NICE National Institute for Health and Care Excellence

NICE guidance

Tofacitinib for moderately to severely active ulcerative colitis

Technology appraisal guidance
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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 Tofacitinib is recommended, within its marketing authorisation, as an option for treating moderately to severely active ulcerative colitis in adults when conventional therapy or a biological agent cannot be tolerated or the disease has responded inadequately or lost response to treatment. It is recommended only if the company provides tofacitinib with the discount agreed in the commercial arrangement.

Why the committee made these recommendations

Clinical trial evidence shows that tofacitinib is more effective than placebo for treating moderately to severely active ulcerative colitis. An indirect comparison suggests that for people who have not had a TNF-alpha inhibitor, tofacitinib is more effective than adalimumab and golimumab as maintenance treatment. For people who have had a TNF-alpha inhibitor, tofacitinib is more effective than adalimumab as induction treatment. No other statistically significant differences between tofacitinib and biological therapies were identified.

Based on the health-related benefits and costs compared with conventional therapy and biologicals, tofacitinib is recommended as a cost-effective treatment for moderately to severely active ulcerative colitis in adults whose disease has responded inadequately to, or who cannot tolerate, conventional or biological therapy.

2 Information about tofacitinib

Marketing authorisation

2.1 Tofacitinib (Xeljanz, Pfizer) 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 biologic agent'.

Dosage in the marketing authorisation

2.2 The recommended dosage of tofacitinib for induction is 10 mg taken orally twice daily for 8 weeks, then 5 mg taken twice daily for maintenance. If adequate therapeutic benefit is not achieved by week 8 the induction dose can be taken for an additional 8 weeks (16 weeks in total). Induction therapy should be stopped if there is no evidence of therapeutic benefit by week 16.

For patients whose disease has responded inadequately to tumour necrosis factor antagonist therapy, consider continuing the 10-mg twice-daily dose for maintenance in order to maintain therapeutic benefit. If response decreases to tofacitinib 5 mg taken twice daily as maintenance therapy, consider increasing the dose to 10 mg taken twice daily.

When the disease has responded adequately to tofacitinib, corticosteroids may be reduced or stopped in accordance with standard care.

Price

2.3 The list price of a 56-tablet pack of 5-mg tofacitinib is £690.03; the list price of a 56-tablet pack of 10-mg tofacitinib is £1,380.06 (excluding VAT; British national formulary [BNF] online 2018). The average cost per patient for the first year is estimated at £10,350.45 and for the subsequent year is estimated at £8,970.39.

The company has a commercial arrangement. This makes tofacitinib 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 Pfizer and a review of this submission by the evidence review group (ERG). See the committee papers for full details of the evidence.

Clinical management

Tofacitinib will be used in the same place in the treatment pathway as biological therapies

3.1 The clinical expert explained that current clinical management of moderate to severely active ulcerative colitis is conventional therapies (aminosalicylates, corticosteroids or thiopurines). If there is inadequate response or loss of response, patients may be offered a biological therapy (a tumour necrosis factor [TNF] alpha inhibitor such as infliximab, adalimumab and golimumab or the anti-integrin agent vedolizumab). The clinical expert stated that tofacitinib could be offered instead of biological therapy. He highlighted that moderately to severely active ulcerative colitis is typically managed according to the patient's history, treatment response and tolerance of individual therapies. It is therefore important to have a range of treatment options available. The clinical expert further explained that the disease does not respond in 30% of patients having biological therapies and that, for those with a response, 20% will eventually lose this response. He explained that if there is inadequate or loss of response to the first biological therapy a second biological therapy may be offered, but there is a 30% chance that the disease will not respond. The committee concluded that tofacitinib will be used in the same place in the treatment pathway as biological therapies; that is, in second- and third-line treatment for ulcerative colitis.

Tofacitinib offers an important new treatment option for ulcerative colitis

3.2 The patient experts explained that moderately to severely active ulcerative colitis

has a major effect on people's lives and can be socially isolating. Symptoms include frequent bloody diarrhoea, abdominal pain, symptoms elsewhere in the body (such as the joints, eyes, skin and liver) and fatigue. Complications such as intestinal perforation and abscesses may need surgery. The clinical expert stated that many people who have ulcerative colitis are teenagers and younger adults. They explained that tofacitinib is a novel treatment with a different mode of action compared with biological therapies (see section 3.1). The clinical and the patient experts also highlighted that tofacitinib is taken orally, which has major benefits for patients and the NHS. The clinical expert noted that because of its molecular structure, tofacitinib has less chance of immunogenicity and loss of response over time compared with biological therapies. The committee concluded that tofacitinib offers an important new treatment option for people with ulcerative colitis.

Clinical evidence

The OCTAVE trials are suitable for decision-making

3.3 The clinical-effectiveness evidence for tofacitinib comes from 3 placebo-controlled, double-blinded randomised controlled trials:

- Induction treatment: the OCTAVE Induction 1 and 2 trials included 598 patients and 541 patients, respectively, with moderately to severely active ulcerative colitis. They were randomised to have tofacitinib (10 mg twice daily) or placebo. The primary outcome was remission, measured using the Mayo score. Secondary outcomes included mucosal healing, Inflammatory Bowel Disease Questionnaire, SF-36 and EQ-5D. All outcomes were measured at 8-week follow-up.
- Maintenance treatment: the OCTAVE Sustain trial included 593 patients whose disease had had a clinical response to tofacitinib in OCTAVE Induction 1 or 2. Patients took either tofacitinib (5 mg or 10 mg) or placebo, twice daily. The primary outcome was remission. Secondary outcomes included sustained steroid-free remission measured at 24 weeks, mucosal healing, and clinical response and clinical remission at 52-week follow-up.

Additional clinical evidence came from a small trial and OCTAVE Open, an ongoing open-label long-term extension trial. This included patients from OCTAVE Induction 1 and 2 whose disease did not respond to tofacitinib. The committee concluded that the trials are adequate and suitable for decision-making.

Tofacitinib is more effective than placebo for induction and maintenance treatment regardless of previous TNF-alpha inhibitor use

3.4 The committee noted that in OCTAVE Induction 1 remission at week 8 was seen in 18.5% of patients having tofacitinib 10 mg, compared with 8.2% in the placebo group ($p=0.007$). In OCTAVE Induction 2 remission at week 8 was 16.6% for tofacitinib and 3.6% for placebo ($p<0.001$). In OCTAVE Sustain, 40.6% of patients having tofacitinib 10 mg were in disease remission at week 52, compared with 11.1% in the placebo group ($p<0.001$). Similarly, 34.3% of patients in the tofacitinib 5 mg group were in disease remission at week 52 ($p<0.001$). The committee noted that the mean differences between tofacitinib and placebo in OCTAVE Induction 1 and 2 are in favour of tofacitinib and are statistically significant at the end of the induction phase (week 8). A similar effect was observed in OCTAVE Sustain for both dosages of tofacitinib (5 mg and 10 mg), with the difference in comparison with placebo being greater for tofacitinib 10 mg at the end of the maintenance phase (week 52). The subgroup results for prior TNF-alpha inhibitor exposure status, which were used by the company in their economic modelling, show a similar effect. The ERG explained that the OCTAVE trials were not powered to test the statistical significance of subgroup analyses so the results should be interpreted with caution. The committee concluded that tofacitinib is more effective than placebo for induction and maintenance treatment of moderate to severe disease, regardless of whether TNF-alpha inhibitors have been taken previously.

Adverse events

Tofacitinib has an acceptable safety profile

3.5 The company collected safety data from all the OCTAVE trials. Serious adverse events affected fewer than 10% of patients. There were 5 deaths, of which 1 was considered to be related to tofacitinib. Serious infections occurred only in patients having tofacitinib rather than placebo, with the exception of OCTAVE Sustain in which 2 patients taking placebo had serious infections. The clinical expert explained that the serious infections were non-specific and that they would not influence the decision to prescribe a biological instead of tofacitinib. The company highlighted that tofacitinib is also used for rheumatoid arthritis and that long-term safety data (over 9 years) are available. The committee concluded that tofacitinib's safety profile is acceptable.

Indirect treatment comparison

The company's indirect comparison was generally well conducted

3.6 The company presented 2 network meta-analyses according to previous TNF-alpha inhibitor use for induction and maintenance treatment with tofacitinib. Analyses were done for the outcomes of clinical response, clinical remission and mucosal healing:

- The TNF-alpha inhibitor 'naive' network included people who had not taken a TNF-alpha inhibitor. It estimated the relative efficacy of tofacitinib compared with placebo, adalimumab, golimumab, infliximab, and vedolizumab.
- The TNF-alpha inhibitor 'exposed' network included people who had taken TNF-alpha inhibitors. It estimated the relative efficacy of tofacitinib compared with placebo, adalimumab and vedolizumab.

  In the TNF-alpha inhibitor naive group all active treatments showed a statistically significant improvement for all outcomes compared with placebo. In the maintenance phase tofacitinib showed a statistically significant

improvement in clinical remission and clinical response compared with adalimumab and golimumab 50 mg. No other statistically significant differences were found in the TNF-alpha inhibitor naive group. In the TNF-alpha inhibitor exposed group tofacitinib and vedolizumab showed a statistically significant improvement in all outcomes compared with placebo. In the induction phase tofacitinib showed a statistically significant improvement in clinical remission and clinical response compared with adalimumab. No other statistically significant differences were found in the TNF-alpha inhibitor exposed group. The ERG noted that the indirect comparison was generally well conducted. The ERG replicated the company's indirect treatment comparison and preferred the random-effects models, because the fixed-effects models may underestimate the uncertainty caused by heterogeneity between the studies included in the networks. It explored the impact of a random-effects model for TNF-alpha inhibitor naive and exposed groups for maintenance treatment with tofacitinib in its preferred analyses. The random-effects model showed wider credible intervals and some variation in the median estimates for adalimumab and golimumab as maintenance treatment for the TNF-alpha inhibitor naive group. This is because smaller size studies are given more weight in the random-effects model (ERG) than the fixed-effects model (company). The ERG noted that adalimumab was included in the network, but the company did not provide results for adalimumab for the TNF-alpha inhibitor exposed group and did not explain why. It considered that adalimumab is a relevant comparator and included it in its base case. The committee concluded that both the company's and the ERG's analyses should be taken into account in decision-making, and that the indirect comparison was generally well conducted.

Indirect treatment comparisons for serious infection should be taken into account in decision-making

3.7 The company developed an indirect treatment comparison of serious infections for the induction-treatment group only. Because of the lack of events in the placebo groups (see section 3.5), credible intervals of treatment effects are very wide. This causes high uncertainty in the results for both the random and fixed models. The ERG did an alternative analysis to adjust for the lack of events in the

placebo groups, using a frequentist framework (which means adding 0.5 when there is a 0 event). This resulted in a non-significant increased risk of serious infection with tofacitinib. The committee noted that no safety issues have been reported in clinical practice (see section 3.5) and concluded that both the company's and the ERG's analyses should be taken into account in decision-making.

The company's economic model

The model is appropriate for decision-making

3.8 The company developed a Markov model for the TNF-alpha inhibitor naive and exposed populations, comparing tofacitinib with appropriate comparators for these 2 subgroups. The model used the results from the indirect comparison networks (see section 3.6). The model for the TNF-alpha inhibitor naive group compared tofacitinib with conventional treatment (placebo), adalimumab, golimumab, infliximab, and vedolizumab. The model for the TNF-alpha inhibitor exposed group compared tofacitinib with conventional therapy (placebo) and vedolizumab. The committee noted that the company did not include adalimumab in its analysis of the TNF-alpha inhibitor exposed group (see section 3.5). The Markov model included 9 health states and considered the costs and health benefits from the perspective of the NHS, discounted by 3.5% per year over a time horizon of a lifetime. Clinical response, clinical remission and serious infections were included in the model. The ERG agreed with the company's approach. The committee concluded that the model structure is appropriate for its decision-making.

Utility values in the economic model

The utility values are appropriate and consistent with previous NICE technology appraisals for ulcerative colitis

3.9 The committee discussed the utility values used in the company's model. The

company used published utility values (Woehl et al. 2008) for the health states of active disease (0.47), response (0.87), remission (1.00) and post-surgery (0.82). The committee noted that EQ-5D data were collected in the OCTAVE trials and it questioned the use of published utility values instead of trial-based utility values, which are generally preferred. The company explained that because 'responders' to tofacitinib from OCTAVE Induction were re-randomised to OCTAVE Sustain (see section 3.3), the EQ-5D data are difficult to interpret and not reliable for use in the model. It also highlighted that both clinical response and remission were only assessed at week 8 and week 52, and no data are available from other time points. The ERG noted that utility values from Woehl et al. 2008 were used in previous NICE technology appraisals for ulcerative colitis (that is, NICE technology appraisal guidance on vedolizumab and infliximab, adalimumab and golimumab). A patient expert agreed that the utility for active disease (0.47) reflects her experience with the disease. The committee concluded that utility values from Woehl et al. are appropriate and consistent with previous NICE technology appraisals for ulcerative colitis.

Resource use in the economic model

The cost effectiveness of tofacitinib is unlikely to change when the induction period is extended to 16 weeks

3.10 The committee noted that the company had not modelled the effect of extending the induction period for patients with a delayed response (that is, response after 8 weeks). It noted that the summary of product characteristics indicates that when an adequate therapeutic benefit has not been achieved by week 8, the induction dose of 10 mg twice daily can be extended for an additional 8 weeks (16 weeks total). The company explained that it did not model this scenario because of a lack of data for the comparators. The committee acknowledged that people may also continue taking TNF-alpha inhibitors beyond the usual time for assessment of response, in the hope of a delayed response. It considered that an extra 8 weeks of the higher induction dose would not be expected to have a major effect on the relative cost effectiveness. The committee concluded that the cost effectiveness of tofacitinib is unlikely to change when the induction period is extended to 16 weeks.

Cost-effectiveness estimates

The company's base-case results suggest that tofacitinib is cost effective for moderate to severe ulcerative colitis

3.11 The company presented fully incremental analyses and pairwise analyses comparing all treatments with conventional therapy for people who have, or have not, taken TNF-alpha inhibitors previously. The committee noted that the company's base case included the discount agreed in the commercial arrangement for tofacitinib and the list price for the other treatments. It was aware that the model had been corrected by the ERG for minor issues and that this did not have a significant impact on the results:

- TNF-alpha inhibitor 'naive': the cost-effectiveness results showed that adalimumab, golimumab and infliximab are dominated by tofacitinib (that is, they cost more and produce fewer quality-adjusted life years [QALYs]). The incremental cost-effectiveness ratio (ICER) for tofacitinib compared with conventional therapy is £8,564 per QALY gained. Tofacitinib produced fewer QALYs than vedolizumab, but at a lower cost. This resulted in an incremental saving of £615,077 per QALY lost for tofacitinib compared with vedolizumab at list price.
- TNF-alpha inhibitor 'exposed': the ICER for tofacitinib compared with conventional therapy is £10,311 per QALY gained. Tofacitinib produced fewer QALYs than vedolizumab, but at a lower cost. This resulted in an incremental saving of £7,838,381 per QALY lost for tofacitinib compared with vedolizumab at list price.

  The committee also considered the cost-effectiveness results including the discount agreed in the commercial arrangement for vedolizumab (the ICERs are commercial-in-confidence). It concluded that this does not affect the cost effectiveness of tofacitinib.

Tofacitinib remains a cost-effective option in the company's scenario analyses in which a 10 mg dose of tofacitinib is taken long-term

3.12 The clinical expert explained that some patients may take a 10-mg dose long-term. This is likely to be people who have previously had TNF-alpha inhibitors. The company explored a scenario in which a proportion of patients had a 10 mg dose long-term. The committee noted that this increased the ICER for tofacitinib compared with conventional therapy from £10,301 to £13,947 per QALY gained. It also noted that dose escalation is used for the comparator biological therapies, particularly when taken after TNF-alpha inhibitor therapy. It concluded that the company's base case should have included a proportion of patients having the higher dose long-term, but the resulting small increase in the ICER would not stop tofacitinib being cost effective.

The ERG's base-case results confirm that tofacitinib is cost effective for moderate to severe ulcerative colitis

3.13 The ERG's base case included the following data and assumptions:

- a similar average age for patients in the TNF-alpha inhibitor 'naive' and 'exposed' groups (rather than different ages, which was assumed by the company)
- using efficacy results from the indirect treatment comparison, based on the random-effects model (see section 3.6)
- using safety results from the indirect treatment comparison, based on the frequentist framework (see section 3.7)
- including the cost of stoma care (the company did not include the cost of stoma care for the post-colectomy health states).

  Taking into account the commercial arrangements for tofacitinib and vedolizumab, the committee concluded that the ERG's base case shows tofacitinib is a cost-effective option for people with moderate to severe ulcerative colitis when conventional therapy or a biological cannot be

tolerated or the disease has responded inadequately or lost response to treatment.

Tofacitinib remains a cost-effective option in the ERG's scenario analyses

3.14 The committee discussed the ERG's scenario analyses that had the most impact on the ICER, including:

- using utility values from the OCTAVE trials (see section 3.9)
- assuming 6.5 outpatient visits per year for all patients on maintenance therapy, which matches the treatment stopping rules for tofacitinib (4.5 outpatient visits per year were assumed by the company)
- reducing the health-state resource use to match clinical practice
- exploring the effect of switching within or between classes of biological therapies.

In all the ERG's scenario analyses, tofacitinib remains a cost-effective option for people with moderate to severe ulcerative colitis when conventional therapy or a biological cannot be tolerated or the disease has responded inadequately or lost response to treatment.

Innovation

Tofacitinib is innovative

3.15 The company stated that tofacitinib is innovative and the first therapy in its class for ulcerative colitis. The clinical experts explained that this is an oral therapy, and that it represents a step-change in the management of the disease. They also noted that tofacitinib is a small molecule. This gives it the advantage of less immunogenicity and loss of response over time compared with biological agents. The committee considered these factors to be important and concluded that

tofacitinib is innovative.

Conclusion

Tofacitinib is a cost-effective use of NHS resources

3.16 The committee concluded that tofacitinib shows clinical benefit compared with placebo for people with moderately to severely active ulcerative colitis, irrespective of previous TNF-alpha inhibitor exposure. It noted that when the commercial arrangements for tofacitinib and vedolizumab are included, the ICERs remain within the range normally considered a cost-effective use of NHS resources. The committee concluded that it can recommend tofacitinib as a cost-effective use of NHS resources for people with moderately to severely active ulcerative colitis when conventional therapy or a biological cannot be tolerated or the disease has responded inadequately or lost response to treatment.

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 moderate to severe ulcerative colitis and the doctor responsible for their care thinks that tofacitinib 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 A.

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.

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