NICE National Institute for Health and Care Excellence

NICE guidance

Ixekizumab for treating axial spondyloarthritis

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 are 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.

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.

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1 Recommendations

1.1 Ixekizumab is recommended as an option for treating active ankylosing spondylitis that is not controlled well enough with conventional therapy, or active non-radiographic axial spondyloarthritis with objective signs of inflammation (shown by elevated C-reactive protein or MRI) that is not controlled well enough with non-steroidal anti-inflammatory drugs (NSAIDs), in adults. It is recommended only if:

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

1.2 Assess response to ixekizumab after 16 to 20 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 communication difficulties, or physical, psychological, sensory or learning disabilities that could affect responses to the BASDAI and spinal pain VAS questionnaires, and make any appropriate adjustments.

1.4 These recommendations are not intended to affect treatment with ixekizumab 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

When people cannot have TNF-alpha inhibitors or they have not worked well enough the current treatment option is conventional therapy. This includes NSAIDs and physiotherapy. Secukinumab is also an option for treating radiographic disease but there is not enough data to reliably compare it with ixekizumab.

Evidence from clinical trials shows that ixekizumab is effective compared with placebo. The cost-effectiveness estimates for ixekizumab compared with conventional therapy are within what NICE usually considers cost effective. Therefore, ixekizumab is recommended.

2 Information about ixekizumab

Marketing authorisation indication

2.1 Ixekizumab (Taltz, Eli Lily) is indicated for 'the treatment of adult patients with active ankylosing spondylitis [radiographic axial spondyloarthritis] who have responded inadequately to conventional therapy, and active non-radiographic axial spondyloarthritis with objective signs of inflammation as indicated by elevated C-reactive protein (CRP) and/or magnetic resonance imaging (MRI) who have responded inadequately to non-steroidal anti-inflammatory drugs (NSAIDs)'.

Dosage in the marketing authorisation

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

Price

2.3 The list price of ixekizumab is £1,125 for 1 pre-filled syringe containing 80 mg per 1 ml solution (excluding VAT; BNF online, accessed March 2021). The annual cost is £16,875 for 15 injections in year 1 and £14,625 for 13 injections in year 2 (excluding VAT; BNF online, accessed March 2021).

2.4 The company has a commercial arrangement. This makes ixekizumab 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 Eli Lily, a review of this submission by the evidence review group (ERG), NICE's technical report, and responses from stakeholders. See the committee papers for full details of the evidence.

The appraisal committee was aware that several issues were resolved during the technical engagement stage, and agreed that:

- The company's approach to modelling functional impairment after treatment discontinuation is appropriate (issue 5, see technical report, page 21).
- The choice of utility regression equation in the economic model is not relevant to the company's updated version of the model because all treatments result in equivalent quality-adjusted life years (QALYs; issue 6, see technical report, page 21).
- The use of a modification factor to convert clinical effectiveness estimates across active ankylosing spondylitis (radiographic disease) populations who have, and have not, had a biologic is not relevant to the company's updated version of the model (issue 7, see technical report, page 21).

It recognised that there were remaining areas of uncertainty associated with the analyses presented (see technical report, pages 23 to 31), and took these into account in its decision making. It discussed the following issues (issues 1, 2 and 3), which were outstanding after the technical engagement stage.

Clinical need and current management

Axial spondyloarthritis is a debilitating condition

3.1 Axial spondyloarthritis is a chronic rheumatic condition characterised by inflammation of the sacroiliac joints and spine, although other joints can be affected. It can lead to functional impairment (difficulties doing day-to-day activities). It can also be associated with conditions affecting the eyes, bowel and skin. Axial spondyloarthritis is an umbrella term. It includes radiographic disease, known as ankylosing spondylitis (AS), in which inflammatory changes in the sacroiliac joints or spine can be seen on X-ray, and non-radiographic axial spondyloarthritis (nr-axSpA). Non-radiographic means there is no visible

structural damage on X-ray but inflammation is visible on MRI or the person has symptoms. The committee heard from the patient expert that symptoms are often present for a long time (7 to 10 years) before the diagnosis is made, because symptoms can be non-specific and difficult to differentiate from other conditions. Symptoms usually begin in adolescence or early adulthood and include chronic back pain, stiffness, joint and tendon pain, arthritis and swelling of the fingers. A patient group explained in its written submission that many people experience depression, fatigue and poor sleep. This can have a profound effect on quality of life and affect education, work and the establishment of social frameworks and relationships. The committee concluded that axial spondyloarthritis is a painful and debilitating condition that can severely affect quality of life.

A new treatment option would be valuable for patients

3.2 The patient organisation submission included a survey of 303 people with axial spondyloarthritis and their carers, which showed a high unmet clinical need for new treatments. More than half the people surveyed believed that current treatments for axial spondyloarthritis are not sufficient. For some people, no medication has been effective. Others cannot tolerate current treatments, and for some the efficacy of treatment has worn off over time. There were also worries about possible side effects with current treatments and concerns for people with severe disease who do not meet the criteria for current biologic therapy. Ixekizumab works differently to tumour necrosis factor (TNF)-alpha inhibitors. It would be particularly beneficial to people with nr-axSpA for whom TNF-alpha inhibitors are the only biologics currently available. Ixekizumab would also provide an additional treatment option for people with radiographic disease. The patient expert stated that having a choice of treatments is important to meet individual needs. The committee concluded that the availability of an effective new treatment option would be valuable for people with axial spondyloarthritis.

Ixekizumab would be used when TNF-alpha inhibitors are not suitable or have not worked well enough

3.3 Conventional therapy for axial spondyloarthritis includes non-steroidal anti-inflammatory drugs (NSAIDs) and physiotherapy. NICE technology appraisal guidance recommends TNF-alpha inhibitors for disease that has not responded

adequately to conventional therapy. Ixekizumab and secukinumab are both interleukin (IL)-17-a inhibitors. NICE's technology appraisal guidance recommends secukinumab as a treatment option for active ankylosing spondylitis that has responded inadequately to NSAIDs or TNF-alpha inhibitors. Secukinumab is currently being appraised for treating nr-axSpA. The committee recalled that in previous technology appraisals of TNF-alpha inhibitors and secukinumab, clinical experts stated that the response criteria used in clinical practice for deciding to continue treatment were:

- a reduction in the 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 scope for ixekizumab issued by NICE is for people with axial spondyloarthritis for whom NSAIDs or TNF-alpha inhibitors are inadequately effective, not tolerated or contraindicated. In its response to technical engagement, the company stated that ixekizumab would be used primarily when TNF-alpha inhibitors are not suitable or have not controlled the condition well enough. The clinical experts explained that IL-17-a inhibitors are most needed by people with tolerability issues or contraindications to TNF-alpha inhibitors, or with disease that does not respond to TNF-alpha inhibitors (that is, primary non-response) or in whom the response is poor or lost after TNF-alpha inhibitor therapy. IL-17-a inhibitors would not be expected to replace TNF-alpha inhibitors as the standard first-line treatment because they are more expensive than the biosimilar TNF-alpha inhibitors and there is less clinical experience with using them. The committee concluded that ixekizumab would be used when TNF-alpha inhibitors are contraindicated or otherwise not suitable, after primary non-response to a TNF-alpha inhibitor or after a poor response or loss of response to TNF-alpha therapy.

Conventional therapy is the most reliable comparator for ixekizumab

3.4 The committee considered the most relevant comparators, given the treatment position for ixekizumab described in section 3.3. For active AS, the comparators in the NICE scope were TNF-alpha inhibitors, secukinumab and conventional therapy without biologics. For nr-axSpA the comparators in the NICE scope were TNF-alpha inhibitors and conventional therapy without biologics. The committee concluded that TNF-alpha inhibitors were not relevant comparators

because ixekizumab would be used for people in whom TNF-alpha inhibitors are contraindicated or otherwise not suitable, or after non-response or poor response to TNF-alpha inhibitors (see section 3.3). The committee acknowledged that secukinumab was a comparator in the scope for AS, however it considered that there was insufficient clinical evidence to allow a robust comparison between secukinumab and ixekizumab (see section 3.8). Following consultation on the appraisal consultation document, the committee noted the company's comment that not all people for whom TNF-alpha inhibitors have worked inadequately would stop biologic therapy and return to conventional therapy. Some people may have the newer TNF-alpha inhibitor options such as golimumab or certolizumab pegol, on the rationale that even a sub-optimal response to these therapies may be greater than the expected response to conventional therapy alone. The committee accepted that this may reflect clinical practice in some circumstances. However, it concluded that conventional therapy was the most reliable comparator for ixekizumab because there was direct evidence for this from the COAST trials for both the AS and nr-axSpA populations (see section 3.5). In contrast, the comparisons between ixekizumab and TNF-alpha inhibitors used results from an indirect comparison that the committee did not consider to be robust (see section 3.6), or an assumption of a class effect for biologic drugs that has not been established (see section 3.8).

Treatment effects are not reliably generalisable across active ankylosing spondylitis and non-radiographic axial spondyloarthritis

3.5 Active AS and nr-axSpA have traditionally been considered as 2 distinct disease entities. The company argued that clinical practice has moved towards classifying axial spondyloarthritis as a continuous disease spectrum with active AS and nr-axSpA being subtypes of the same condition. The company believed that the response rates to ixekizumab would be generalisable across the AS and nr-axSpA populations. The clinical experts agreed that axial spondyloarthritis is a disease spectrum containing radiographic and non-radiographic subtypes. However, they explained that factors such as the extent of radiographic damage, inflammatory burden, disease duration and treatment history are likely to differ in AS and nr-axSpA, which may affect treatment outcomes. The committee accepted that axial spondyloarthritis is a continuous spectrum of disease. However, it concluded that the response rate to ixekizumab could not be reliably generalised across the AS and nr-axSpA populations because of

differences in patient characteristics and disease presentation.

Clinical evidence

Ixekizumab is effective compared with placebo

3.6 The main clinical trial evidence came from 3 international placebo-controlled randomised controlled trials in people who had an inadequate response or intolerance to NSAIDs. Two of the trials were in AS: COAST-V included 341 people who had not had a biologic before, and COAST-W included 316 people who had previously had at least 1 biologic (a TNF-alpha inhibitor). The COAST-X study included 303 people with nr-axSpA who had never had a biologic. The clinical experts confirmed that the patients in the COAST trials were representative of people having treatment in the NHS. The ERG considered that patient baseline characteristics were well balanced across the arms within each trial. The primary outcome was the proportion of patients who had an Assessment in Spondyloarthritis International Society (ASAS) 40 response (improvement of at least 40% in at least 2 units in 3 of the 4 main domains of ASAS and no worsening in the remaining domains) at week 16. Secondary endpoints were the proportion of patients whose Bath Ankylosing Spondylitis Disease Activity Index score improved by 50% from baseline (BASDAI 50), and the change in the Bath Ankylosing Spondylitis Functional Index (BASFI) score from baseline. Ixekizumab showed a statistically significant clinical effect compared with placebo for all primary and secondary outcome measures. The company also presented evidence from the COAST-Y study, an ongoing, multicentre, long-term extension study to evaluate the maintenance of treatment effect with ixekizumab. COAST-Y includes people who completed COAST-V, COAST-W, and COAST-X and continued having ixekizumab up to 116 weeks after their first dose. The company stated the results of COAST-Y provide evidence to support the maintenance of treatment effects for ixekizumab on ASAS 40 response, BASDAI 50 response and the BASFI change from baseline. The committee concluded that ixekizumab is an effective treatment compared with placebo.

The company's network meta-analysis

Results of the network meta-analysis in the company's original submission are uncertain and not suitable for decision making

3.7 In the absence of direct evidence, the original company submission included a network meta-analysis (NMA) that compared the relative efficacy of ixekizumab and the comparators in the scope (see section 3.4). It used placebo as the common comparator. The company did separate NMAs for the AS populations who had and had not had a biologic before, and the nr-axSpA population that had not had a biologic. This was in line with COAST-V, COAST-W and COAST-X, respectively. The company did 'base-case' NMAs that included studies known to be in the relevant patient population, and 'sensitivity' NMAs that included additional studies with mixed populations or that were unclear about previous biologic treatment. The ERG considered the company's methods to be appropriate. However, it noted that the company's base-case NMAs were too sparsely populated to generate results for all relevant comparator treatments, so the cost-effectiveness results were informed by the sensitivity NMAs. The ERG was concerned about the substantial differences in the absolute effect estimates generated by the base-case and sensitivity NMAs. It considered the sensitivity NMAs to be less reliable than the base-case NMAs because of high levels of heterogeneity, and concluded that 3 of the sensitivity NMAs for the AS population were not robust. The committee agreed with the ERG that the results of the NMAs were not robust and were therefore not suitable for decision making.

There is insufficient evidence to compare the effectiveness of ixekizumab and secukinumab

3.8 Secukinumab was a comparator in the NICE scope for the AS population (see section 3.4). In its original submission, the company indicated that there was insufficient published data available to allow for a full comparison of the effectiveness of ixekizumab and secukinumab. Following technical engagement, the company updated its NMAs to include data from the PREVENT trial, which compared secukinumab with placebo in an nr-axSpA population. The company argued that results for the nr-axSpA population are generalisable to the AS population because axial spondyloarthritis is a disease spectrum (see section 3.5). The ERG noted substantial differences between the response rates

for ixekizumab in COAST-V, which included an active AS population, and COAST-X, which included an nr-axSpA population. Both populations had not had a biologic. The ERG stated that if these differences were because of underlying disease biology then it would be unreliable to use results from the nr-axSpA population as a proxy for results in AS. If the differences in the response rates were because of differences in patient characteristics, then results from the nr-axSpA population could only be used to inform the effectiveness of ixekizumab for patients with AS if appropriate adjustments were made for these patient characteristics. The committee concluded that insufficient evidence was presented to allow for a robust comparison of ixekizumab and secukinumab, given that treatment effectiveness was not considered to be generalisable across AS and nr-axSpA populations (see section 3.5).

Assumptions about a class effect

It is not reasonable to assume a class effect for all biologic treatments

3.9 Following technical engagement, the company considered it reasonable to assume that all biologic treatments for axial spondyloarthritis have equivalent efficacy (that is, there is a class effect for all TNF-alpha and IL-17-a inhibitors). It commented that the evidence demonstrates that the pathophysiology of axial spondyloarthritis is driven by dysregulation of inflammatory cytokines, in which both TNF-alpha inhibitors and IL-17-a inhibitors play key roles. The company also highlighted that the updated NMAs found no statistically significant difference between TNF-alpha inhibitors and IL-17-a inhibitors for any of the outcomes assessed. The clinical experts explained that IL-17-a inhibitors are expected to have similar effectiveness to TNF-alpha inhibitors in clinical practice, but this has not been investigated in head-to-head clinical trials. They explained that application of a class effect for all biologics may be an oversimplification because TNF-alpha inhibitors and IL-17-a inhibitors have different mechanisms of action. This is a potential advantage of IL-17-a inhibitors after non-response or poor response to TNF-alpha inhibitors. The committee concluded that a class effect had not been established for all TNF-alpha inhibitors and IL-17-a inhibitors.

Cost effectiveness

The results of the model using the network meta-analysis are not reliable for decision making

3.10 The company presented a Markov model to estimate the cost effectiveness of ixekizumab compared with TNF-alpha inhibitors, secukinumab (for AS only) and conventional therapy in people for whom NSAIDs or TNF-alpha inhibitors had been inadequately effective, not tolerated, or contraindicated. The committee recalled that conventional therapy was the most reliable comparator (see section 3.4). The committee considered that the structure of the model was appropriate. However, the efficacy inputs in the original version of the model were informed by the results of the NMA, which the committee considered were not robust (see section 3.7). The committee also noted that the company's incremental cost-effectiveness ratios (ICERs) for ixekizumab compared with conventional therapy were above the range NICE normally considers cost effective (that is, £20,000 to £30,000 per QALY gained). The committee concluded that the results of the model using the NMA were not reliable for decision making.

The company's updated model assuming a class effect for biologic treatments is not appropriate

3.11 After technical engagement, the company updated its cost-effectiveness analysis. It applied a class effect across the IL-17-a inhibitors and TNF-alpha inhibitors. It presented 2 analyses. One analysis was for the AS population who previously had a biologic, in which the efficacy inputs for all biologics were assumed to equal the efficacy of ixekizumab in COAST-W. The other analysis was for the nr-axSpA population who had not had a biologic, in which the efficacy inputs for all biologics were assumed to equal the efficacy of ixekizumab in COAST-X. This was intended as a proxy for the use of ixekizumab in a nr-axSpA population who had had a biologic, in the absence of trial data for this group. The assumption of a class effect meant that there were equivalent QALYs for all biologics. However, the QALYs differed across the analyses for the AS population, who had had a biologic, and the nr-axSpA populations, who had not. The committee appreciated the need to find alternative ways to model the efficacy of the treatments given the limitations of the NMAs. However, it was not persuaded that a class effect had been demonstrated across all biologics

(see section 3.9). The committee was also concerned that the company had not presented an ICER for ixekizumab compared with conventional therapy in its updated analyses. The committee considered this was the key comparator in situations when ixekizumab would be used in clinical practice (see section 3.4). It concluded that the updated version of the model could not be used for decision making.

The company's analyses comparing ixekizumab with conventional therapy using direct evidence from the COAST trials are appropriate

3.12 The appraisal consultation document stated that further analyses are needed to assess the cost effectiveness of ixekizumab. The most reliable comparator for ixekizumab in the populations for whom it would be used is conventional therapy (see section 3.4). The committee had concluded that an analysis comparing ixekizumab with conventional therapy using direct evidence from the COAST trials would be the most robust way of assessing the cost effectiveness of ixekizumab. Following consultation, the company presented updated analyses. These compared ixekizumab with conventional therapy for the AS population who had never had a biologic (using data from COAST-V), the AS population who had had at least 1 biologic (using COAST-W data) and the nr-axSpA population who had never had a biologic (using COAST-X data). The committee noted the lack of direct evidence on ixekizumab in nr-axSpA following inadequate or loss of response to TNF-alpha inhibitors. However, it was reassured that the COAST trials covered the treatment pathway, for people who both had and had not had a biologic before, and the full spectrum of axial spondyloarthritis. The committee concluded that the company's revised analyses were suitable for decision making.

Ixekizumab is cost effective compared with conventional therapy

3.13 The ICERs for ixekizumab compared with conventional therapy using direct data from the COAST trials for the AS population were £18,775 per QALY gained for people who had not had a biologic before and £19,012 for those who had. The ICER for the nr-axSpA population who had never had a biologic was £24,772. The ICERs were within the range NICE normally considers cost effective. Therefore, the committee concluded that ixekizumab could be recommended as an option for treating AS and nr-axSpA in adults when TNF-

alpha inhibitors have not controlled the condition well enough, or these are not suitable.

Conclusion

Ixekizumab is a cost-effective treatment for AS and nr-axSpA when TNF-alpha inhibitors are not suitable or have not worked well enough

3.14 Ixekizumab would be offered to people who cannot have TNF-alpha inhibitors or when they have not worked well enough. The most reliable comparator in these populations is conventional therapy. Evidence from the COAST trials shows that ixekizumab is effective compared with placebo, which is a proxy for conventional therapy. The company's cost-effectiveness estimates for ixekizumab compared with conventional therapy using direct evidence from the COAST trials were within the range NICE normally considers cost effective. Therefore, ixekizumab is recommended as an option for treating AS and nr-axSpA in adults when TNF-alpha inhibitors have not controlled the condition well enough, or these are not suitable.

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.

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 or active non-radiographic axial spondyloarthritis, and the doctor responsible for their care thinks that ixekizumab 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) and a technical adviser.

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Accreditation