NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Draft guidance consultation

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

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

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

The evaluation 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 age, disability, gender reassignment, pregnancy and maternity, race, religion or belief, sex or sexual orientation?

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- After considering these comments, the committee will prepare the final draft guidance.
- Subject to any appeal by stakeholders, the final draft guidance may be used as the basis for NICE's guidance on using risankizumab in the NHS in England.

For further details, see NICE's manual on health technology evaluation.

The key dates for this evaluation are:

- Closing date for comments: 17th February 2023
- Second evaluation committee meeting: 7th March 2023
- Details of membership of the evaluation committee are given in section 4

1 Recommendations

1.1 Risankizumab is not recommended, within its marketing authorisation, for treating moderately to severely active Crohn's disease in people 16 years and over that has not responded well enough or lost response to conventional treatment or a biological treatment, or when these treatments are not tolerated or suitable.

1.2 This recommendation is not intended to affect treatment with risankizumab 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. For young people, this decision should be made jointly by the clinician, the young person, and their parents or carers.

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 adalimumab, infliximab, ustekinumab and vedolizumab). Risankizumab is another biological treatment.

Clinical trial evidence suggests that risankizumab reduces symptoms and increases the likelihood of disease remission compared with placebo whether used as a first or second biological treatment. It is not clear how risankizumab compares with other biological treatments. This is because risankizumab has only been compared indirectly with them and the results are uncertain because of differences between the populations included in the trials and how the trials were carried out.

The company’s economic model estimates that risankizumab is less effective and more expensive than other biological treatments for people having a first biological treatment. The cost-effectiveness estimates for risankizumab for people who have already had a biological treatment are above the range NICE considers a cost-

effective use of NHS resources. These estimates are uncertain because the company's economic model does not reflect NHS clinical practice and new analyses are needed. So, risankizumab is not recommended.

2 Information about risankizumab

Marketing authorisation indication

2.1 Risankizumab (Skyrizi, AbbVie) is indicated for 'the treatment of patients 16 years and older with moderately to severely active Crohn's disease who have had an inadequate response to, lost response to, or were intolerant to conventional therapy or a biologic therapy, or if such therapies are not advisable'.

2.2 The CE mark for the on-body device that is used to deliver the 360 mg risankizumab solution for injection has not been granted yet. If risankizumab was recommended for moderately to severely active Crohn's disease it would only be available in the UK for this indication after this CE mark is granted.

Dosage in the marketing authorisation

2.2 The dosage schedule is available in the summary of product characteristics for risankizumab.

Price

2.3 The company have stated that the list prices of 600-mg concentrate for solution for infusion (induction treatment) and the on-body device with 360-mg solution for injection (maintenance treatment) are confidential until they are commercially available and cannot be reported here.

2.4 The company has a commercial arrangement. This makes risankizumab available to the NHS with a discount and it would have also applied to this indication if the technology had been recommended.

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.

Crohn's disease

3.1 Crohn's disease is a debilitating chronic relapsing systemic inflammatory bowel disease. It causes inflammation and mucosal ulceration anywhere in the digestive system. It is a lifelong condition. Symptoms include diarrhoea, abdominal pain, fatigue, loss of appetite, weight loss, blood or mucus in stool, and anaemia. Symptoms may vary over time and can last anywhere from a few days to several months. Persistent inflammation can lead to scarring of the bowel and further complications needing surgical treatment. Current treatments aim to relieve symptoms, promote mucosal healing, and maintain or improve quality of life by causing disease remission while minimising drug-related toxicity. However, Crohn's disease often relapses and people can experience acute exacerbations (flares). Crohn's disease can present a major barrier to a person's ability to participate in daily life, severely affecting their self-esteem, social functioning, work, personal relationships, family life and other activities. One patient expert explained that treatments that induce remission are of great importance to patients, because debilitating symptoms are not controlled unless the condition is in remission. Treatments which induce remission can also delay the need for surgery which is of importance to patients. People with Crohn's disease fear the loss of remission and the arrival of flares because of the major impact these have on their life. The committee concluded that Crohn's disease can have a profound effect on people's quality of life and ability to do day-to-day activities.

Clinical management

Treatment options

3.2 Traditionally, the initial treatment for Crohn's disease is conventional treatment with corticosteroids and immunomodulators such as azathioprine, mercaptopurine and methotrexate. If these treatments fail, patients are offered biological treatments. The clinical experts stated that tumour necrosis factor-alpha (TNF-alpha) inhibitors (infliximab or adalimumab, including biosimilars) are usually used first. Ustekinumab or vedolizumab are used when a TNF-alpha inhibitor has failed, is contraindicated or cannot be tolerated (NICE technology appraisal guidance on infliximab and adalimimuab, ustekinumab and vedolizumab). The patient expert noted that NICE's technology appraisal guidance on infliximab and adalimumab, and ustekinumab, recommends that when more than 1 treatment is suitable the least expensive option should be used. NICE recommendations for infliximab, adalimumab, ustekinumab, and vedolizumab also state that the benefit of continuing these agents should be assessed at 1 year. The clinical experts explained that, when there is evidence of clinical benefit, therapy continues beyond 1 year and that stopping effective treatments would be very rare. The clinical experts stated that if the treatment no longer works (including after a dose increase if relevant), another biological treatment would be considered. The clinical experts stated that although there are several clinically effective biological treatments for Crohn's disease, these do not cause long-term disease remission for everyone and people may have a sequence of biological treatments. The clinical and patient experts agreed that it is very important to have a range of treatment options to enable more people to gain and regain remission and delay surgery. The committee concluded that the availability of a further treatment option to improve symptoms and bring the disease into remission would be highly valued by people with Crohn's disease.

Risankizumab and comparators

3.3 Risankizumab is a novel treatment with a different mechanism of action to existing treatments. The company proposed it can be used either after conventional treatment (referred to as the conventional care failure

population) or after a biological treatment (biological treatment failure population) as an additional biological option. The clinical experts explained that treatment is not dependent on disease location. They agreed with the company's positioning of risankizumab in the clinical pathway and that it was relevant to consider both the conventional care failure and biological treatment failure population. However, they noted that it would probably be used more after biological treatment. This is because TNF-alpha inhibitors are an effective and cheap treatment option (because biosimilars are available), and as such most people have them first. The patient expert highlighted the need for patients to have access to the most effective treatment first, because it can take years before they find an effective treatment and the process can delay finding a treatment that causes disease remission. The committee concluded that risankizumab could be used as an option both in the conventional care failure and biological treatment failure populations. The committee further concluded that the relevant comparators for the conventional care failure population are adalimumab, infliximab and ustekinumab. The relevant comparators for the biological treatment failure population are vedolizumab and ustekinumab.

Clinical trials

3.4 The clinical evidence is from the phase 3 ADVANCE, MOTIVATE and FORTIFY trials. ADVANCE (n=931) and MOTIVATE (n=618) are multicentre, double-blind, placebo-controlled randomised induction trials. They recruited people with moderately to severe active disease that had an inadequate response to conventional treatments (MOTIVATE) or biological treatments (ADVANCE and MOTIVATE). Moderately to severe active disease was defined by a Crohn's Disease Activity Index (CDAI) score of 220 to 450, average stool frequency of 4 or more or abdominal pain score of 2 or more, and Simple Endoscopic Score for Crohn's disease (SES-CD) of 6 or more (4 or more for isolated ileal disease). People had intravenous 600 mg or 1,200 mg risankizumab or placebo at weeks 0, 4 and 8. People whose disease did not respond at week 12 had

a second induction with risankizumab (1,200 mg intravenously, 360 mg subcutaneously or 180 mg subcutaneously). The company used data from ADVANCE or MOTIVATE for the induction regimen covered by the marketing authorisation for risankizumab that is 600mg, or placebo. Of these 219 people in ADVANCE were in the conventional care failure population subgroup and 292 were in the biological treatment failure population subgroup. All 378 people in MOTIVATE who had 600mg risankizumab or placebo had had a previous biological treatment. People whose disease responded to treatment entered FORTIFY, a phase 3 multicentre, double-blind, placebo-controlled partially randomised maintenance trial. FORTIFY substudy 1 (n=542) re-randomised people to subcutaneous 180 mg or 360 mg risankizumab or placebo every 8 weeks for 52 weeks. The company included data from FORTIFY from people who had 1 induction with intravenous risankizumab and the treatment regimen covered by the marketing authorisation for risankizumab, that is who had 360 mg risankizumab or placebo (n=305). Of these, 80 people were in the conventional care failure population subgroup and 225 people were in the biological treatment failure population. The committee concluded that the data that the company presented from the trial was generalisable to how risankizumab would be used in clinical practice.

Primary outcomes

3.5 The co-primary outcomes for all 3 trials were clinical remission and endoscopic response. Clinical remission was measured by a CDAI score below 150 or patient-reported outcomes on stool frequency and abdominal pain (both outcomes were collected in all trials). The SES-CD was used to measure endoscopic response (co-primary outcome alongside either measure of clinical remission). The clinical experts explained that the CDAI is used primarily in clinical trials as a measure of remission but not in clinical practice because of the time needed to complete the measurements included in this index. The clinical experts stated that the Harvey-Bradshaw Index is broadly comparable to the CDAI and is used in clinical practice. A clinical expert stated that the SES-CD is

used increasingly in clinical practice. The committee concluded that the measures of remission assessed in the trial would give applicable estimates of expected remission and endoscopic response rates in clinical practice.

Results

3.6 The results from the induction studies suggest that risankizumab is associated with higher rates of clinical remission and endoscopic response compared with placebo in the conventional care failure and biological treatment failure populations. The results from FORTIFY suggest that risankizumab is associated with higher rates of endoscopic response compared with placebo in the conventional care failure and biological treatment failure populations. The committee noted that the FORTIFY subgroup results in the conventional care failure and biological treatment failure populations were not statistically significant for clinical remission assessed by CDAI. The committee concluded that risankizumab is associated with higher rates of clinical remission and endoscopic response compared with placebo when used as a first biological treatment or after a previous biological treatment.

Clinical effectiveness

Network meta-analyses

3.7 Because of the lack of direct comparative evidence, the company did network meta-analyses for induction and maintenance treatment in the conventional care failure and biological treatment failure populations. The outcomes assessed were clinical remission and response (defined by CDAI). The company used a Bayesian risk difference fixed effects model. For the network meta-analyses for maintenance treatment the company split the clinical trial evidence into 2 separate networks (risankizumab and ustekinumab, and adalimumab, infliximab and vedolizumab). It stated it chose this approach because:

- of differences in drug mechanism of action, induction duration and half-life
- single network analyses lacked face validity (the estimated rates of remission were higher in people treated with placebo)
- of methodological challenges in accounting for the heterogeneity.

The EAG disagreed with the company on:

- Splitting networks. The EAG noted that connections in network meta-analyses should be based on comparator connections, not drug characteristics. It also noted ustekinumab and vedolizumab, used in the different networks, have a similar half-life and are comparable treatment options. The EAG presented results using a single network. The committee agreed that a single network was more appropriate.
- Use of a fixed effect rather than a random effects model. The EAG agreed with the company that there were several differences between the trials which made doing network meta-analyses more challenging. This included differences in baseline risks, stratification by the conventional care failure and biological treatment failure populations, and an observed temporal effect in which remission rates in placebo groups appeared higher in later trials. Given these differences, using a random effects model is more appropriate. The committee noted the company's concerns that its exploration of a random effects model produced results with wide confidence intervals and included values which favoured placebo over biological treatments. However, the committee agreed with the EAG that a random effects model was preferable.
- Lack of adjustment for baseline risks or temporal effect. The EAG noted that the company's risk difference approach is not an adjustment for heterogeneity. The committee agreed that there was no evidence that the company's approach minimised differences between placebo group results between trials in the network. The EAG preferred to include an

adjustment for the temporal effect observed in placebo remission rates. The committee agreed an adjustment for temporal effect was needed.

Overall, the committee concluded that it preferred the EAG's approach because it was more methodologically appropriate, but that the relative clinical effectiveness of risankizumab compared with other biological treatments was highly uncertain with either approach. The committee further noted that models using risk ratios rather than risk differences, given the heterogeneity of studies in the network, may be more informative to compare risankizumab with the other biological treatments. This is because relative effect tends to be more stable across risk groups than absolute risk and also it would allow further exploration of data to improve the precision of the modelled comparative effectiveness estimates (by using an informative prior) to be more straightforward.

On-body device

3.8 Risankizumab maintenance treatment will be delivered by a single-use on-body injector with a single-use cartridge. However, in FORTIFY (see section 3.4) risankizumab was administered in 4 subcutaneous injections using a syringe. The committee was satisfied that results from other trials showed bioequivalence of risankizumab administered using the on-body device and using subcutaneous injections. However, it noted that the level of adherence to treatment could differ from that observed in the trial because of lack of experience with the device. The patient experts said that a new treatment option is needed regardless of the delivery method, noting that they are likely to prefer the on-body device to the 4 injections that were used in the trial. However, they explained that some drug delivery can be painful and that they do not know what it will be like with the on-body device. They highlighted a need for a quiet and 'less jarring' drug delivery mechanism than that associated with some other subcutaneous therapies for Crohn's disease. The EAG said that the implications for costs and patient outcomes are unknown. The committee concluded that the on-body device is likely to be welcomed by people with

Crohn's disease, but agreed that further exploratory analyses are needed (see section 3.14).

Company's economic model

Model structure

3.9 The company presented a model comparing risankizumab with other biological treatments in the conventional care failure and biological treatment failure populations. It consisted of a short-term induction phase (a decision tree) and a long-term maintenance phase (a Markov state transition model). It assumes that people with moderately to severely active Crohn's disease have the same mortality as the general population. The maintenance phase modelled people having risankizumab or other biological treatments after a response to induction, or having conventional care if their Crohn's disease had not responded to induction therapy. After the first biological treatment all people were modelled to have conventional care. With each maintenance treatment people were modelled to be in one of 4 health states – remission (CDAI below 150), mild disease (CDAI 150 to below 220), moderate to severe disease (CDAI 220 to below 600) and surgery. It assumes that people with moderate to severe disease could have surgery (constant rate across treatment arms based on NHS hospital episode statistics annual rates) and after 8 weeks they return to CDAI-based health state. The EAG explained that the CDAI used in the model to define clinical response and remission, and the severity of the disease, is not used in clinical practice. However, the clinical experts explained that the CDAI measure correlates with the Harvey-Bradshaw Index which is commonly used in clinical practice. The EAG further explained that the model does not reflect the lifelong relapsing–remitting nature of Crohn's disease because it does not allow patients to have multiple biological treatments. Instead, it assumes all people have conventional care after a biological treatment. The company explained that a similar structure was used in previous NICE technology appraisals of treatments for Crohn's disease. The clinical experts agreed

with the EAG that the model does not reflect the current clinical pathway. Overall the committee concluded that although a CDAI-based model may be appropriate, the model is not suitable for decision-making because it did not reflect the treatment pathway in which people can have more than 1 biological treatment.

Treatment duration

3.10 In the model people could either discontinue treatment because of a lack of efficacy or once they had reached assumed maximum treatment duration. The company assumed a 1-year maximum treatment duration. The EAG assumed 20-year maximum treatment duration and applied the company's rate of discontinuing treatment because of a lack of efficacy for 20 years. The company explained that 1-year maximum duration is consistent with modelling in previous NICE technology appraisals of treatments for Crohn's disease. The EAG noted that most patients were still on treatment at 1 year in FORTIFY and that 1 year does not reflect the lifelong nature of Crohn's disease. The clinical and patient experts agreed with the EAG that 1-year maximum treatment duration does not reflect clinical practice and would not be fair for patients. The company confirmed that in clinical practice it was not intended that there would be a 1-year stopping rule for risankizumab. The committee concluded that the 1-year maximum treatment duration assumption in the model was too short and that the EAG's 20-year maximum treatment duration is more reflective of clinical practice in England and appropriate for decision-making.

Transition matrices in the maintenance model

3.11 The chance of moving between CDAI-defined remission, mild, and moderate to severe health states in the maintenance model was estimated using data on the proportions of people in these health states from ADVANCE and MOTIVATE at the end of the induction and at the end of FORTIFY (52 weeks). The company developed an ordered probit model which estimated the chance of being in each health state at 26 weeks and used further modelling assumptions to model the chance of

moving between each health state for each 2-week cycle of the model. For the comparators, there was a further adjustment (calibration) made so that the proportions of people modelled to be in remission reflected the network meta-analyses results at 52 weeks. The company did this by adjusting the chance of transitioning by 1 health state transition point only, between remission and mild health states. The EAG noted that the company's modelling approach meant that the modelled results including further calibration for cycle length and comparator network meta-analyses results did not align with the ordered probit results at 26 weeks. It explained that calibration of the comparators adjusting both 26- and 52-week health state transition points for both mild and moderate to severe transition, as well as the transition from remission to mild, achieved the most consistent results with the underlying data. The EAG also used a different modelling approach for changing transition probabilities to a 2-week cycle length and aligned transition probabilities to both the ordered probit model and network meta-analyses estimates, because it was more methodologically appropriate. In addition, the EAG used its preferences for the network meta-analyses. The committee concluded that it preferred the EAG approach.

Other assumptions

3.12 The model assumes that dose escalation may occur on comparator treatments. In the modelling this only affects cost, but not clinical effectiveness. The EAG suggested that because dose escalation is only used for comparators it may favour risankizumab in the cost-effectiveness analysis. The company used clinical data for standard doses in the model. The committee noted that high-dose data are available in the studies included in the network meta-analyses. The committee concluded that, if possible, further exploration of these assumptions would be helpful.

Cost-effectiveness results

3.13 Because there are confidential prices for comparators the exact cost-effectiveness results cannot be reported here. In the conventional care

failure population, risankizumab was dominated meaning it was more expensive and less effective than another biological treatment, in both the EAG and the company's preferred base case. In the biological treatment failure population, the incremental cost-effectiveness ratios (ICERs) for risankizumab were above £30,000 per quality-adjusted life years (QALY) gained in both the EAG and company's preferred base case. The results in both populations suggest that risankizumab is not cost effective. However, because the model is not suitable for decision-making (see section 3.9), the committee concluded that ICERs are not suitable for decision-making.

New analyses are needed

3.14 The committee found the model structure not suitable for decision-making (see section 3.9) and also recalled the limitations of the network meta-analyses comparing the clinical effectiveness of risankizumab with the biological treatments in both the conventional care failure and biological treatment failure populations (see section 3.7). It further noted the minimal QALY gain in the current cost-effectiveness analyses. The committee noted that cost-comparison analyses may be considered in NICE technology appraisals if it is shown that a technology has the same clinical effectiveness as a technology which has already been recommended by NICE for the same indication. It agreed that given the uncertainty of the network meta-analyses and the potential similarity of the biological treatments being compared, a cost comparison may be appropriate. Therefore the committee would like to see updated network meta-analyses, for the company to explore the similarity of the biological treatments and cost-comparison analyses if appropriate. It reiterated its preference for the company to:

- use a single network with an adjustment for temporal effect, using risk ratios rather than risk difference and presenting the credible intervals around the estimates

- explore random effects models as well as fixed-effect models (see section 3.7).

However, if the company chooses to present updated results using cost-utility analyses, a new model that explores the sequence of biological treatments is needed. The committee asks the company to apply its preference in regard to model structure (see section 3.9), treatment duration (see section 3.10), transition matrices in the maintenance model (see section 3.11) and other assumptions (see section 3.12). It would also welcome exploratory analyses around the effects of the on-body device on treatment discontinuation and wastage (see section 3.8). The committee concluded that further analyses are needed from the company.

Conclusion

3.15 The committee found the company's model unsuitable for decision-making (see section 3.9) and asked the company to provide new analyses (see section 3.13). The current model also estimated that risankizumab is less effective and costs more than other treatments in people having a first biological treatment. The cost-effectiveness estimates for people having risankizumab after a biological treatment are above the range considered to be a cost-effective use of NHS resources (see section 3.13). This means risankizumab cannot be recommended for treating moderately to severely active Crohn's disease.

Other factors

Equality issues

3.16 No equality or social value judgement issues were identified.

4 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

James Fotheringham
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.

Marcela Haasova
Technical lead

Mary Hughes
Technical adviser

Jeremy Powell
Project manager

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