NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Appraisal consultation document

Ustekinumab for treating moderately to severely active ulcerative colitis

The Department of Health and Social Care has asked the National Institute for Health and Care Excellence (NICE) to produce guidance on using ustekinumab 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?

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 ustekinumab 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: 11th February 2020

Second appraisal committee meeting: 25th February 2020

Details of membership of the appraisal committee are given in section 5.

1 Recommendations

1.1 Ustekinumab is not recommended, within its marketing authorisation, 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.

1.2 This recommendation is not intended to affect treatment with ustekinumab that was started in the NHS before this guidance was published. People having treatment outside this recommendation may continue without change to the funding arrangements in place for them before this guidance was published, until they and their NHS clinician consider it appropriate to stop.

Why the committee made these recommendations

Clinical trial evidence shows that ustekinumab is more effective than placebo for treating moderately to severely active ulcerative colitis. For induction (the first 8 weeks of treatment), indirect comparisons suggest that ustekinumab may be more effective than adalimumab for some people. For maintenance treatment, the results of the indirect comparisons are very uncertain.

The cost-effectiveness estimates vary from slightly below to above the range normally considered to be a cost-effective use of NHS resources. And there is considerable uncertainty about these estimates. Therefore, ustekinumab cannot be recommended.

2 Information about ustekinumab

Marketing authorisation indication

2.1 The marketing authorisation for ustekinumab includes the following indication: ‘treatment of adult patients with moderately to severely active ulcerative colitis who have had an inadequate response with, lost

response to, or were intolerant to either conventional therapy or a biologic or have medical contraindications to such therapies'.

Dosage in the marketing authorisation

2.2 Induction treatment is administered intravenously as a weight-based dose of about 6 mg per kg.

2.3 Maintenance treatment is administered as a subcutaneous injection of a fixed dose of 90 mg, with the first dose given at week 8 after induction. After this, dosing every 12 weeks is recommended. Patients who have not had an adequate response 8 weeks after the first subcutaneous dose (week 16) may have a second subcutaneous dose at this time, to allow for delayed response. Patients who lose response on dosing every 12 weeks may benefit from an increase in dosing frequency to every 8 weeks. Patients may subsequently have ustekinumab every 8 weeks or every 12 weeks according to clinical judgement.

Price

2.4 The list price is £2,147 per 130-mg vial of concentrate for solution for infusion, and £2,147 per 90-mg vial of solution for injection (excluding VAT; British national formulary online accessed January 2020).

2.5 The annual treatment costs are £14,482 in the induction year, and £9,304 per year for maintenance treatment (year 2 onwards).

2.6 The company has agreed a confidential pricing arrangement for ustekinumab with the Commercial Medicines Unit.

3 Committee discussion

The appraisal committee (section 5) considered evidence submitted by Janssen, 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 none of the issues raised during the technical engagement stage had been fully resolved. Therefore it considered all the feedback received from consultees and commentators, the ERG's report on the company's response to engagement and other issues that had not been consulted on during engagement.

Clinical need and current management

Living with moderately to severely active disease is physically and emotionally challenging

3.1 The patient expert explained that the experience of living with moderately to severely active ulcerative colitis varies on an individual level, but in their experience it is extremely challenging. They explained that, in the 5 years between initial diagnosis and the point at which they had surgery, they had only experienced about 18 months in total when their disease was not active. During periods of active disease, they never had fewer than 4 to 5 bowel movements per day. They experienced constant pain, sleep deprivation (caused by being awake in the night to go to the toilet) and depression. They also explained that using corticosteroids is associated with side effects and contributes to low mood. They commented that the effects of the disease and side effects of medication can be moderated, to an extent, by individual circumstances including a patient's support network and responsibilities. But they explained that feeling out of control is an important and common issue for many people with moderately to severely active ulcerative colitis. The clinical experts said that the patient expert's comments reflect the experience of patients that they see in practice. The patient and clinical experts also agreed that while surgery can be an effective treatment for some patients, outcomes are variable and abdominal scarring can significantly affect sexual and reproductive function. The committee also took account of comments submitted in writing by patient experts and research undertaken by the company, which highlighted the effects of the disease and current treatments, including surgery, on daily activities, relationships, self-esteem and body

image. It concluded that living with moderately to severely active disease is physically and emotionally challenging.

There is an unmet need for new treatments that reduce the need for corticosteroids or surgery

3.2 The clinical experts recognised that NICE already recommends several treatment options for when conventional therapy or a biological agent cannot be tolerated, or the disease has responded inadequately or lost response to treatment. They commented that all these treatments are similarly effective because no single agent offers better clinical efficacy and lower risk of side effects overall. However they stated that, in current practice, most patients will be offered a tumour necrosis factor [TNF]-alpha inhibitor first. This is because biosimilars are available in this class, which have a lower price. The cheapest infliximab biosimilar is usually prescribed first. If a patient has a loss of response and has produced antibodies, they would be offered another TNF-alpha inhibitor. If a patient has not produced antibodies and their disease has responded inadequately or lost response to treatment with 1 TNF-alpha inhibitor, then other treatments (vedolizumab and tofacitinib) are considered. One expert noted that a patient's choice of treatment is often influenced by the drugs' safety profiles, and that in their experience tofacitinib is sometimes more effective but associated with more severe side effects. The clinical and patient experts agreed that, despite the availability of other treatments, there is still an unmet need for new, non-surgical treatment options because many people have an inadequate response to current therapies or they stop working. The committee heard that the only option for these people, other than surgery, is long-term corticosteroid use. This is associated with side effects. The patient expert also noted that ustekinumab's mode and frequency of administration during maintenance treatment may be more convenient than that of some other current treatments. The committee concluded that new medical treatment options would be welcome.

Clinical evidence

The UNIFI trial shows that ustekinumab is more effective than placebo at inducing and maintaining remission and response in all patients

3.3 UNIFI is a randomised, placebo-controlled trial of patients who had had an inadequate disease response to, or unacceptable side effects from, biological treatments (TNF-alpha inhibitors or vedolizumab) or conventional non-biological therapy (corticosteroids or the immunomodulators azathioprine or mercaptopurine). It had an induction-phase study and a maintenance-phase study. There were 961 patients in the induction study, with outcomes measured at week 8 in the intention-to-treat (ITT) analyses and at week 16 in the non-ITT analyses. 523 patients with disease that had responded after 8 weeks of induction treatment with ustekinumab were entered into the ITT population of the maintenance study, and re-randomised to determine what maintenance treatment they would have (ustekinumab or placebo). The maintenance study also included 2 non-randomised populations: patients whose disease had responded to placebo during induction treatment (sample size and results not reported) and patients who had had more than 8 weeks of induction therapy with ustekinumab and were in response at week 16 (n=157; described by the company as 'delayed responders'). The company reported results for the ITT population for the following subgroups:

- a 'biologic-failure' subgroup of people who had had at least 1 biological treatment (a TNF-alpha inhibitor or vedolizumab) and either their disease did not respond or lost an initial response, or they could not tolerate it
- a 'non-biologic failure' subgroup of people who had never had a biological treatment, but that also included some people who had had biological treatments but not had a documented 'biological failure'.

At the end of induction treatment, rates of clinical remission and response were statistically significantly higher in the ustekinumab 6 mg per kg and 130 mg groups than the placebo group. This result was the same for both the non-biologic failure and biologic-failure subgroups, and for the overall ITT population. At week 44 of the maintenance phase, a statistically significantly greater proportion of patients who had had both ustekinumab maintenance doses were in clinical remission than those who had had placebo. This result was the same for both the non-biologic failure and biologic-failure subgroups, and for the overall ITT population. The committee noted that these subgroups were defined differently to those in the NICE scope, and that in many trials of ulcerative colitis therapies patients are classified based on biological-treatment exposure status rather than biological-treatment failure status. The committee heard that there was considerable overlap in the definitions, however, with 94% of patients in the UNIFI non-biologic failure subgroup having had no previous exposure to biological therapy. The committee concluded that UNIFI data are generalisable to the population who would be eligible to have treatment with ustekinumab in the NHS. It also concluded that the results demonstrated that ustekinumab is more effective than placebo at inducing and maintaining remission and response in all patients covered by the marketing authorisation.

Issues raised about UNIFI at technical engagement have been resolved and do not affect the interpretation of the trial results

3.4 The committee reviewed the following points raised in technical report issue 1:

- The UNIFI clinical-response results reported in the company submission (CS) do not appear to match those in the New England Journal of Medicine (NEJM) trial report, published in September 2019.
- It is not clear from the information in the CS that blinding was maintained between induction week 8 and the maintenance phase, or that baseline characteristics of patients in the re-randomised groups

were well balanced. Therefore it is not possible to assess whether the study is at high risk of bias.

- The results for placebo 'non-responders' who had 6 mg per kg ustekinumab intravenously at week 8 and were assessed at week 16 are not reported in the CS.

The committee considered a summary of the company's responses to these points, which consisted of further explanations and data. The committee agreed with the ERG that the company's response demonstrated that there are no important discrepancies between the CS and the NEJM article, and that UNIFI is at low risk of bias. The committee considered new UNIFI data that the company provided for patients who had 6 mg per kg ustekinumab intravenously at week 8 and who were assessed at week 16. It agreed that the new data did not change the interpretation of the results for the ITT population in the induction study.

Indirect treatment comparisons

The exclusion of trials carried out in Asian countries from the network meta-analyses (NMAs) has little effect on the cost-effectiveness estimates

3.5 The company identified 5 trials from Asian countries in its systematic literature review. However it decided to exclude these studies from the NMAs that informed its cost-effectiveness analyses. The company tested the effect of its approach by doing sensitivity NMAs that included data from the Asian trials. The ERG identified some methodological problems with these sensitivity NMAs and feedback was sought on these points during technical engagement (see technical report issue 2). The company's response to technical engagement issue 2 resolved one, but not all, of the ERG's concerns about the sensitivity NMAs. The ERG explained that some of the company's inclusion and exclusion decisions about the sensitivity NMAs remained inappropriate. The ERG did, however, note that the Asian trials were relatively small. The overall effect on the results of the sensitivity NMAs was therefore likely to be low, and

the main NMAs produced similar results to the sensitivity NMAs. The ERG concluded that excluding the Asian trials from the NMAs had little effect on the cost-effectiveness estimates. The committee noted that responses to technical engagement indicated that there was no clinical rationale for excluding the Asian trials, and that it would have been more appropriate for them to be included in the analyses that informed the economic model. Overall, it agreed with the ERG that this issue has little effect on the cost-effectiveness estimates and decided to further consider the NMAs that excluded the Asian trials.

The maintenance-phase NMAs are uncertain but provide more robust estimates of relative effectiveness than the company's unadjusted indirect treatment comparison (ITC)

3.6 The committee agreed with the ERG that the company's induction-phase NMAs were methodologically robust and provided a suitable source of clinical data for the transition probabilities in the induction phase of the model. However, the committee noted that estimating the relative effectiveness of ustekinumab and its comparators in the maintenance phase by combining data from different trials was methodologically challenging, because of the lack of head-to-head trial data and differences in the trial designs. It was aware that the company had explored both the adjusted NMA and the unadjusted indirect comparison methods, and that the company's preference was to use the results of its unadjusted ITC to inform the cost-effectiveness estimates. The committee was aware that the ERG considered the results of the company's unadjusted ITC to be unreliable, and had therefore used results from the company's and its own NMAs to inform its exploratory analyses. The committee was aware that feedback had been sought at technical engagement (see technical report issues 4 and 5) to try to understand if any of the methods explored by the company and the ERG were more appropriate, or if other types of analyses should have been done. The committee reviewed the responses to the engagement issues 4 and 5 and noted the following:

- No new data have been provided to support the assertion that heterogeneity in the placebo arms of the re-randomised maintenance-phase data is mainly caused by the continuing effects of induction treatment.
- The company asserted that drug half-life is a cause of the continuing effects of induction treatment being observed during the maintenance phase. But evidence provided by a comparator company suggests there is no correlation between drug half-life and placebo-arm response rates.
- The ERG and the company agreed that further analyses using existing data are unlikely to reduce the outstanding uncertainties.

The clinical experts commented that multiple differences between the trials mean that they are not comparable. For example, the approaches to corticosteroid tapering varied. The committee considered the different approaches to combining the maintenance phase trial data. It agreed with the ERG that the unadjusted ITC methods preferred by the company are not recommended and the results of these analyses are not robust enough to inform decision making. The committee concluded that both maintenance-phase NMAs had limitations and the results are very uncertain, but because no alternative data are available the results provided the best available estimates of relative effectiveness.

The pooling of the standard and escalated-dose effects in the maintenance phase has little effect on the results

3.7 The committee noted that the company and the ERG had not agreed a preferred approach for the pooling of standard and escalated efficacy dose effects during the maintenance phase (technical report issue 7). The committee concluded that this was a relatively minor issue compared with the other uncertainties in the maintenance analyses and did not have a major effect on decision making.

The company's economic model

The model is appropriate for decision making

3.8 The company estimated the cost effectiveness of ustekinumab 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 2 subgroups defined by biological-treatment failure status, but not for the overall population. The committee noted that the ERG had used the same model for its base-case analyses, but with different assumptions including the proportions of patients experiencing response and remission after the failure of initial treatment. The committee considered the health-state definitions, recalling the clinical experts' comments that many patients in the population of interest have chronically active disease that is controlled with the long-term use of corticosteroids. The committee concluded that the company's 'active disease' health-state definition (Mayo score between 6 and 12 points, 'remission or response without remission not achieved') did not necessarily apply to this group of patients. The clinical experts commented that if patients taking corticosteroids long term stop treatment, they are likely to start experiencing active disease again over time. On this basis, the committee accepted that, although the model structure did not explicitly account for patients with disease that was being controlled through the long-term use of corticosteroids, for the purposes of the model, these patients could be considered similar to those with active disease. It therefore concluded that the model structure was suitable for decision making.

The committee accepted the assumption that 30% of patients would have escalated doses of maintenance treatment

3.9 The committee noted that in response to technical engagement issue 6, the company had adjusted its base-case assumptions about dose escalation for patients having maintenance infliximab to reflect the ERG's

preference. The ERG assumed that for all drugs included in the analysis, 30% of patients would have an escalated maintenance dose, even though the escalated dose for infliximab is not licensed in the UK. The committee noted that other responses to engagement indicated that off-label use of escalated-dose infliximab is common UK practice but that escalation rates vary between biological therapies. The clinical experts agreed that infliximab dose escalation is common practice but noted that the variation in escalation rates across treatments cited in the engagement responses was not realistic. The committee recognised that there was some uncertainty about this issue. It concluded that this was not a major driver of cost effectiveness, and it was willing to accept the company's revised assumption.

Response rates and remission rates are uncertain for patients with disease that does not respond or loses response to initial therapy

3.10 The committee noted that ulcerative colitis is not always a chronically active disease and many people with ulcerative colitis have ongoing periods of relapse and remission. The company and ERG base-case analyses used different assumptions for response rates and remission rates in patients whose disease did not respond or lost response to initial therapy. The committee noted that the responses to technical engagement issue 3 had not provided any additional clarity on this issue because the additional evidence provided by the company was of low quality. Comments from a patient organisation suggested that most patients continue to experience active disease until surgery or death, but this is not the same as assuming that no patients experience an improvement in symptoms. The company, the ERG and the clinical experts all acknowledged that there is limited evidence about the course of the disease after initial treatment failure. However, the clinical experts stated that for patients such as those in the UNIFI trial they would not expect many, if any, patients to experience an improvement in symptoms unless they were on corticosteroids. The committee considered that the

ERG's assumption might be considered optimistic. It concluded that it was not possible to estimate the rates of response and remission for patients with disease that did not respond or lost response to initial therapy, but it was likely to be nearer the company's assumption of a 0% response rate.

Utility values in the economic model

The utility values are uncertain and the choice of inputs has a large effect on the cost-effectiveness estimates

3.11 The committee noted that the company and the ERG had used the same utility values in their base cases but that other sources of utility data are available. They could have used values for response, response without remission, and active ulcerative colitis health states based on EQ-5D-5L data collected in UNIFI. The committee noted that the data selected by the company and the ERG for these health states came from a publication by Woehl et al. 2008. The utility value for the 'active disease' state in this publication was considerably lower (0.41) than the equivalent value derived from the UNIFI EQ-5D-5L data. Because of this, the choice of utility data inputs has a large effect on the cost-effectiveness estimates. The committee noted that the Woehl et al. 2008 data had been considered in all previous ulcerative colitis appraisals but that the reliability of the utility estimates had also been a source of controversy in all the previous appraisals. The committee noted that the Woehl et al. 2008 publication is only available as an abstract that includes little information about the study methodology or the characteristics of the patients it included. Consequently, it is difficult to judge whether the patients in Woehl et al. 2008 are representative of the population of interest. The committee noted that the sample size of Woehl et al. 2008 is smaller than the sample included the UNIFI EQ-5D analyses. It also noted that the ERG cited consistency with other appraisals as the only reason for choosing the Woehl et al. 2008 data over the UNIFI data, and that they considered the UNIFI analyses to be well conducted. The committee acknowledged that there were limitations with the trial-based utility values.

It noted that the trial data had been 'cross-walked' to the EQ-5D-3L scale and that results from this mapping analysis lacked some face validity because the maximum values for all health states were found to be the same (0.92). The committee also recognised that the UNIFI EQ-5D data may be subject to placebo effects. It noted that the length of time over which the data were collected was probably inadequate for estimating the real effect of the disease on health-related quality of life. The committee recalled the patient expert's description of the disease experience, and decided that it was plausible that some of the effects on health-related quality of life (such as feeling out of control) might not have been captured in either the Woehl et al. 2008 or the UNIFI analyses. The committee concluded that both data sources had some strengths and some limitations, and the choice of data sources had a large effect on the cost-effectiveness estimates.

Cost-effectiveness estimates

The most plausible incremental cost-effectiveness ratios (ICERs) for ustekinumab are highly uncertain

3.12 The committee considered the ERG's cost-effectiveness estimates, which incorporated the confidential comparator discounts. The committee noted that the ERG had presented a number of scenarios, which included the confidential patient access schemes and also the Commercial Medicines Unit prices for the comparators and for ustekinumab. The committee recalled that it had not accepted the company's unadjusted ITC (see section 3.6). It therefore concluded that the company's revised base case and any scenarios that were informed by these analyses should not inform its decision making. It also recalled that the ERG's base-case assumption that 5.5% of patients would experience response every 8 weeks, after not responding or losing response to initial therapy, was unrealistic and that an assumption of between 0% and 1% of patients was more likely (see section 3.10). The committee therefore considered that the key scenarios are those in which:

- the estimates of clinical effectiveness used to inform transition probabilities in the maintenance phase were derived from either the company's 1-year conditional-on-response NMA or the ERG's maintenance-only NMA, and
- response rates and remission rates for patients with disease that did not respond or lost response to initial therapy were assumed to be 0% or 1%.

The committee noted that the ICERs for all the key scenarios across both subgroups, using the utility values from Woehl et al. 2008, are:

- above £30,000 per quality-adjusted life year (QALY) gained compared with the next most cost-effective therapy in the fully incremental analyses when ustekinumab was not dominated or extendedly dominated by the other comparators (that is, an intervention is dominated if it has higher costs and worse outcomes than an alternative intervention). These ICERs are commercial in confidence and cannot be reported here
- between £24,849 and £35,512 per QALY gained compared with conventional therapy in the pairwise analyses.

The committee recognised that these cost-effectiveness estimates are sensitive to changes in the following 3 parameters, all of which are very uncertain:

- the estimates of clinical effectiveness used to inform transition probabilities in the maintenance phase (see section 3.6)
- response rates and remission rates for patients with disease that did not respond or lost response to therapy (see section 3.10)
- the source of the utility data (see section 3.11). For example, using the UNIFI data instead of Woehl et al. 2008 increases the company base-case ICER compared with CT by £55,344 and £61,651 per QALY

gained for the non-biologic failure and biologic-failure groups respectively.

The committee therefore concluded that the ICERs for all the key scenarios are highly uncertain.

Conclusion

Ustekinumab is not recommended

3.13 Depending on the assumptions made, the ICERs varied from marginally below to above the range that would be considered a cost-effective use of NHS resources. However, because of the high level of uncertainty around a number of the parameters, the committee concluded that ustekinumab cannot be recommended for treating moderate to severely active ulcerative colitis.

4 Proposed date for review of guidance

4.1 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.

Brian Shine
Chair, appraisal committee
January 2020

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.

Juliet Kenny
Technical lead

Joanna Richardson
Technical adviser

Thomas Feist
Project manager

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