NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Final appraisal document

Upadacitinib for treating active ankylosing spondylitis

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

1 Recommendations

1.1 Upadacitinib is recommended as an option for treating active ankylosing spondylitis that is not controlled well enough with conventional therapy in adults, only if:

- tumour necrosis factor (TNF)-alpha inhibitors are not suitable or do not control the condition well enough, and
- the company provides upadacitinib according to the commercial arrangement (see section 2.4).

1.2 Assess response to upadacitinib after 16 weeks of treatment. Continue treatment only if there is clear evidence of response, defined as:

- a reduction in the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) score to 50% of the pre-treatment value or by 2 or more units and
- a reduction in the spinal pain visual analogue scale (VAS) by 2 cm or more.

1.3 Take into account any physical, sensory or learning disabilities, or communication difficulties that could affect the responses to the BASDAI and spinal pain VAS and make any appropriate adjustments.

1.4 If people and their clinicians consider upadacitinib to be one in the range of suitable treatments which includes secukinumab and ixekizumab, the least expensive should be chosen (taking into account administration costs, dosage, price per dose and commercial arrangements)

1.5 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

Upadacitinib is proposed as an alternative to biological therapies already recommended by NICE (secukinumab and ixekizumab) for treating active ankylosing spondylitis in adults. Evidence from clinical trials shows that upadacitinib is more effective than placebo. Indirect comparisons suggest that upadacitinib is likely to provide similar health benefits compared with secukinumab.

Although the committee was presented with evidence for a cost comparison including both ixekizumab and secukinumab, upadacitinib compared with secukinumab was the most relevant comparison in line with current NHS practice. The total costs associated with upadacitinib are similar to or lower than those associated with secukinumab and ixekizumab. Therefore, upadacitinib is recommended as an option for use in the NHS for active ankylosing spondylitis that is not controlled well enough with conventional therapy and when TNF-alpha inhibitors are not suitable or do not control the condition well enough.

2 Information about upadacitinib

Marketing authorisation indication

2.1 Upadacitinib (RINVOQ, AbbVie) is “indicated for the treatment of active ankylosing spondylitis in adult patients who have responded inadequately to conventional therapy”.

Dosage in the marketing authorisation

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

Price

2.3 The list price is £805.56 per 28-tablet pack, with each tablet containing 15 mg of upadacitinib (excluding VAT; BNF online, accessed June 2022).

The annual cost of treatment with 1 15 mg tablet per day is £10,508.24 (excluding VAT; BNF online, accessed June 2022)

2.4 The company has a commercial arrangement (simple discount patient access scheme). This makes upadacitinib available to the NHS with a discount. The size of the discount is commercial in confidence. It is the company's responsibility to let relevant NHS organisations know details of the discount.

3 Committee discussion

The appraisal committee considered evidence submitted by AbbVie, a review of this submission by the evidence review group (ERG), and responses from stakeholders. See the committee papers for full details of the evidence.

Decision problem

A cost comparison analysis with secukinumab as the comparator was the most appropriate decision problem

3.1 The company proposed that upadacitinib should be considered in adults as an alternative to the currently NICE recommended IL-17 inhibitors secukinumab and ixekizumab for ankylosing spondylitis that is not controlled well enough with conventional therapy and when TNF-alpha inhibitors are not suitable or do not control the condition well enough (biologic-experienced population). The company's proposed decision problem was narrower than upadacitinib's marketing authorisation because it excluded people who had TNF-alpha inhibitors. However, the committee agreed that the proposed population was consistent with previous NICE recommendations for IL-17 inhibitors for ankylosing spondylitis, and with their use in clinical practice. The company presented a comparison with 2 NICE-recommended IL-17 inhibitors (NICE technology appraisal guidance on secukinumab for treating non-radiographic axial spondyloarthritis and ixekizumab for treating axial spondyloarthritis). The committee agreed that this was consistent with the

criteria for a cost-comparison appraisal (see section 3.7). The clinical expert explained that secukinumab was likely to be chosen over ixekizumab by clinicians. The committee was aware that secukinumab was recommended for ankylosing spondylitis in 2016, while ixekizumab was recommended in 2021. It considered both comparators relevant but reasoned that secukinumab is more established in NHS clinical practice than ixekizumab. The committee recalled that NICE's technology appraisal guidance on secukinumab and ixekizumab recommends that treatment should stop if there is an inadequate response at 16 weeks or after 16 to 20 weeks, respectively. An adequate response is defined as:

- a reduction in the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) score to 50% of the pre-treatment value or by 2 or more units and
- a reduction in the spinal pain visual analogue scale (VAS) by 2 cm or more.

The committee considered that it would be reasonable to apply the same approach for this appraisal. It concluded that secukinumab was the more relevant comparator and represented the decision problem which had the most validity to NHS clinical practice.

Clinical effectiveness

Upadacitinib is more clinically effective at reducing symptom burden than placebo

3.2 Upadacitinib has been studied in 1 randomised controlled trial including approximately 420 adults with active ankylosing spondylitis (SELECT-AXIS2). It was compared with placebo. In SELECT-AXIS2, upadacitinib was associated with statistically significant improvements compared with placebo in primary and secondary outcomes, including the Assessment in Spondyloarthritis international Society 40% (ASAS40) response, BASDAI50 and total back pain score. The clinical expert explained that

the ASAS score is mostly used in clinical trials as a measure of treatment effect. In clinical practice, the BASDAI or back pain score are used to assess treatment response (see section 3.1). Upadacitinib was associated with higher ASAS40 and BASDAI50 responses, and total back pain score improvement at week 14 than placebo (results cannot be shown here because of confidentiality). People having upadacitinib also had statistically significantly higher scores in the Ankylosing Spondylitis Quality of Life (ASQoL) measure. The committee concluded that upadacitinib was more clinically effective than placebo.

The company's network meta-analyses are suitable for decision making

3.3 The company did a series of network meta-analyses comparing upadacitinib to secukinumab on measures of efficacy, including ASAS40 and BASDAI50 response rates. It provided results with fixed effect and random effects models for people with ankylosing spondylitis that has not been treated with biologic therapies (biologic-naïve population). The company did not carry out any analyses comparing upadacitinib to secukinumab for people with ankylosing spondylitis that has been treated with 1 or more biologic therapies (biologic-experienced population). It argued that the published secukinumab trials included few people with people with ankylosing spondylitis that has been treated with biologic therapies. Also, it indicated that the inclusion criteria and patient populations in the secukinumab trials were different from the SELECT-AXIS2 trial. The network meta-analyses for the biologic-naïve population did not find any significant differences between upadacitinib and secukinumab for any of the outcomes analysed. However, the ERG indicated that the results are uncertain and that this could favour upadacitinib. The company extrapolated the results of the biologic-naïve population analyses to the biologic-experienced population based on clinician opinion that upadacitinib would have similar efficacy in both populations. The clinical expert confirmed that they would expect upadacitinib would have similar efficacy in both populations. The committee concluded that the network meta-analyses estimate were

uncertain, but they supported the company's position that upadacitinib is likely to have similar clinical effectiveness to secukinumab.

The company's economic model

It is plausible that the long-term efficacy of upadacitinib is equivalent to the secukinumab, but it is uncertain

3.4 The methods guide states that a cost-comparison analysis requires that the technology have similar health benefits to the comparator over the average time on treatment. The company network meta-analyses compared upadacitinib with secukinumab for outcomes measured between 12 and 16 weeks and found no significant differences (see section 3.3). The ERG indicated that there is limited long term data available for upadacitinib's efficacy, which adds uncertainty to the assumption of clinical equivalence between upadacitinib and secukinumab. The ERG also noted that in previous appraisals in ankylosing spondylitis, companies presented trial data for 2 to 5 years of follow up which showed that drug responses were maintained in the long term. The company stated that there is evidence available for upadacitinib's efficacy in the long term (up to 2 years) which shows maintenance of response, but only for biologic-naïve populations. The clinical expert stated that long-term efficacy of upadacitinib (a small molecule drug) was expected to be similar or greater than biological drugs such as secukinumab. This is because biologic drugs can cause an immune response that can lead to their gradual destruction and loss of efficacy over time. However, this is less likely to happen with small molecules such as upadacitinib. The committee considered this explanation biologically plausible. However, it concluded that there was still substantial uncertainty around long term efficacy because of potential safety concerns and whether people will take upadacitinib as intended (see section 3.5 and section 3.6).

There is uncertainty about whether upadacitinib has equivalent discontinuation as secukinumab

3.5 Differences in discontinuation can lead to differences in efficacy and costs between the technology and comparators. The company assumed upadacitinib has an annual discontinuation rate of 11%, based on the rate used in the appraisal of secukinumab. However, it presented limited data on discontinuation rates. The ERG indicated there may be differences in adherence between upadacitinib and secukinumab because upadacitinib is taken daily and this may affect adherence. The company stated that there is no evidence to support the assumption of worse adherence with upadacitinib compared with secukinumab. The clinical expert added that, in their experience, if a drug is working then adherence is likely to be high. The patient expert confirmed this and stated it is unlikely for someone to forget to take the drug because the effect of the disease on all parts of life was so substantial. They also explained that the effect of injectable biologics wears off in the days before the next dose and symptoms worsen as a result. The committee concluded that, whilst there was no evidence to suggest that discontinuation would be different between upadacitinib and secukinumab, there was residual uncertainty which could favour either technology.

There may be additional monitoring costs for upadacitinib that the company did not include in the cost comparison model

3.6 The company base case in the cost comparison model included only drug acquisition, administration and monitoring costs. The ERG raised the issue that the costs of adverse effects and some monitoring costs were excluded. The company did not include annual lipid monitoring in its base case but provided a scenario with these costs included. The ERG base case included these costs and also had slightly different drug acquisition costs, which were due to differences in the assumed duration of a trimester (13.04 weeks compared with 12 weeks assumed by the company). These differences meant that the calculated number of doses of secukinumab in a year were higher in the ERG base case. Also, the

ERG excluded administration costs from its base case because patients would receive training to administer subcutaneous injections when they first start treatment, but do not need it for later lines of subcutaneous treatment. The company stated that they agreed with the ERG base case. The committee considered that the changes proposed in the ERG base case did not have a large effect on the cost-comparison estimates. The ERG also considered that the exclusion of the costs of adverse events could bias the analysis towards upadacitinib if the adverse event profile was different to the comparators in the long term. The clinical expert explained that it was unlikely that adverse events with upadacitinib would be different compared to secukinumab. They highlighted that even if incidence of some viral infections was higher with upadacitinib, this would be made up by the lack of inflammatory bowel issues associated with IL-17 inhibitors such as secukinumab. The committee accepted this but questioned whether, in light of the MHRA safety warning for tofacitinib, there may be additional monitoring costs for upadacitinib, such as electrocardiograms for cardiovascular monitoring or screening for malignancies which, could incur substantial additional costs. The clinical expert stated that they would take into account the MHRA safety warning, and the individual risk of each patient before deciding whether to use upadacitinib. So it is unlikely that additional monitoring costs would be incurred. The committee noted this but concluded that it was still highly uncertain if upadacitinib would incur additional monitoring costs in the longer term as many of these costs were tied to long term safety, which they also considered uncertain.

Cost effectiveness estimates

The total costs associated with upadacitinib are similar to or lower than those associated with secukinumab and ixekizumab

3.7 The company presented a cost-comparison analysis that modelled the total costs of upadacitinib and secukinumab and over 10 years. The committee considered that the comparison against secukinumab was the

most important and represented the most valid decision problem. It considered that the clinical evidence available supported the assumption of clinical equivalence between upadacitinib and secukinumab. The committee preferred the ERG's base case model. Taking into account the confidential patient access schemes for upadacitinib and secukinumab, the committee concluded that the total costs associated with upadacitinib were similar to or lower than those associated with secukinumab (the exact results cannot be reported here because the discounts are confidential).

Upadacitinib is recommended as an option for treating active ankylosing spondylitis in adults

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

- upadacitinib provided similar overall health benefits to secukinumab or ixekizumab and
- the total costs associated with upadacitinib were similar to or lower than the total costs associated with secukinumab or ixekizumab.

The committee therefore recommended upadacitinib as an option for treating active ankylosing spondylitis in adults. It concluded that the recommendations for upadacitinib should be consistent with the company's proposal and NICE's technology appraisal guidance recommendations for secukinumab and ixekizumab, that is:

- when there are objective signs of inflammation (shown by elevated C-reactive protein or MRI) and
- when the condition has not responded to conventional therapy and
- when TNF-alpha inhibitors are not suitable or do not control the condition well enough and

- when treatment is stopped at 16 weeks if the condition has not responded adequately.

Other factors

Equality

3.9 No equality issues were identified that were not addressed in recommendation 1.3.

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 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. Because upadacitinib has been recommended through the fast track appraisal process, NHS England and commissioning groups 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 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 active ankylosing spondylitis that is not controlled well enough with conventional therapy in adults, TNF-alpha inhibitors are not suitable or do not control the condition well enough 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 Date for review of guidance

5.1 The guidance on this technology will be considered for review 3 years after publication. The guidance executive will decide whether the technology should be reviewed based on information gathered by NICE, and in consultation with consultees and commentators.

Charles Crawley
Chair, appraisal committee
August 2022

6 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 B.

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.

George Braileanu

Technical lead

Adam Brooke

Technical adviser

Daniel Davies

Project manager

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