NICE National Institute for Health and Care Excellence

NICE guidance

Upadacitinib for previously treated moderately to severely active Crohn's disease

Technology appraisal guidance
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www.nice.org.uk/guidance/ta905

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

1.1 Upadacitinib is recommended as an option for treating moderately to severely active Crohn's disease in adults, only if:

- the disease has not responded well enough or lost response to a previous biological treatment or
- a previous biological treatment was not tolerated or
- tumour necrosis factor (TNF)-alpha inhibitors are contraindicated.

Upadacitinib is only recommended if the company provides it according to the commercial arrangement.

1.2 If people with the condition and their clinicians consider upadacitinib to be 1 of a range of suitable treatments, after discussing the advantages and disadvantages of all the options, use the least expensive. Take into account the administration costs, dosage, price per dose and commercial arrangements.

1.3 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

Standard treatments for moderately to severely active Crohn's disease when conventional treatments stop working are biological treatments (such as TNF-alpha inhibitors, ustekinumab or vedolizumab).

Clinical trial evidence shows that upadacitinib increases the likelihood of disease remission compared with placebo. Indirect comparisons of upadacitinib with ustekinumab and vedolizumab suggest that it is as effective.

A cost comparison suggests that upadacitinib has a similar or lower cost than vedolizumab and ustekinumab. 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 Crohn's disease who have had an inadequate response, lost response or were intolerant to either conventional therapy or a biologic 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 list price per 28-tablet pack of upadacitinib is £805.56 for 15-mg tablets, £1,281.54 for 30-mg tablets and £2,087.10 for 45-mg tablets (excluding VAT; BNF online, accessed May 2023).

2.4 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 evaluation committee considered evidence submitted by AbbVie, a review of this submission by the external assessment group (EAG), and submissions from stakeholders. See the committee papers for full details of the evidence.

The condition

Living with the condition

3.1 Crohn's disease is a life-long inflammatory condition of the gastrointestinal tract. It is characterised by recurrent relapses with acute exacerbations and periods of remission. Symptoms include diarrhoea, abdominal pain, fatigue, weight loss and blood or mucus in stools. The patient experts explained that the disease is unpredictable and can have a profound and devastating impact on all aspects of life, including work, education and social life. Treatments for moderately to severely active Crohn's disease include conventional therapy such as glucocorticoids and immunomodulators. This is followed by biological treatments if there is inadequate response, intolerance or contraindication to conventional therapy. The clinical experts explained that there is an unmet need for new treatments for Crohn's disease, particularly for people whose disease is refractory or has lost response to treatment. They also explained that upadacitinib has a different mechanism of action to other treatments. Therefore, it may be effective for a proportion of people whose disease does not respond to these existing treatments. The patient experts explained that having more treatment options available is important, because not all available treatments work for everyone. They also highlighted that upadacitinib is an oral drug, which is a benefit over other treatment options. The committee concluded that more treatment options for severely to moderately active Crohn's disease would be welcomed.

Decision problem

Comparators

3.2 The company proposed that upadacitinib should be considered for moderately to severely active Crohn's disease in adults who have had a biological therapy that was not tolerated or did not work well enough, or when a tumour necrosis factor (TNF)-alpha inhibitor is unsuitable. It would be an alternative to the biological treatments ustekinumab and vedolizumab. This is a narrower population than the marketing authorisation for upadacitinib, which also allows use after conventional therapy only, or if conventional therapy is not tolerated or is contraindicated (see section 2.1). The clinical experts explained that the company's positioning of upadacitinib is appropriate and would reflect its use in clinical practice. The EAG highlighted that, in addition to ustekinumab and vedolizumab, the TNF-alpha inhibitors infliximab and adalimumab may also be relevant comparators, because they are recommended for severe Crohn's disease (NICE's technology appraisal guidance on infliximab and adalimumab for the treatment of Crohn's disease). The clinical experts explained that TNF-alpha inhibitors are usually used as first-line advanced therapy. They explained that if ustekinumab is used as first-line advanced therapy, in line with NICE's technology appraisal guidance on ustekinumab for moderately to severely active Crohn's disease after previous treatment, it is usually because TNF-alpha inhibitors are unsuitable. In this case, it is inappropriate to use TNF-alpha inhibitors and so vedolizumab is usually used as second-line biological treatment. The committee concluded that the company's positioning of upadacitinib as an alternative to vedolizumab and ustekinumab was appropriate.

Comparators for people with risk factors

3.3 The clinical expert submissions highlighted a safety review of Janus Kinase inhibitors, such as upadacitinib. The safety review led to an update of the special warnings and precautions for use in the summary of product characteristics for upadacitinib. It states that for some people, upadacitinib should only be used if there are no other suitable

treatments. It applies to people aged 65 years and older, people with a history of atherosclerotic cardiovascular disease or other cardiovascular risk factors, and people with malignancy risk factors. The clinical experts explained that clinical judgement is needed to determine the suitability of upadacitinib for each person based on the risks and benefits of treatment. They stated that ustekinumab and vedolizumab remain the relevant comparators for the subgroups highlighted in the special warning. This is because there are no treatment alternatives for these people and retreatment would be offered instead of best supportive care. The committee concluded that ustekinumab and vedolizumab were relevant comparators for the whole population proposed by the company.

Clinical effectiveness

Data sources

3.4 Three clinical trials compared upadacitinib with placebo: U-EXCEL, U-EXCEED and U-ENDURE. U-EXCEL and U-EXCEED were studies of upadacitinib induction treatment. They both included a randomised-controlled period for 12 weeks (part 1) and an extended treatment period. U-EXCEL (n=526 for part 1) included people whose disease had had inadequate response or were intolerant to conventional therapy only (conventional care failure) or to biological treatment (biological failure). U-EXCEED (n=495 for part 1) included only a biological failure population. The committee noted that it was appropriate to consider the biological failure subgroup because this was in line with where the company had positioned upadacitinib in the treatment pathway (see section 3.2). For the biological failure population, both trials showed a statistically significant improvement in the rate of clinical remission and endoscopic response with a 45-mg induction dose of upadacitinib compared with placebo at 12 weeks. The third study, U-ENDURE, was a study of upadacitinib maintenance treatment. It was a randomised controlled trial that also included people who had had conventional care failure or biological failure. Cohort 1 of U-ENDURE (n=502) included people who had had clinical response after 12 weeks of upadacitinib in either U-EXCEL or U-EXCEED. For the biological failure population, cohort 1 of

U-ENDURE showed a statistically significant improvement in rates of clinical remission and endoscopic response with a 15-mg and 30-mg maintenance dose of upadacitinib compared with placebo at 52 weeks. The data is confidential and cannot be reported here. The committee concluded that upadacitinib was more clinically effective than placebo in the biological failure population for both induction and maintenance treatment.

Clinical-effectiveness network meta-analyses

3.5 There were no trials directly comparing upadacitinib with ustekinumab or vedolizumab. So, the company did network meta-analyses to indirectly compare the clinical effectiveness of these treatments. It presented separate network meta-analyses for induction and maintenance treatment for the biological failure and conventional care failure subgroups. The EAG explained that for induction treatment in the biological failure population, the network meta-analysis indicated that upadacitinib is more effective than ustekinumab and vedolizumab for the outcome of clinical remission. For clinical response it has similar efficacy. For maintenance treatment in the biological failure population, the network meta-analysis indicated that upadacitinib has similar efficacy to ustekinumab and vedolizumab for the outcome of clinical remission. The EAG highlighted that only people who had achieved clinical response during induction treatment were enrolled into the trials of maintenance treatment in the network meta-analysis. Therefore, the EAG considered that a limitation of the maintenance treatment network meta-analysis was that it could not provide evidence of effectiveness for people whose disease had not previously responded to upadacitinib. However, the clinical experts explained that only people whose disease has responded to induction treatment would be offered maintenance treatment in practice. The company also explained that all the trials in the maintenance network meta-analysis were designed so that only people whose disease had responded to induction treatment were included in the maintenance treatment trial. Therefore, it believed the studies included in the network meta-analysis were comparable. The EAG accepted that there was no better method that could have been used to demonstrate clinical effectiveness of maintenance treatment given the available evidence for upadacitinib and its comparators. The committee

concluded that the network meta-analyses results supported the company's position that upadacitinib has similar clinical effectiveness to ustekinumab and vedolizumab.

Safety analysis

Adverse events network meta-analyses

3.6 The company presented network meta-analyses for induction and maintenance treatment to compare the adverse event outcomes of upadacitinib with ustekinumab and vedolizumab. The results showed that for both induction and maintenance treatment, serious adverse events were comparable between arms, with the credible intervals spanning the line of no effect for all comparisons. The EAG highlighted that discontinuation of treatment due to adverse events occurred more often with upadacitinib. However, the credible intervals crossed the line of no effect for all comparisons. The clinical expert explained that discontinuation rates are low for all the drugs and are therefore of limited relevance in clinical practice. The committee concluded that the network meta-analyses indicated that upadacitinib was likely to have a similar adverse event profile to ustekinumab and vedolizumab.

Cost comparison

Cost-comparison estimates

3.7 The company presented a base case cost-comparison analysis that modelled the total costs of upadacitinib, ustekinumab and vedolizumab over 1 year. This included the costs for induction and maintenance treatment. It also presented an analysis that showed the total costs of each treatment in the second and subsequent years of treatment. It considered that the clinical evidence available supported the assumption of clinical equivalence between upadacitinib, ustekinumab and vedolizumab. The company and the EAG also ran several scenario analyses that demonstrated the impact on the total costs of each treatment compared with the base case. This included changing the

proportion of people having the different available doses of each drug and using different sources for intravenous drug administration costs. Taking into account the confidential prices for upadacitinib, ustekinumab and vedolizumab, the committee concluded that the total costs associated with upadacitinib were similar to or lower than the costs for ustekinumab and vedolizumab. The discounts for all treatments are confidential, so the incremental costs cannot be shared here.

Conclusion

Recommendation

3.8 The committee concluded that the criteria for a cost comparison recommendation were met because:

- upadacitinib provided similar overall health benefits to those of ustekinumab or vedolizumab, and
- the total costs associated with upadacitinib were similar to or lower than the total costs associated with ustekinumab or vedolizumab.

The committee therefore recommended upadacitinib as an option for moderately to severely active Crohn's disease when the disease has not responded well enough or lost response to previous biological treatment or a previous biological treatment was not tolerated, or if a TNF-alpha inhibitor is contraindicated.

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. Because upadacitinib has been recommended through the cost-comparison process, NHS England and integrated care boards have agreed to provide funding to implement this guidance 30 days after 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 Crohn's disease 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 committees are standing advisory committees of NICE. This topic was considered by committee A.

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

Radha Todd
Chair, technology appraisal committee A

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.

Albany Chandler
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