Healthcare Improvement Scotland | SMC Advice on new medicines

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SMC2097

# ixekizumab 80mg solution for injection in pre-filled syringe or pen (Taltz®)

Eli Lilly and Company Ltd

7 September 2018

The Scottish Medicines Consortium (SMC) has completed its assessment of the above product and advises NHS Boards and Area Drug and Therapeutic Committees (ADTCs) on its use in NHSScotland. The advice is summarized as follows:

**ADVICE**: following a full submission

**ixekizumab (Taltz®)** is accepted for restricted use within NHSScotland.

**Indication under review:** ixekizumab, alone or in combination with methotrexate, is indicated 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.

**SMC restriction:** patients whose disease has not responded adequately to at least two conventional DMARDs given either alone or in combination, and who have had an inadequate response to a tumour necrosis factor (TNF)-inhibitor.

Two phase III studies demonstrated superiority of ixekizumab when compared with placebo in reducing signs and symptoms of psoriatic arthritis in patients who had not previously received a biologic medication and those with an inadequate response or intolerance to TNF-inhibitors.

This SMC advice takes account of the benefits of a Patient Access Scheme (PAS) that improves the cost-effectiveness of ixekizumab. This advice is contingent upon the continuing availability of the PAS in NHS Scotland or a list price that is equivalent or lower.

**Chairman**
**Scottish Medicines Consortium**

## Indication

Ixekizumab, alone or in combination with methotrexate, is indicated 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.[1]

## Dosing Information

160mg by subcutaneous injection (two 80mg injections) at week 0, followed by 80mg (one injection) every four weeks thereafter.

For psoriatic arthritis patients with concomitant moderate to severe plaque psoriasis, the recommended dosing regimen is the same as for plaque psoriasis: 160mg by subcutaneous injection (two 80mg injections) at week 0, followed by 80mg (one injection) at weeks 2, 4, 6, 8, 10, and 12, then maintenance dosing of 80mg (one injection) every four weeks.

Consideration should be given to discontinuing treatment in patients who have shown no response after 16 to 20 weeks of treatment. Some patients with initially partial response may subsequently improve with continued treatment beyond 20 weeks.

Ixekizumab is intended for use under the guidance and supervision of a physician experienced in the diagnosis and treatment of conditions for which it is indicated.[1]

## Product availability date

March 2018

## Summary of evidence on comparative efficacy

Ixekizumab is a humanised monoclonal antibody that selectively binds to interleukin 17A (IL-17A). Elevated IL-17A levels have been shown to have a role in signalling in the formation of psoriatic lesions, as well as in synovial inflammation, cartilage destruction, and bone erosion. Neutralisation of IL-17A has been shown to inhibit this and reduce disease activity in patients with psoriatic arthrtitis.[1, 2]

SMC has previously reviewed ixekizumab for the treatment of moderate to severe plaque psoriasis and restricted use to patients who have failed to respond to, or are intolerant of, standard systemic therapies (including ciclosporin, methotrexate and phototherapy), or have a contraindication to these treatments (SMC ID 1223/17). This advice remains in place.

This submission relates to the treatment of active psoriatic arthritis. The company has requested that SMC considers ixekizumab when positioned for use in adults whose disease has not responded adequately to at least two conventional DMARDs given either alone or in combination, or who have received a biologic but their disease has not responded within the first 12 weeks or has stopped responding after 12 weeks, or if tumour necrosis factor (TNF)-inhibitors are contraindicated but would otherwise be considered.

Evidence to support the use of ixekizumab in psoriatic arthritis comes from two randomised, double-blind, placebo-controlled, phase III studies, SPIRIT-P1 and SPIRIT-P2. Both studies included patients who were at least 18 years old with psoriatic arthritis for ≥6 months who met the Classification Criteria for Psoriatic Arthritis (CASPAR). They were required to have ≥3 of 68 tender joint count, ≥3

of 66 swollen joint count, and current or previous plaque psoriasis.[2-4] SPIRIT-P1 included patients who were not previously treated with a biologic medicine for psoriatic arthritis or plaque psoriasis and were also required to have either one or more hand or foot joint erosions; or C-reactive protein (CRP) >6 mg/L.[2, 3] Patients recruited to SPIRIT-P2 had previously received one or more conventional DMARDs (methotrexate, sulfasalazine, leflunomide or hydroxychloroquine) and had prior treatment with at least one and not more than two TNF-inhibitors. At least one TNF-inhibitor must have been discontinued due to either an inadequate response or intolerance. [2, 4]

In both studies patients were randomised equally to receive ixekizumab 160mg initially then 80mg every two weeks, ixekizumab 160mg initially then 80mg every four weeks (the licensed dose), or placebo, all by subcutaneous injection for 24 weeks. [2-4] SPIRIT-P1 also included an adalimumab arm in which patients received adalimumab 40mg subcutaneously every two weeks for 24 weeks although the study was not powered to test for comparisons between ixekizumab and adalimumab.[2, 3] Treatment with concomitant medicines was allowed, including one conventional DMARD (methotrexate, leflunomide, sulfasalazine or hydroxychloroquine only), weak potency topical corticosteroids, oral corticosteroids (up to prednisolone 10mg/day or equivalent), opiates (up to 30mg/day morphine or equivalent), non-steroidal anti-inflammatory drugs (NSAIDs) or cyclo-oxygenase-2 inhibitors but they must have been receiving treatment at a stable dose prior to baseline. [2-4]

Patients were assessed at week 16 and those who did not meet pre-defined criteria for changes in both tender joint count and swollen joint count from baseline were defined as inadequate responders. Inadequate responders received rescue medication and either remained on their originally assigned dose of ixekizumab or, if receiving adalimumab or placebo, were re-randomised equally to receive ixekizumab 160mg initially then 80mg every two weeks or 80mg every four weeks. Inadequate responders from the adalimumab group received eight weeks of placebo as a washout therapy prior to initiating ixekizumab treatment at week 24.[2-4] Only the licensed dose of ixekizumab will be discussed further.

The primary outcome in both studies was the proportion of patients achieving an American College of Rheumatology response of at least 20% (ACR20) at week 24.[2-4] Results for primary and key secondary outcomes significantly favoured ixekizumab compared with placebo as detailed in table 1. Ixekizumab was superior to placebo for the patient reported outcomes Health Assessment Questionnaire-Disability Index (HAQ-DI) and Short Form Health Survey Physical Component Score (SF-36 PCS) assessed at 12 and 24 weeks.[2-4]

**Table 1: Primary and selected secondary outcomes from SPIRIT-P1 and SPIRIT-P2 at week 24.**[3, 4]

| | SPIRIT-P1 | | | SPIRIT-P2 | |
|---|---|---|---|---|---|
| | Ixekizumab every four weeks (n=107) | Placebo (n=106) | Adalimumab (n=101) | Ixekizumab every four weeks (n=122) | Placebo (n=118) |
| Proportion of patients achieving ACR20 | 58% | 30% | 57% | 53% | 19% |
| Proportion of patients achieving ACR50 | 40% | 15% | 39% | 35% | 5.1% |
| Proportion of patients achieving ACR70 | 23% | 5.7% | 26% | 22% | 0 |

| | | | | | |
|---|---|---|---|---|---|
| Proportion of patients achieving MDA | 30%* | 15% | 32% | 28% | 3.4% |
| Proportion of patients achieving PASI 75 | 71% | 10% | 54% | 56% | 15% |
| HAQ-DI, LSM change from baseline | -0.44 | -0.18 | -0.37 | -0.6 | -0.2 |
| DAS28-CRP, LSM change from baseline | -1.96 | -0.84 | -1.74 | -2.1 | -0.8 |
| mTSS, LSM change from baseline | 0.17* | 0.49 | 0.10 | - | - |
| SF-36 PCS, LSM change from baseline | 7.5 | 2.9 | 6.8 | 8.9 | 3.3 |

p≤0.001 for all comparisons between ixekizumab and placebo apart from *p≤0.025. The SPIRIT-P1 study was not powered to test equivalence or non-inferiority of ixekizumab versus adalimumab. ACR20/50/70: American College of Rheumatology response of at least 20/50/70%, DAS28-CRP: 28 joint disease activity score using CRP, HAQ-DI: Health Assessment Questionnaire-Disability Index, mTSS: van der Heijde modified Total Sharp Score, PASI 75: at least a 75% improvement in Psoriasis Area and Severity Index (PASI), LSM: least square mean, MDA: minimal disease activity; SF-36: short-form 36, PCS: physical component summary.

In the subgroup of patients in SPIRIT-P1 who had previously received a conventional DMARD, there was a significantly higher percentage of patients who achieved ACR20 response at week 24 in the ixekizumab group compared with the placebo group (60% versus 31%).[2] ACR50/70 and PASI 75 outcome responses were similar to the full population in the ixekizumab and placebo groups.[2] Ixekizumab was also superior to placebo for the primary outcome in subgroups of patients in SPIRIT-P2 who had previously had an inadequate response to one TNF-inhibitor, two TNF-inhibitors or an intolerance to TNF-inhibitors and in patients taking concomitant DMARDs or not.[4]

There was an open-label extension period from week 24 to week 52 and a long-term open-label extension period up to week 156 in SPIRIT-P1. In SPIRIT-P2, there was an open-label extension period from week 24 to week 156. Patients who were initially randomised to ixekizumab continued on the same dose. Patients who were still receiving placebo at week 24 were re-randomised equally to ixekizumab 160mg loading dose then 80mg every two or four weeks. Those who were receiving adalimumab at week 24 were also re-randomised equally to ixekizumab 80mg every two or four weeks from week 32 without a loading dose, following an eight week placebo washout period. Ninety-one percent of patients entered the extension phase of SPIRIT-P1 and 73% of patients completed up to week 52. ACR20/50/70 and PASI 75 response rates and improvement in HAQ-DI were mainly sustained at week 52 and week 108 in patients initially randomised to ixekizumab and generally similar therapeutic effect was observed in those who were re-randomised. Patients in the ixekizumab group had a numerically larger mTSS change from baseline at week 52 compared with patients initially randomised to placebo or adalimumab (both switched to ixekizumab at Week 16 or 24). [6, 7] Week 52 results from the extension period of SPIRIT-P2, which included 61% of all randomised patients, showed that efficacy of ixekizumab may continue in patients who completed the extension period.[8]

*Other data were also assessed but remain commercially confidential.**

## Summary of evidence on comparative safety

In SPIRIT-P1 treatment-emergent adverse effects were reported more frequently in the ixekizumab every four weeks group (66% [71/107]) and the adalimumab group (64% [65/101]) than the placebo group (47% [50/106]). Serious adverse events were reported by 5.6% (6/107) of patients in the ixekizumab group, 5% (5/101) of the adalimumab group and 1.9% (2/106) of the placebo group. Two patients in each group discontinued treatment due to an adverse event.[3]

Infections were the most frequently reported adverse events in 28% (30/107), 26% (26/101) and 26% (27/106) of the ixekizumab, adalimumab and placebo groups respectively. Injection site reactions were reported more frequently in the ixekizumab group (24% [26/107]) than the adalimumab group (5.9% [6/101]) or the placebo group (4.7% [5/106]). Hepatic events occurred more frequently in the adalimumab group, 13%, compared with 4.7% in the ixekizumab group and 6.6% in the placebo group.[3]

The safety profile of ixekizumab was similar in SPIRIT-P2.

Women of childbearing potential should use an effective method of contraception during treatment and for at least 10 weeks after treatment.[1]

## Summary of clinical effectiveness issues

Ixekizumab is the second IL-17 inhibitor to be licensed for psoriatic arthritis after secukinumab.

Psoriasis is a common, chronic, inflammatory, immune-mediated condition mainly affecting the skin and potentially joints. Approximately 20% of people with psoriasis also have psoriatic arthritis. Psoriatic arthritis is a painful, relapsing and remitting, life-long, inflammatory arthritis which can be debilitating and cause progressive joint damage. It has a negative impact on quality of life similar to ischaemic heart disease, diabetes, depression and cancer. Swollen joints, joint deformity and physical disability are visible in patients with psoriatic arthritis and can lead to feelings of stigmatisation. Severe psoriasis and psoriatic arthritis are associated with an increase in the standardised mortality ratio.[9]

Treatment for psoriatic arthritis includes NSAIDs (for short-term symptom relief), DMARDs and intra-articular corticosteroid injections, depending on the pattern and severity of the arthritis. Initially, conventional DMARDs such as methotrexate, sulfasalazine and leflunomide are recommended.[9] Biologic DMARDs (eg TNF-inhibitors) are considered where the psoriatic arthritis has not responded to adequate trials of at least two conventional DMARDs, administered either individually or in combination. In practice, if the first biologic DMARD fails another biologic DMARD may be used from the same or from a different class. In practice, the targeted synthetic DMARD (apremilast) may be used if biologic DMARDs are considered inappropriate.[12]

The submitting company has requested that SMC considers ixekizumab when positioned for use in adults with active psoriatic arthritis whose disease has not responded adequately to at least two conventional DMARDs given either alone or in combination, or who have received a biologic but their disease has not responded within the first 12 weeks or has stopped responding after 12 weeks,

or if TNF-inhibitors are contraindicated but would otherwise be considered. Clinical experts consulted by SMC state that secukinumab would be the most likely comparator.

The SPIRIT-P1 and SPIRIT-P2 studies included adult patients with active psoriatic arthritis. Patients in SPIRIT-P1 were not required to have had a previous inadequate response, or be intolerant to a conventional DMARD and were excluded if they had received a biologic DMARD. However only 14% of patients had never used a conventional DMARD and therefore there was a large subgroup of patients who were conventional DMARD-experienced and therefore representative of the licensed indication. Within this subgroup it is not known how many patients had received at least two prior conventional DMARDs. Over half of patients in SPIRIT-P1 were receiving methotrexate. In SPIRIT-P2 patients were required to have previously received a conventional DMARD and have had an inadequate response or intolerance to a TNF-inhibitor which represents part of the proposed positioning.[3, 4]

SPIRIT-P1 and SPIRIT-P2 showed superiority of ixekizumab compared with placebo for the primary outcome of proportion of patients achieving ACR20 and a number of secondary outcomes, assessing disease activity, disability, quality of life, and, in SPIRIT-P1, joint damage. The minimal disease activity outcome may be particularly relevant to the EULAR recommended clinical objectives of disease remission or minimal disease activity.[3, 4]

The double-blind placebo-controlled phase of SPIRIT-P1 and SPIRIT-P2 included 24 weeks of treatment which can be considered suitable for short-term outcomes such as disease activity but effect on joint damage may require longer-term data. SPIRIT-P1 aimed to assess the effect of ixekizumab on inhibition of radiographic progression however the EMA concluded it was difficult to make any conclusions from the results due to the short follow-up time. Week 52 results identified that patients in the ixekizumab group had a numerically larger mTSS change from baseline compared with patients initially randomised to placebo or adalimumab, both groups changed to ixekizumab at Week 16 or 24.[2] Data on radiographic progression were not collected in SPIRIT-P2.

In SPIRIT-P2 patients who had previously received more than two TNF-inhibitors or previously received interleukin-17 or interleukin-12 / 23 inhibitors were excluded. In addition, patients in both studies were excluded if they used conventional DMARDs other than methotrexate, leflunomide, sulfasalazine, or hydroxychloroquine in the eight weeks prior to baseline, and they were also excluded if they were taking more than one conventional DMARD. These factors could potentially affect the generalisability of the studies to the Scottish population.

There are no data related to a relevant comparator in the population of patients in SPIRIT-P2 who had previously received a conventional DMARD and also had a previous inadequate response or intolerance to a TNF inhibitor and represent part of the proposed positioning.

Since comparative data are limited, the submitting company presented results of Bayesian network meta-analyses (NMAs) of 16 studies to compare ixekizumab with other biologic DMARDs in patients with active psoriatic arthritis. The first NMA included 14 studies in a biologic-naïve patient population and the comparators were adalimumab, secukinumab, golimumab, infliximab, etanercept, apremilast, and certolizumab pegol. The target population included patients with active psoriatic arthritis but was not restricted to the proposed positioning. The second NMA of two studies compared ixekizumab with ustekinumab in a biologic-experienced patient population. In addition, a sensitivity analysis was conducted in the biologic-experienced population including secukinumab (the most relevant comparator) and certolizumab pegol. Some studies included in the NMAs however contained mixed populations. These comparators were used in the economics.

Efficacy outcomes included were ACR20/50/70, PASI50/75/90/100, improvements in Psoriatic arthritis Response Criteria (PsARC) and change from baseline in HAQ-DI.

There was heterogeneity across the included studies with respect to baseline characteristics and time points used for outcomes included in the NMAs. There was also variation in event rates for some outcomes in the placebo groups of the studies.

The results of the NMA suggest that infliximab and golimumab may be superior to ixekizumab and that apremilast may be inferior for some of the outcomes in the biologic-naïve NMA. It is difficult to draw firm conclusions about the other comparisons; credible intervals were wide (potentially due to small number of studies) and some included one. Overall, despite the limitations, it is reasonable to suggest comparable efficacy between ixekizumab and biologic DMARD comparators based on the results of the NMAs.

Ixekizumab would provide another treatment option for patients with psoriatic arthritis who have failed on treatment with two conventional DMARDs or had an inadequate response to or are intolerant to a biologic DMARD. This may represent the patient population who are more difficult to treat. Clinical experts consulted by SMC considered that the place in therapy for ixekizumab would be as an alternative to secukinumab. It is administered subcutaneously every four weeks so is not likely to have a major impact on the patient or the service. For patients with concomitant moderate to severe plaque psoriasis, the dose regimens for both ixekizumab and secukinumab are the same as for plaque psoriasis. In the case of ixekizumab this involves more frequent dosing over the initial 12-week period, whereas secukinumab requires double dosing for both initial and maintenance treatment which also applies to patients who have had an inadequate response to TNF-inhibitors.

## Summary of comparative health economic evidence

The company submitted a cost- minimisation analysis comparing ixekizumab to a number of comparators including adalimumab, apremilast, certolizumab pegol, etanercept, golimumab, infliximab, secukinumab and ustekinumab in patients with active psoriatic arthritis whose disease has not yet responded adequately to trials of at least two conventional DMARDs given either alone or in combination, or who have not been able to tolerate or have a contraindication to DMARD therapy. The time horizon in the analysis was 10 years. Based on SMC expert responses, secukinumab appears to be the comparator most likely to be displaced in Scotland. It is worth noting that the company has presented results for two subgroups i.e. those with concomitant moderate to severe psoriasis and those without, due to the dosing of ixekizumab being slightly different in these two groups. The analysis also included the higher dose of secukinumab licensed for patients with concomitant moderate to severe psoriasis or who have had an inadequate response to TNF-inhibitors.

The clinical data used to support the assumption of comparable efficacy came from the NMAs as discussed in the clinical section of the DAD. Based on this analysis, infliximab and golimumab appear to be superior to ixekizumab and apremilast was inferior for some of the outcomes in the biologic-naïve NMA. Overall, based on the results of the NMAs, ixekizumab appears to be comparable to other biologic DMARDs in terms of efficacy.

Medicines acquisition costs were included in the analysis. For patients without moderate to severe psoriasis medicines acquisition costs for ixekizumab were based on two 80mg injections at week 0,

followed by 80mg (one injection) every 4 weeks thereafter. For patients with moderate to severe psoriasis dosing was more frequent i.e. for ixekizumab drug costs were based on two 80mg injections at week 0, followed by 80mg (one injection) at weeks 2, 4, 6, 8, 10 and 12, then maintenance dosing of 80mg (one injection) every 4 weeks. Administration costs for subcutaneous treatments were not included for any subcutaneous biologic DMARD, as costs were assumed to be the same for all treatments i.e. a home care delivery system is assumed to be provided for all subcutaneous biologic DMARD treatments. IV administration costs were included for infliximab. No adverse event costs were included in the analysis.

A patient access scheme (PAS) was submitted for ixekizumab and was assessed as acceptable for implementation by the Patient Access Scheme Assessment Group (PASAG). PAS discounts are in place for secukinumab and certolizumab pegol and these were included in the results used for decision-making by SMC by using estimates of the comparator PAS prices.

**Table 2: Base case results without PAS (for patients without concomitant moderate to severe psoriasis)**

| Treatment | Total cost over 10 years | Incremental costs over 10 years | Incremental average costs per year |
|---|---|---|---|
| ixekizumab | £128,137 | - | - |
| secukinumab (150mg) (TNF naive) | £65,383 | £62,755 | £6,275 |
| secukinumab (300mg) (TNF failure) | £130,766 | -£2,628 | -£263 |
| adalimumab | £78,809 | £49,329 | £4,933 |
| apremilast | £61,515 | £66,622 | £6,662 |
| etanercept | £73,406 | £54,731 | £5,473 |
| golimumab | £78,809 | £49,329 | £4,933 |
| infliximab | £106,625 | £21,513 | £2,151 |
| ustekinumab | £83,607 | £44,530 | £4,453 |
| certolizumab pegol | £81,081 | £47,056 | £4,705 |

*A negative figure denotes incremental savings with ixekizumab

**Table 3: Base case results without PAS (for patients with concomitant moderate to severe psoriasis)**

| Treatment | Total cost over 10 years | Incremental cost/savings over 10 years | Incremental average cost/savings per year |
|---|---|---|---|
| ixekizumab | £131,512 | - | - |
| secukinumab (150mg) | N/A | N/A | N/A |
| secukinumab (300mg) | £130,766 | £747 | £75 |
| adalimumab | £78,809 | £52,704 | £5,270 |
| apremilast | £61,515 | £69,997 | £7,000 |
| etanercept | £73,406 | £58,106 | £5,811) |
| golimumab | £78,809 | £52,704 | £5,270 |
| infliximab | £106,625 | £24,888 | £2,489 |

| | | | |
|---|---|---|---|
| ustekinumab | £83,607 | £47,905 | £4,791 |
| certolizumab pegol | £81,081 | £50,431 | £5,043 |

*A negative figure denotes incremental savings

As noted, the results presented do not take account of the PAS for secukinumab and certolizumab pegol or the PAS for ixekizumab but these were considered in the results used for decision-making at SMC. SMC is unable to present the results provided by the company which used an estimate of the PAS price for secukinumab and certolizumab pegol due to commercial confidentiality and competition law issues.

There were a number of limitations within the analysis, including the following;

- The company provided results for two subgroups in their economic analysis i.e. those with concomitant moderate to severe psoriasis and those without (as the dosing of ixekizumab is different in these groups). However, as SMC has previously accepted ixekizumab (SMC ID 1223/17), for restricted use in patients with moderate to severe psoriasis, the most relevant results for decision making are considered to be for patients without concomitant moderate to severe psoriasis (Table 2). As shown in table 2, the economic results are markedly different versus secukinumab dependent on whether or not a patient is TNF-naïve or TNF-experienced given the different dosing (and hence cost) of secukinumab.
- There was a lack of focus regarding the most appropriate comparator. As such there are a large set of results to interpret. However, based on SMC expert responses secukinumab appears to be the comparator most likely to be displaced in Scotland.

Despite these issues, the economic case was considered to be demonstrated in patients whose disease has not responded adequately to at least two conventional DMARDs given either alone or in combination, and who have had an inadequate response to a TNF inhibitor.

*Other data were also assessed but remain commercially confidential.**

## Summary of patient and carer involvement

The following information reflects the views of the specified Patient Groups.

- We received patient group submissions from The Psoriasis Association and the Psoriasis and Psoriatic Arthritis Alliance (PAPAA), both organisations are registered charities.

- PAPAA has not received any pharmaceutical company funding in the past two years. The Psoriasis Association has received 4.1% pharmaceutical company funding in the past two years, including from the submitting company.

- Psoriatic arthritis is painful and debilitating and very often affects people in young or mid adulthood. Symptoms such as pain, fatigue, stiffness and swelling can make it difficult to carry out normal everyday tasks. It can flare up unpredictably and this impacts greatly on the ability of people with the condition to work or study consistently, or make future

commitments. Living with a multi-factorial disease and treatment regimes that are often difficult to use or have unpleasant side-effects is demoralising and can have a huge impact on mental health, quality of life, family and other relationships.

- Non-steroidal anti-inflammatory drugs and steroid injections are used to improve the symptoms of psoriatic arthritis but disease modifying treatments are needed to ensure long-term management and stability and prevent irreversible joint damage. A number of biologic and non-biologic disease-modifying treatments are available but not everyone will achieve an adequate response with them.

- Ixekizumab would provide an additional biologic disease-modifying treatment option which may be of particular benefit to people whose options for treating and managing their psoriatic arthritis are running out. Every person with psoriatic arthritis is different, and what works for one will not necessarily work for another. Therefore, the patient groups support the availability of the widest possible range of effective treatments.

## Additional information: guidelines and protocols

Available guidelines pre-date the availability of ixekizumab.

The 2010 SIGN guideline for the diagnosis and management of psoriasis and psoriatic arthritis in adults states that treatment for psoriatic arthritis may include NSAIDs (for short-term symptom relief), DMARDs and intra-articular corticosteroid injections, depending on the pattern and severity of the arthritis. Initially, conventional DMARDs such as methotrexate, sulfasalazine and leflunomide are recommended. The biologic DMARDs adalimumab, etanercept or infliximab are recommended for treatment of active psoriatic arthritis in patients who have failed to respond to, are intolerant of, or have had contraindications to, at least two disease-modifying therapies.[9]

National Institute for Health and Care Excellence (NICE) (Multiple) Technology Appraisal Guidance number 199 on etanercept, infliximab and adalimumab for the treatment of psoriatic arthritis was adopted by Healthcare Improvement Scotland (HIS) in August 2010. This recommends biologic DMARDs etanercept, infliximab and adalimumab for the treatment of active and progressive psoriatic arthritis in adult patients with peripheral arthritis with three or more tender joints and three or more swollen joints, and the psoriatic arthritis has not responded to adequate trials of at least two conventional DMARDs, administered either individually or in combination. [10]

HIS also adopted NICE MTA number 445 on certolizumab pegol and secukinumab for treating active psoriatic arthritis after inadequate response to DMARDs in May 2017. This recommends certolizumab pegol and secukinumab alone, or in combination with methotrexate as options for treating active psoriatic arthritis in adults only if used as described in the NICE Technology Appraisal 199 or if the person has received a TNF-inhibitor but their disease has stopped responding after the first 12 weeks. Secukinumab is also recommended as a treatment option in patients who have not responded to TNF-inhibitors within the first 12 weeks, or where TNF-inhibitors are contraindicated but would otherwise be considered. [11]

The European League against Rheumatism (EULAR) published updated recommendations in 2015. These comprise five overarching principles and ten recommendations, covering pharmacological therapies for psoriatic arthritis. The overarching principles address the need for shared decision-making and treatment objectives, that is, treatment should be aimed at reaching the target of

remission or, alternatively, minimal/low disease activity, by regular monitoring and appropriate adjustment of therapy. The recommendation indicate that initially in patients with psoriatic arthritis, NSAIDs may be used to relieve musculoskeletal signs and symptoms. Conventional DMARDs are recommended as an initial therapy after failure of NSAIDs and local therapy for active disease, followed, if necessary, by a biologic DMARD or a targeted synthetic DMARD. The first biologic DMARD would usually be a TNF-inhibitor. Biologic DMARDs targeting interleukin (IL)-12/23 (ustekinumab) or IL-17 pathways (secukinumab) may be used in patients for whom TNF-inhibitors are inappropriate and a targeted synthetic DMARD such as apremilast, a phosphodiesterase 4-inhibitor, if biologic DMARDs are inappropriate. If the first biologic DMARD strategy fails, any other biologic DMARD or targeted synthetic DMARD may be used.[12]

The 2012 British Society for Rheumatology guidelines are currently under review.

## Additional information: comparators

Relevant comparators include biologic DMARDs: etacercept, infliximab, adalimumab, golimumab, certolizumab (all TNF-inhibitors), secukinumab (IL-17 inhibitor), ustekinumab (IL-12/23 inhibitor) and apremilast (phosphodiesterase 4 inhibitor).

Clinical experts considered secukinumab is the most relevant comparator.

## Cost of relevant comparators

| Medicine | Dose Regimen | Cost per year (£) |
|---|---|---|
| **ixekizumab** | **160mg SC at week 0, followed by 80mg SC every 4 weeks or 80mg SC at weeks 2, 4, 6, 8, 10, 12 then every 4 weeks.** | **First year: 16,875 or 20,250**<br>**Subsequent years: 14,625** |
| secukinumab | 150 mg or 300mg SC every week for 5 doses, then once every month. | First year: 9,750 or 19,500<br>Subsequent years: 7,313 or 14,625 |
| golimumab | 50mg SC once a month, patients body weight >100kg who do not achieve an adequate clinical response after 3 or 4 doses, consider increasing to 100mg once a month. | First year: 9,156 to 16,022<br>Subsequent years: 9.156 to 18,311 |
| infliximab | 5 mg/kg IV infusion, then 5 mg/kg at 2 and 6 weeks after the first infusion, then every 8 weeks thereafter. | First year: 12,064<br>Subsequent years: 9,802 |

| | | |
|---|---|---|
| ustekinumab | 45 mg SC, followed by a 45 mg dose 4 weeks later, and then every 12 weeks thereafter. Alternatively, 90mg patients with body weight >100kg. | First year: 12,882<br>Subsequent years: 9,304 |
| certolizumab | 400mg SC at weeks 0, 2, 4 then 200mg every 2 weeks. | First year: 10,368<br>Subsequent years: 9,295 |
| adalimumab | 40mg SC every 2 weeks. | 9,156 |
| etanercept | 25mg SC twice weekly or 50mg weekly. | 8,366 |
| apremilast | 10 mg orally on day 1, then 10 mg twice daily on day 2, then 10 mg in the morning and 20 mg in the evening on day 3, then 20 mg twice daily on day 4, then 20 mg in the morning and 30 mg in the evening on day 5, then maintenance 30 mg twice daily. | First year: 7,140<br>Subsequent years: 7,150 |

*Doses are for general comparison and do not imply therapeutic equivalence. Costs from BNF online (MIMs for apremilast titration pack) on 29 July 2018. Costs calculated using the full cost of vials/ampoules assuming wastage. Costs do not take any patient access schemes into consideration. Cost for infliximab assumes a bodyweight of 70kg. Costs for infliximab and etanercept reflect the lowest list prices for the reference and biosimilar products. SC: subcutaneous, IV: intravenous.*

## Additional information: budget impact

The submitting company estimated there would be 257 patients eligible for treatment with ixekizumab in all years. The estimated uptake rate was 5% in year 1 (13 patients), rising to 25% in year 5 (64 patients).

SMC is unable to publish the with PAS budget impact due to commercial in confidence issues. A budget impact template is provided in confidence to NHS health boards to enable them to estimate the predicted budget with the PAS.

*Other data were also assessed but remain commercially confidential.**

References

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This assessment is based on data submitted by the applicant company up to and including 17 August 2018.

**Agreement between the Association of the British Pharmaceutical Industry (ABPI) and the SMC on guidelines for the release of company data into the public domain during a health technology appraisal: http://www.scottishmedicines.org.uk/About_SMC/Policy*

Medicine prices are those available at the time the papers were issued to SMC for consideration. SMC is aware that for some hospital-only products national or local contracts may be in place for comparator products that can significantly reduce the acquisition cost to Health Boards. These contract prices are commercial in confidence and cannot be put in the public domain, including via

the SMC Detailed Advice Document. Area Drug and Therapeutics Committees and NHS Boards are therefore asked to consider contract pricing when reviewing advice on medicines accepted by SMC.

Patient access schemes: A patient access scheme is a scheme proposed by a pharmaceutical company in order to improve the cost-effectiveness of a medicine and enable patients to receive access to cost-effective innovative medicines. A Patient Access Scheme Assessment Group (PASAG), established under the auspices of NHS National Services Scotland reviews and advises NHS Scotland on the feasibility of proposed schemes for implementation. The PASAG operates separately from SMC in order to maintain the integrity and independence of the assessment process of the SMC. When SMC accepts a medicine for use in NHS Scotland on the basis of a patient access scheme that has been considered feasible by PASAG, a set of guidance notes on the operation of the scheme will be circulated to Area Drug and Therapeutics Committees and NHS Boards prior to publication of SMC advice.

**Advice context:**

*No part of this advice may be used without the whole of the advice being quoted in full.*

*This advice represents the view of the Scottish Medicines Consortium and was arrived at after careful consideration and evaluation of the available evidence. It is provided to inform the considerations of Area Drug & Therapeutics Committees and NHS Boards in Scotland in determining medicines for local use or local formulary inclusion. This advice does not override the individual responsibility of health professionals to make decisions in the exercise of their clinical judgement in the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.*