusted life years (QALYs) being accrued. The EAG acknowledged that its own modelling approach had some limitations. It did not include surgery and it allowed for a more expensive second-line treatment option than might be used in clinical practice. But, it did more closely reflect NHS practice than the company's approach. The committee highlighted that a preferable model would include likely sequences of treatment that are used in NHS practice, but acknowledged that it is unlikely that data exists to populate such a model. The committee agreed that neither treatment pathway reflected NHS practice but concluded that the EAG's simplified adjustment of the model was preferred for decision making.

Use of trial-based utility estimates

3.9 The company's utility values for remission, response without remission and active ulcerative colitis came from Woehl et al. 2008. The company noted that this was consistent with previous appraisals in ulcerative colitis. It suggested that utility values collected in real-world clinical practice (as done in Woehl et al. 2008) can provide more representative values of the population having treatment than those collected in clinical trials. The EAG preferred to use health state utility values from EQ-5D data collected in the upadacitinib trials in its base case, in line with the NICE reference case. It noted that these utility estimates were mostly higher than in the source used by the company. The committee noted that the Woehl et al. 2008 data used by the company had been considered in previous ulcerative colitis appraisals but that the reliability of the utility estimates had also been a source of discussion. The committee noted that utility values for remission, response without remission, and active ulcerative colitis health states were collected in upadacitinib trials and therefore could have been used. The committee concluded that using the upadacitinib trial-based utility estimates is preferred.

Maintenance dose assumption

3.10 The committee recalled that upadacitinib maintenance treatment is 15 mg ('standard') or 30 mg ('high') daily dosing. The company and EAG agreed that, as was done for comparator drugs, it would be assumed that upadacitinib is prescribed in a 70:30 ratio of 'standard' to 'high' doses in the maintenance phase. The committee was concerned that this assumption was not based on evidence and that the true proportions of people who would have standard or high dose levels of these treatments was uncertain. However, it noted that this assumption was consistent with the approach taken in [NICE's technology appraisal guidance on ustekinumab](#). The committee reviewed alternative explorations of the ratio and noted these did not have a substantial impact on costs or effects. The committee concluded that some people have a high dose of maintenance treatment, but the proportion is uncertain.

Cost-effectiveness estimates

Company and EAG cost-effectiveness estimates

3.11 Fully incremental analyses were done on the company's and EAG's preferred base cases by prior biological treatment status. For the biologic-naive subgroup, the analyses compared upadacitinib with adalimumab, adalimumab biosimilar, golimumab, infliximab, infliximab biosimilar, tofacitinib, ustekinumab and vedolizumab. For the biologic-exposed subgroup, upadacitinib was compared with adalimumab, adalimumab biosimilar, tofacitinib, ustekinumab and vedolizumab. The committee recalled that there was some uncertainty associated with the results of the network meta-analyses (see [section 3.5](#)). It also recalled that neither the company's nor the EAG's model truly reflected NHS clinical practice but that the EAG's simplified approach was preferred (see [section 3.8](#)). The proportion of people who have high-dose maintenance treatment in clinical practice is also uncertain (see [section 3.10](#)). Looking at the cost-effectiveness results from the EAG's model, upadacitinib had the greatest net health benefit suggesting that it is a cost-effective use of NHS resources compared with existing NICE-recommended treatments.

However, the committee noted that the differences between costs and QALYs were very small, and noted the uncertainties described above.

The committee agreed it was likely that upadacitinib is a cost-effective use of NHS resources when conventional or biological treatments are not tolerated or are not working well enough. The committee concluded that upadacitinib is considered cost effective for treating moderately to severely active ulcerative colitis.

Other factors

Choosing the most appropriate treatment

3.12 The committee recalled that treatment of ulcerative colitis is highly individualised based on a range of factors. It also recalled that upadacitinib is likely to be a cost-effective use of NHS resources. But, it noted that because the cost-effectiveness estimates were similar it could not consider it in preference to other options. This is because the value that each provides is uncertain and likely to vary from case to case. It recalled that a range of treatments are already available for people with moderately to severely active ulcerative colitis, including some that have not yet been widely used in clinical practice (see [section 3.5](#)). The committee concluded that healthcare professionals should choose the most appropriate treatment after discussing the advantages and disadvantages of the treatments available with the person having treatment. If patients and clinicians consider upadacitinib to be one of a range of suitable options, they should choose the least expensive treatment (taking into account drug administration costs, dose needed and frequency, and product price per dose). This may vary from person to person because of differences in how the drugs are taken and treatment schedules.

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 integrated care boards, NHS England and, with respect to their public health functions, local authorities to comply with the recommendations in this evaluation 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 guidance 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 draft guidance.
- 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 moderately to severely active ulcerative colitis 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 Evaluation committee members and NICE project team

Evaluation committee members

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

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

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

Chair

Charles Crawley

Chair, Technology appraisal evaluation committee B

NICE project team

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

Catherine Spanswick

Technical lead

Carl Prescott

Technical adviser

Jeremy Powell

Project manager

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