NICE National Institute for Health and Care Excellence

NICE guidance

Ixekizumab for treating active psoriatic arthritis after inadequate response to DMARDs

Technology appraisal guidance
Published: 8 August 2018

www.nice.org.uk/guidance/ta537

Your responsibility

The recommendations in this guidance represent the view of NICE, arrived at after careful consideration of the evidence available. When exercising their judgement, health professionals are expected to take this guidance fully into account, alongside the individual needs, preferences and values of their patients. The application of the recommendations in this guidance is at the discretion of health professionals and their individual patients and do not override the responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or their carer or guardian.

All problems (adverse events) related to a medicine or medical device used for treatment or in a procedure should be reported to the Medicines and Healthcare products Regulatory Agency using the Yellow Card Scheme.

Commissioners and/or providers have a responsibility to provide the funding required to enable the guidance to be applied when individual health professionals and their patients wish to use it, in accordance with the NHS Constitution. They should do so in light of their duties to have due regard to the need to eliminate unlawful discrimination, to advance equality of opportunity and to reduce health inequalities.

Commissioners and providers have a responsibility to promote an environmentally sustainable health and care system and should assess and reduce the environmental impact of implementing NICE recommendations wherever possible.

Contents

1 Recommendations

1.1 Ixekizumab alone, or with methotrexate, is recommended as an option for treating active psoriatic arthritis in adults, only if:

- it is used as described in NICE's technology appraisal guidance on etanercept, infliximab and adalimumab for the treatment of psoriatic arthritis (recommendations 1.1 and 1.2) or
- the person has had a tumour necrosis factor (TNF)-alpha inhibitor but their disease has not responded within the first 12 weeks or has stopped responding after the first 12 weeks or
- TNF-alpha inhibitors are contraindicated but would otherwise be considered (as described in NICE's technology appraisal guidance on etanercept, infliximab and adalimumab for the treatment of psoriatic arthritis).

  Ixekizumab is only recommended if the company provides it according to the commercial arrangement.

1.2 Assess the response to ixekizumab after 16 weeks of treatment. Only continue treatment if there is clear evidence of response, defined as an improvement in at least 2 of the 4 Psoriatic Arthritis Response Criteria (PsARC), 1 of which must be joint tenderness or swelling score, with no worsening in any of the 4 criteria. People whose disease has a Psoriasis Area and Severity Index (PASI) 75 response but whose PsARC response does not justify continuing treatment should be assessed by a dermatologist, to determine whether continuing treatment is appropriate based on skin response (as described in NICE's technology appraisal guidance on etanercept, infliximab and adalimumab for the treatment of psoriatic arthritis, recommendation 1.3).

1.3 When using the PsARC, healthcare professionals should take into account any physical, sensory or learning disabilities or communication difficulties that could affect a person's responses to components of the PsARC and make any adjustments they consider appropriate.

1.4 When using the PASI, healthcare professionals should take into account skin

colour and how this could affect the PASI score, and make the clinical adjustments they consider appropriate.

1.5 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

Ixekizumab is a biological therapy, several of which are already recommended by NICE for treating psoriatic arthritis. Clinical trial evidence shows that ixekizumab is more effective than placebo at treating joint and skin symptoms. An indirect comparison suggests that ixekizumab is likely to be as effective at improving symptoms as some of the current treatments used in the NHS for psoriatic arthritis.

The cost-effectiveness estimates show that for some groups of people with psoriatic arthritis, ixekizumab is the most cost-effective treatment option. For other groups, the difference in health benefits between ixekizumab and the most cost-effective treatment is very small. Overall, the cost effectiveness of ixekizumab is acceptable when it is used after 2 disease-modifying anti-rheumatic drugs, as the first biological therapy, or after treatment with a TNF-alpha inhibitor. Therefore, it can be recommended.

2 Information about ixekizumab

Marketing authorisation indication

2.1 Ixekizumab (Taltz, Eli Lilly) has a marketing authorisation, alone or in combination with methotrexate, 'for the treatment of active psoriatic arthritis in adult patients who have responded inadequately to, or who are intolerant to one or more disease-modifying anti-rheumatic drug (DMARD) therapies'.

Dosage in the marketing authorisation

2.2 160 mg by subcutaneous injection (2×80 mg injections) at week 0, followed by 80 mg (1 injection) every 4 weeks thereafter.

For patients with concomitant moderate to severe plaque psoriasis, the recommended dosing regimen is 160 mg by subcutaneous injection (2×80 mg injections) at week 0, followed by 80 mg (1 injection) at weeks 2, 4, 6, 8, 10 and 12, then maintenance dosing of 80 mg (1 injection) every 4 weeks.

Consideration should be given to stopping treatment in patients whose disease has shown no response after 16 to 20 weeks of treatment. Some patients with initial partial response may subsequently improve with continued treatment beyond 20 weeks.

Price

2.3 The list price for ixekizumab is £1,125 per 80-mg syringe.

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 Lilly and a review of this submission by the evidence review group (ERG). See the committee papers for full details of the evidence.

The condition

Psoriatic arthritis can substantially decrease quality of life

3.1 The patient experts explained that psoriatic arthritis can affect people at a young age (peak onset is 30 to 50 years old) and is a lifelong condition. Symptoms including joint stiffness, fatigue and pain can make day-to-day activities difficult and have a serious negative effect on people's quality of life. Most people develop joint symptoms a few years after skin psoriasis and adding a painful joint disease to the skin symptoms can have a substantial psychological impact. The committee concluded that psoriatic arthritis can substantially decrease quality of life.

Treatment pathway and current management

Ixekizumab will be used in people who have had at least 2 DMARDs

3.2 The committee was aware that the marketing authorisation for ixekizumab indicates treatment after 1 or more disease-modifying anti-rheumatic drugs (DMARDs). However, the company did not submit any clinical- or cost-effectiveness analyses for the population who have had 1 conventional DMARD because this is not in line with British Society for Rheumatology guidelines and previous NICE technology appraisal guidance. These recommend people have 2 conventional DMARDs before biological therapies. The clinical experts confirmed that in the NHS, people usually have 2 DMARDs before moving on to

non-conventional DMARDs. DMARDs are usually trialled sequentially, but people who have severe symptoms may have 2 or more DMARDs at the same time. This is because 1 DMARD alone is unlikely to be effective at controlling the disease. The committee concluded that ixekizumab would be used in people who have had at least 2 DMARDs and that the company's positioning of ixekizumab in the treatment pathway was in line with clinical practice, and therefore appropriate.

Patients and clinicians would welcome an additional effective treatment option

3.3 The clinical experts explained that a tumour necrosis factor (TNF)-alpha inhibitor is usually offered as the first biological therapy, unless it is contraindicated. They added that ixekizumab has a different mechanism of action and would be a useful additional treatment option because there are only a limited number of biological therapies that are not TNF-alpha inhibitors. Ixekizumab, like secukinumab, inhibits interleukin-17A. The clinical experts stated that it is useful to have options within the same class of drug because the adverse events people have with drugs in the same class can be different. Also, the disease may not respond to 1 therapy in a class, but it may respond to another in the same class. However, they explained that there was no evidence for this in psoriatic arthritis, as there is in psoriasis. The committee also noted that in the trial, the evidence for ixekizumab in people who have had a biological therapy was specifically after TNF-alpha inhibitors. The patient experts explained that because the disease can stop responding to biological DMARDs over time, and because psoriatic arthritis is a lifelong disease, all treatment options can be exhausted by some people. Also, people's symptoms and responses to therapies can be heterogeneous; some people have symptoms that improve with a certain treatment but other people may prioritise improvements in other symptoms for which the same therapy is less effective. The committee concluded that patients and clinicians would welcome an additional effective treatment option.

Clinical trial evidence

Ixekizumab reduces joint and skin symptoms compared with

placebo

3.4 The clinical-effectiveness evidence for ixekizumab came from 2 randomised, double-blinded, placebo-controlled trials. SPIRIT-P1 included patients who had not had previous treatment with a biological DMARD but all of the patients in SPIRIT-P2 either had disease that had previously had an inadequate response to or could not tolerate a TNF-alpha inhibitor. In both trials, a statistically significantly higher proportion of people having ixekizumab had reductions in joint and skin symptoms as assessed by the Psoriatic Arthritis Response Criteria (PsARC) and Psoriasis Area and Severity Index (PASI) 75 respectively at 12 weeks, compared with placebo. A statistically significantly higher proportion of people having ixekizumab also saw improvements in their ability to do daily activities compared with placebo, as assessed by the health assessment questionnaire disability index (HAQ-DI). The committee concluded that ixekizumab is an effective treatment compared with placebo.

The SPIRIT trials are generalisable to NHS clinical practice

3.5 The committee noted that the SPIRIT trials included few patients from the UK. Also, 15% of patients in SPIRIT-P1 had not had any previous DMARDs and only a small number had had 2 or more previous DMARDs. The committee was therefore concerned that the trials might not reflect clinical practice in the NHS, where most people only have biological therapies after 2 previous DMARDs (see section 3.2). The clinical experts noted that although only a small number of patients had 2 or more previous DMARDs in the SPIRIT trials, most patients had had at least 1. They explained that in their experience, the efficacy of a biological therapy does not differ between those who have had 1 previous DMARD and those who have had 2 previous DMARDs. This was supported by a company post-hoc analysis, which pooled all the patients across the SPIRIT trials who had had 2 or more previous DMARDs. Although this analysis was based on non-randomised data and therefore subject to potential bias, it suggested similar efficacy of ixekizumab in this group of patients as in the overall trial populations. The committee concluded that the results of the SPIRIT trials were generalisable to the NHS.

Network meta-analysis

The results of the network meta-analysis for the no previous biological DMARD population are uncertain but are suitable for decision-making

3.6 Some of the comparator trials included in the no previous biological DMARD network included a mix of patients who had 1 or 2 previous DMARDs, because there was not enough data for separate networks. The committee recalled the clinical expert comments explaining that although this does not reflect clinical practice in the NHS, treatment efficacy is not expected to differ between those who have had 1 previous DMARD and those who have had 2 previous DMARDs (see section 3.5). For some of the comparators included in the NICE scope, the only available data included a mix of patients who had and had not had a previous biological DMARD. This was the case for certolizumab pegol, secukinumab and apremilast. The committee was concerned that the use of mixed population data introduced a large amount of uncertainty into the network meta-analysis. However, the results showed ixekizumab to have similar effectiveness to secukinumab which the clinical experts agreed matched their expectations, as both therapies are interleukin-17A inhibitors. The committee therefore concluded that the network meta-analysis was suitable for decision-making and that ixekizumab is as effective at treating psoriatic arthritis as several of the biological therapies, including secukinumab.

Certolizumab pegol and secukinumab should be included in the previous biological DMARD network meta-analysis

3.7 Because more of the patients in the certolizumab pegol and secukinumab trials had not had a previous biological DMARD (around two thirds), the company only included these comparators in the no previous biological DMARD network. It did not include secukinumab and certolizumab pegol in the base-case network for the population who had had a previous biological DMARD, but did provide a scenario analysis including them. The ERG highlighted that if having previous biological therapy influences a treatment's efficacy, then the network meta-analysis results will not be representative of the treatment effect in each

population. The clinical experts agreed that this was likely to be the case, because in clinical practice they had seen declining efficacy with increasing biological DMARD treatment. However, the committee considered that this problem would affect the analyses for both populations despite a bigger proportion of patients not having had a previous biological DMARD. The committee concluded that certolizumab pegol and secukinumab should be included in the base-case network for the previous biological DMARD population because these comparators reflect clinical practice and were included in the NICE scope. Based on the network meta-analysis including secukinumab and certolizumab pegol, the committee concluded that ixekizumab is as effective at treating psoriatic arthritis in the previous biological DMARD population as several of the biological therapies, including secukinumab and ustekinumab.

The company's economic model

The company's economic model is suitable for decision-making

3.8 The company submitted cost-effectiveness analyses for the populations who have had and have not had a previous biological DMARD and for 3 psoriasis subgroups (psoriatic arthritis without concomitant psoriasis, with concomitant mild to moderate psoriasis and with concomitant moderate to severe psoriasis). The economic model was based on the assessment group's model developed for NICE's technology appraisal guidance on certolizumab pegol and secukinumab. In the model used in this appraisal, ixekizumab and other non-conventional DMARDs were looked at as part of a treatment sequence. The committee noted that as well as different clinical data inputs, the 2 main differences between the company's model and the model used in NICE's technology appraisal guidance on certolizumab pegol and secukinumab were:

- the utility algorithm was derived from data from the SPIRIT trials and
- baseline PASI scores for the psoriasis severity subgroups were derived from the SPIRIT trials.

Scenario analyses using the assumptions accepted by the committee for each of these parameters in NICE's technology appraisal guidance on

certolizumab pegol and secukinumab showed that the incremental cost-effectiveness ratios (ICERs) for ixekizumab were not sensitive to these changes. The committee concluded that the company's economic model was suitable for decision-making.

The ERG's analysis reflects the committee's preferred assumptions

3.9 The ERG's analysis included some assumptions that differed from those used in the company's base case. Specifically, it:

- included corrections for an error in the network meta-analysis results for ixekizumab HAQ-DI and an inconsistency in the way the calculation of PASI change based on PsARC response was reported in the company submission and implemented in the model
- included certolizumab pegol and secukinumab in the previous biological DMARD network meta-analysis
- capped utilities at the general population values, to account for the increasing age of patients in the model
- used a standardised mortality ratio of 1.05 instead of 1.36, derived from a more recent cut of the data.

The committee accepted that these changes were appropriate and noted that none of them individually had a large effect on the ixekizumab ICERs and cumulatively the effect was small.

Cost-effectiveness results

The difference in total QALYs between ixekizumab and secukinumab in the no previous biological DMARD population is small

3.10 The committee noted that in the no previous biological DMARD population, for the no psoriasis and mild to moderate psoriasis subpopulations, secukinumab was the most cost-effective treatment in the fully incremental analysis. Because there are confidential discounts for ixekizumab and some of the comparators, the exact cost-effectiveness results cannot be reported. However, the differences in total quality-adjusted life years (QALYs) between ixekizumab and secukinumab were small and in the moderate to severe subpopulation, ixekizumab was associated with higher total QALYs and lower costs than secukinumab. The committee recalled that these small differences in QALYs were based on uncertain data from the network meta-analysis (see section 3.6). Therefore, the cost-effectiveness estimates of the treatments in this population would be sensitive to small changes in the estimates of total QALYs. The committee concluded that it was important to consider this in its decision-making.

Ixekizumab is the most cost-effective treatment in the previous biological DMARD population

3.11 For the previous biological DMARD population, ixekizumab was the most cost-effective treatment in the fully incremental analysis. However, the committee again noted that the differences in total QALYs between ixekizumab, secukinumab and ustekinumab were small.

Ixekizumab is a cost-effective treatment option for people who have had, and who have not had, a previous biological DMARD

3.12 The committee noted that although ixekizumab was not the most cost-effective option in all of the psoriasis subgroups in the no previous biological DMARD

population, the difference in total QALYs between it and the most cost-effective treatment was very small and based on uncertain data. Ixekizumab was the most cost-effective option in the previous biological DMARD population. Overall, the committee concluded that the cost effectiveness of ixekizumab, with the commercial arrangement, was acceptable when:

- the criteria in NICE's technology appraisal guidance on etanercept, infliximab and adalimumab for the treatment of psoriatic arthritis are met; that is, the person has peripheral arthritis with at least 3 tender joints and at least 3 swollen joints, and the psoriatic arthritis has not responded adequately to trials of at least 2 conventional DMARDs, given either individually or together or
- the person has had a TNF-alpha inhibitor but their disease has not responded within the first 12 weeks or had stopped responding after the 12 weeks or
- TNF-alpha inhibitors are contraindicated but would otherwise be considered (as described in NICE's technology appraisal guidance on etanercept, infliximab and adalimumab for the treatment of psoriatic arthritis).

PsARC response should be assessed at 16 weeks

3.13 The committee noted that the economic analysis was based on the assumption that people whose psoriatic arthritis has not shown an adequate PsARC response at 12 weeks stop ixekizumab treatment. This matches the timing of the primary outcome assessment in the SPIRIT trials. However, the ixekizumab summary of product characteristics states that stopping treatment should be considered if there is no response after 16 to 20 weeks of treatment. The company provided a scenario analysis, which showed that using data for ixekizumab outcomes assessed at 16 weeks in the model resulted in similar ICERs to using 12-week data. The committee concluded that PsARC response should be assessed at 16 weeks to decide if ixekizumab treatment should continue, because this is in line with the summary of product characteristics.

Other factors

Clinicians should take into account factors that may affect PsARC and PASI and make any clinical adjustments needed

3.14 The committee considered that the recommendation to stop treatment based on an inadequate PsARC response (as described in NICE's technology appraisal guidance on etanercept, infliximab and adalimumab for the treatment of psoriatic arthritis) was also appropriate for ixekizumab. It noted that some people may have physical, sensory or learning disabilities or communication difficulties that could affect their responses to components of the PsARC, and concluded that this should be taken into account when using the PsARC. The committee was also aware that the PASI might underestimate disease severity in people with darker skin. The committee concluded that, when using the PASI, healthcare professionals should take into account skin colour and how this could affect the PASI score, and make the clinical adjustments they consider appropriate.

There are no significant health benefits that have not been captured in the QALY

3.15 The committee noted that the company had suggested that ixekizumab is effective at treating symptoms such as nail psoriasis and dactylitis and that improvements in these might not be captured in the EQ-5D and therefore the QALY. However, the clinical experts explained that some of the other treatments also address these symptoms, but these outcomes were not measured in the older clinical trials. Therefore, any additional benefits would also likely apply to some of the comparator treatments. The committee concluded that there were no significant health benefits that had not been captured in the QALY calculation.

4 Implementation

4.1 Section 7(6) of the National Institute for Health and Care Excellence (Constitution and Functions) and the Health and Social Care Information Centre (Functions) Regulations 2013 requires clinical commissioning groups, NHS England and, with respect to their public health functions, local authorities to comply with the recommendations in this appraisal within 3 months of its date of publication.

4.2 The Welsh ministers have issued directions to the NHS in Wales on implementing NICE technology appraisal guidance. When a NICE technology appraisal recommends the use of a drug or treatment, or other technology, the NHS in Wales must usually provide funding and resources for it within 2 months of the first publication of the final appraisal document.

4.3 When NICE recommends a treatment 'as an option', the NHS must make sure it is available within the period set out in the paragraphs above. This means that, if a patient has psoriatic arthritis and the healthcare professional 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 D.

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.

Ross Dent
Technical Lead

Nwamaka Umeweni
Technical Adviser

Kate Moore
Project Manager

ISBN: 978-1-4731-3052-4