Healthcare Improvement Scotland | SMC Advice on new medicines

SMC2440

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

Eli Lilly & Company Ltd

06 May 2022

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 summarised as follows:

ADVICE: following a full submission

ixekizumab (Taltz®) is not recommended for use within NHSScotland.

Indication under review:
Ankylosing spondyloarthritis (radiographic axial spondyloarthritis)
Treatment of adult patients with active ankylosing spondylitis who have responded inadequately to conventional therapy.

Non-radiographic axial spondyloarthritis
Treatment of adult patients with 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 nonsteroidal anti-inflammatory drugs (NSAIDs).

In three phase III studies, ixekizumab, compared with placebo, significantly improved symptoms of active radiographic and non-radiographic axial spondyloarthritis (axSpA) in patients who had not previously received biologic medicines, and in patients with active radiographic axSpA who had an inadequate response or intolerance to TNF-alpha inhibitors.

The submitting company did not present a sufficiently robust economic analysis to gain acceptance by SMC.

Chairman,
Scottish Medicines Consortium

Indication

Ankylosing spondylitis (radiographic axial spondyloarthritis)

Treatment of adult patients with active ankylosing spondylitis who have responded inadequately to conventional therapy.

Non-radiographic axial spondyloarthritis

Treatment of adult patients with 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 nonsteroidal anti-inflammatory drugs (NSAIDs).

Dosing Information

The recommended dose is 160mg (two 80mg injections) by subcutaneous injection at week 0, followed by 80mg every 4 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 axial spondyloarthritis. See the Summary of product characteristics (SPC) for further information.[1]

Product availability date

02 June 2020

Summary of evidence on comparative efficacy

Ixekizumab is a monoclonal antibody, which selectively binds to interleukin 17A (IL-17A), a proinflammatory cytokine. Elevated concentrations of IL-17A have been implicated in the pathogenesis of axial spondyloarthritis (axSpA) by driving inflammation leading to erosive bone damage and pathological new bone formation. Neutralisation of IL-17A by ixekizumab inhibits these actions and mitigates disease activity.[1, 2]

The submitting company has requested that SMC considers ixekizumab when positioned for use in:

- Adult patients with active radiographic axSpA who have responded inadequately to conventional therapy in whom tumour necrosis factor (TNF)-alpha inhibitor treatment is contraindicated or otherwise unsuitable, or does not control the condition well enough
- Adult patients with active non-radiographic axSpA with objective signs of inflammation as indicated by elevated C-reactive protein (CRP) and/or magnetic resonance imaging (MRI) who have responded inadequately to nonsteroidal anti-inflammatory drugs (NSAIDs) in whom

tumour necrosis factor (TNF)-alpha inhibitor treatment is contraindicated or otherwise unsuitable, or does not control the condition well enough.

Evidence to support the indications under review is from three randomised double-blind phase III studies, COAST-V, COAST-W, and COAST-X. All studies recruited adult patients (≥18 years) with axSpA (according to Assessment of Spondyloarthritis International Society [ASAS]) with active disease (based on a Bath Ankylosing Spondylitis Disease Activity Index [BASDAI] score ≥4 and a score of ≥4 on the total back pain numeric rating scale) and a history of back pain for at least 3 months with the age of onset <45 years. In all studies, eligible patients had a history of prior therapy for axSpA of at least 12 weeks prior to screening and had an inadequate response to two or more NSAIDs or had a history of intolerance to NSAIDs. In COAST-V (TNF-alpha inhibitor naïve) and COAST-W (TNF-alpha inhibitor experienced), patients fulfilled the radiological criteria of the modified New York criteria for AS (sacroiliitis grade ≥2 bilaterally or grades 3 to 4 unilaterally). In COAST-W, patients were required to have discontinued one or two TNF-alpha inhibitors, either due to intolerance or an inadequate response (defined as in the opinion of the investigator, an inadequate response to at least 12 weeks of treatment with a TNF-alpha inhibitor at an adequate dose). In COAST-X (TNF-alpha inhibitor naïve) patients had non-radioagraphic axSpA (nr-axSpA), and were biologic-naïve. [2-5]

In the COAST-V study, patients were randomised equally to receive ixekizumab 80mg every 2 weeks, ixekizumab 80mg every 4 weeks, adalimumab 40mg every 2 weeks or matching placebo via subcutaneous injection for 16 weeks. However, the study was not powered to test for differences in comparisons between ixekizumab and adalimumab. In the COAST-W and COAST-X patients were randomised equally to receive ixekizumab 80mg every 2 weeks, ixekizumab 80mg every 4 weeks or matching placebo via subcutaneous injection for 16 weeks. Patients in the ixekizumab groups were randomised equally to receive a first dose of 80mg or 160mg at week 0. Patients could continue to receive sulfasalazine (≤3grams/day), methotrexate (≤25mg/week) or hydroxychloroquine (≤400mg/day), prednisone or equivalent (≤10mg/day), opioid analgesics (equivalent to morphine ≤30mg/day) and NSAIDs provided they were at a stable dose prior to baseline, with no changes permitted during the initial 16 weeks, except for safety reasons. In COAST-V and COAST-W, after the first 16 weeks patients in the placebo or adalimumab groups (COAST-V only) were re-randomised to receive one of the two ixekizumab dosing regimens. All patients continued to receive blinded treatment until week 52, after which patients could enter the open-label extension study COAST-Y. In COAST-X, from week 16 to week 44, patients identified as an inadequate responder could be offered changes to background therapy or biologic rescue therapy (open-label ixekizumab 80mg 2-weekly or subsequent TNF-alpha inhibitor), or both, at the discretion of the investigator, while remaining blinded to the original randomisation treatment assignment. Randomisation was stratified according to country and results of a CRP screening (≤5mg/L or >5mg/L) (COAST-V and COAST-W), MRI and CRP status at screening (MRI-positive and CRP-positive or MRI-positive and CRP-negative or MRI-negative and CRP-positive) (COAST-X), and the number of prior TNF-alpha inhibitors (one or two) (COAST-W).[2-5]

The primary outcome was the proportion of patients achieving an ASAS40 response measured at week 16 in all studies and also at week 52 for COAST-X. This was defined as at least a 40% improvement and an absolute improvement from baseline of at least two units (range 0–10) in at least three out of four patient domains (patient global, spinal pain, function and inflammation), without any worsening in the remaining domain. Efficacy analyses were performed in the intention-to-treat (ITT) population, which included all patients who underwent randomisation, analysed according to the group they were randomised to. In the primary analysis, the ixekizumab groups were assessed according to dosing frequency regardless of starting dose.[2-5]

A hierarchical statistical testing strategy was applied in all studies with no formal testing of outcomes after the first non-significant outcome in the hierarchy. In COAST-V and COAST-W, at week 16 ixekizumab was associated with a statistically significant improvement in ASAS40 response compared with placebo in patients with radiographic axSpA (r-axSpA). This was supported by statistically significant improvements in secondary outcomes included in the hierarchy.[2-4] Results for the primary and hierarchically tested secondary outcomes are presented in table 1 with only the ixekizumab 4-weekly group included, which is the licensed dosing regimen.

Table 1: Primary and secondary outcomes in r-axSpA (COAST-V and COAST-W) at week 16 in the ITT[1-6]

	COAST-V (TNF-alpha inhibitor naïve r-axSpA)			**COAST-W (TNF-alpha inhibitor experienced r-axSpA)**	
	Adalimumab (n=90)	**Ixekizumab 4-weekly (n=81)**	**Placebo (n=87)**	**Ixekizumab 4-weekly (n=114)**	**Placebo (n=104)**
Primary outcome: ASAS40 response at week 16					
Response, %	36%	48%	18%	25%	12%
Difference versus placebo (95% CI), p-value	17% (4.4 to 30)	30% (16 to 43), p<0.001		13% (2.7 to 23), p=0.017	
Secondary outcomes at week 16					
ASAS20 response, %	59%	64%[A]	40%	48%[B]	30%
ASDAS CFB, LSM	-1.30	-1.43[A]	-0.46	-1.16[B]	-0.11
BASDAI50 response, %	32%	42%[A]	17%	22%[C]	9.6%
BASDAI CFB, LSM	-	-	-	-2.17[B]	-0.92
BASFI CFB, LSM	-2.14	-2.39[A]	-1.16	-1.69[B]	-0.64
SF-36 PCS CFB, LSM	6.90	7.70[A]	3.64	6.58[B]	1.36
MRI spine SPARCC CFB, LSM	-11.6	-1.5	-11.0	-2.99[B]	3.29
ASDAS <1.3 (inactive disease), %	16%	16%[A]	2%	-	-
ASDAS <2.1 (inactive or low disease activity), %	-	-	-	18%[B]	4.8%
ASAS-HI CFB, LSM	-2.30	-2.36[B]	-1.25	-1.92[B]	-0.89

ASAS=Assessment of SpondyloArthritis international Society, ASDAS=Ankylosing Spondylitis Disease Activity Score, axSpA=axial spondyloarthritis, BASDAI=Bath Ankylosing Spondylitis Disease Activity Index, BASFI=Bath Ankylosing Spondylitis Functional Index, CI=confidence interval, HI=health index, ITT=intention-to-treat, LSM=least squares mean, CFB=change from baseline, MRI=magnetic resonance imaging, SPARCC=Spondyloarthritis Research Consortium of Canada, SF-36 PCS=Short Form-36 Physical Component Score, TNF=tumour necrosis factor. [A]p-values <0.01 for ixekizumab versus placebo when adjusted for multiplicity, [B]p-value <0.05 for ixekizumab versus placebo when adjusted for multiplicity. Comparisons for adalimumab versus placebo were not adjusted for multiplicity therefore p-value is not indicated. [C]Not included in hierarchy but relevant to economic case

In both studies at week 52, the ASAS40 response rate was maintained for patients who received ixekizumab every 4 weeks during the first 16 weeks; ASAS40 response at week 52 was 53% in COAST-V and 30% in COAST-W. The initial starting dose of 160mg compared with 80mg did not indicate improved results at week 16 in either study.[2-4]

In COAST-X, at week 16, ixekizumab 4-weekly was associated with a statistically significant improvement in ASAS40 response compared with placebo in patients with nr-axSpA. This was supported by statistically significant improvements in key secondary outcomes included in the hierarchy. The results are presented in table 2.[2, 5]

Table 2: Primary and secondary outcomes in TNF-alpha inhibitor naïve nr-axSpA (COAST-X) at week 16 in the ITT[2, 5, 7]

	Ixekizumab 4-weekly (n=96)	Placebo (n=105)
Primary outcome: ASAS40 response at week 16		
Response, %	35%	19%
Difference versus placebo (95% CI), p-value	16% (4.2 to 28), p<0.01	
Secondary outcomes at week 16		
ASDAS CFB, LSM	-1.12[B]	-0.58
BASDAI CFB, LSM	-2.18[B]	-1.51
BASFI CFB, LS	-2.01[C]	-1.34
SF-36 PCS CFB, LSM	8.06[B]	5.21
ASDAS <2.1 response, %	28%[B]	12%
MRI SIJ SPARCC CFB, LSM	-3.38[B]	-0.31

ASAS=Assessment of SpondyloArthritis international Society, ASDAS=Ankylosing Spondylitis Disease Activity Score, axSpA=axial spondyloarthritis, BASDAI=Bath Ankylosing Spondylitis Disease Activity Index, BASFI=Bath Ankylosing Spondylitis Functional Index, CFB=change from baseline, CI=confidence interval, ITT=intention-to-treat, LSM=least squares mean, MRI=magnetic resonance imaging, SIJ=sacroiliac joints, SPARCC=Spondyloarthritis Research Consortium of Canada, SF-36 PCS=Short Form-36 Physical Component Score, TNF=tumour necrosis factor. [A]p-values <0.01 for ixekizumab versus placebo when adjusted for multiplicity, [B]p-value <0.05 for ixekizumab versus placebo when adjusted for multiplicity.

In COAST-X by week 52, 48% of patients had switched to rescue treatment with open-label ixekizumab 2-weekly (including 42% [40/96] in the ixekizumab 4-weekly group and 59% [62/105] in the placebo group). Most patients switched between weeks 16 and 24 and 3% subsequently switched to a TNF-alpha inhibitor. The 52-week period was completed by 88% (265/303), 46% remained in their originally randomised group and 42% were receiving open-label ixekizumab. At week 52, an ASAS40 response was achieved by 30% in the ixekizumab 4-weekly group compared

with 13% in the placebo group. The starting dose of 80mg or 160mg ixekizumab did not affect the ASAS40 results at weeks 16 or 52.[2, 5]

Health Related Quality of Life was assessed using Assessment of Spondyloarthritis International Society-Health Index (ASAS-HI), European Quality of Life – 5 Dimensions 5 Level (EQ-5D-5L), Fatigue Severity Numeric Rating Scale (NRS), Jenkins Sleep Evaluation Questionnaire (JSEQ), Quick Inventory of Depressive Symptomatology—Self-Report 16 Items (QIDS-SR16), Short Form (SF)-36 and Work Productivity Activity Impairment–Spondyloarthritis (WPAI-SpA). Results for ASAS-HI and SF-36 PCS have been reported in Tables 1 and 2.[6-8]

COAST-Y is an ongoing, 104-week long-term extension study including a double-blind, placebo-controlled, randomised withdrawal-retreatment period of patients who had completed the final study visit for COAST-V, COAST-W or COAST-X. Available data at week 64 of COAST-Y suggests ASAS40 and at least a 50% improvement in the Bath Ankylosing Spondylitis Disease Activity Index score from baseline (BASDAI50) responses are maintained for patients taking ixekizumab 4-weekly.[9]

The submitting company performed Bucher indirect treatment comparisons (ITCs) comparing ixekizumab with secukinumab in three populations: biologic-naïve and biologic-experienced r-axSpA (data from COAST-V[3], COAST-W[10], MEASURE-2[11], MEASURE-4[12] and MEASURE-5[13]); and biologic-naïve nr-axSpA (COAST-X[5] and PREVENT[10]). The populations included adult patients who had not previously received biologic medicines (biologic-naïve), or who had an inadequate response or intolerance to TNF-alpha inhibitors (biologic-experienced). The outcomes reported in the ITC were the proportion achieving an ASAS40 response and change from baseline in BASDAI score at 16 weeks for the r-axSpA population, and an ASAS40 response at 16 weeks in the nr-axSpA population. In all three patient populations for the outcomes assessed, the submitting company concluded that no statistically significant difference in efficacy was identified. In addition, they noted that there are insufficient data available to substantiate robustly the assumption of equivalent efficacy between these two treatments.

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

Summary of evidence on comparative safety

Overall, the safety profile for ixekizumab was considered consistent with that observed for other indications. No new safety issues were identified and imbalances in some adverse events (urinary tract infection including pyelonephritis and infectious diarrhoea and depression-related or suicide/self-injury-related adverse events) will be monitored in the post-marketing setting.[2]

An integrated safety analysis was conducted combining data up to 16 weeks from COAST-V, COAST-W and COAST-X. In the integrated safety analysis, the mean duration of treatment was 111 days in the ixekizumab 4-weekly group and 112 days in the placebo group. Any treatment-

emergent adverse event (AE) was reported by 56% (162/291) of patients in the ixekizumab group and 47% (138/294) in the placebo group. In each group respectively, patients reporting a serious AE were 1.7% versus 2.0% and patients discontinuing therapy due to an AE was 3.4% versus 1.4%.[2]

The most frequently reported treatment-emergent AEs of any grade with an incidence >2% in the ixekizumab 4-weekly group versus the placebo group were: nasopharyngitis (8.2% versus 5.1%), upper respiratory tract infection (6.5% versus 3.1%), injection site reaction (4.5% versus 2.4%), arthralgia (3.4% versus 1.4%), hypertension (2.1% versus 2.7%) and diarrhoea (2.7% versus 1.4%). The most common AEs of special interest in the ixekizumab 4-weekly group versus the placebo group were infections (27% versus 16%), injection site reactions (9.3% versus 5.8%), hepatic events (2.7% in both groups), allergic reactions/hypersensitivities (2.4% versus 1.7%) and non-anaphylaxis (2.4% versus 1.4%). See the SPC for further information.[1, 2]

Summary of clinical effectiveness issues

AxSpA is a chronic inflammatory condition that predominantly affects the spine and sacroiliac joints, with or without extra-spinal manifestations (including peripheral arthritis, inflammatory eye conditions, psoriasis and inflammatory bowel disease). The disease can be categorised into two subgroups: r-axSpA (also known as ankylosing spondylitis [AS]) and nr-axSpA. These differ by the presence or absence of defined structural changes in the sacroiliac joints on plain radiography.[14, 15] Guidelines recommend NSAIDs as first-line pharmacological treatment for pain associated with axSpA. TNF-alpha inhibitors are recommended for patients with severe active r-axSpA and severe nr-axSpA whose disease has responded inadequately to, or who cannot tolerate NSAIDs. TNF-alpha inhibitor options include infliximab (severe active r-axSpA only), adalimumab, certolizumab pegol, etanercept and golimumab. Treatment with an alternative TNF-alpha inhibitor is recommended for people who cannot tolerate, or whose disease has not responded to, treatment with the first TNF-alpha inhibitor, or whose disease has stopped responding after an initial response. Anti-IL17 therapy may also be considered if TNF-alpha inhibitor treatment fails.[14, 16] Secukinumab (an anti-IL17 therapy) is licensed and accepted by SMC for the treatment of active r-axSpA which has responded inadequately to conventional therapy (SMC 1159/16) and active nr-axSpA that has responded inadequately to NSAIDs (SMC2308).

The submitting company has requested that SMC considers ixekizumab when positioned for use as described in the clinical efficacy section. COAST-V (r-axSpA) and COAST-X (nr-axSpA) excluded patients who had received prior treatment with biologic disease-modifying antirheumatic drugs (DMARDs); these studies provide evidence in TNF-alpha inhibitor naïve patients. However, the exclusion criteria did not specify that patients should have a contraindication or were unsuitable for TNF-alpha inhibitors and therefore do not match the positioned population. COAST-W provides evidence for patients with r-axSpA who have had an inadequate response or intolerance to TNF-alpha inhibitors; however, there is a lack of data in TNF-alpha inhibitor experienced patients with nr-axSpA and therefore effectiveness in this population is uncertain. The submitting company considered that evidence in TNF-experienced patients with r-axSpA is suitable to inform decision-

making based on comparable levels of inflammation observed on imaging and a similar treatment pathway. Clinical experts consulted by SMC considered that it was reasonable to assume a similar response to ixekizumab in biologic-experienced patients with r-axSpA and nr-axSpA.

Treatment with ixekizumab 4-weekly was superior to placebo, measured by the primary outcome of ASAS40 at week 16 in patients with r-axSpA who were TNF-alpha inhibitor naïve (COAST-V: 48% versus 18%) and TNF-alpha inhibitor experienced (COAST-W: 25% versus 12%). A lower response rate in patients who have previously received TNF-alpha inhibitors was expected. Ixekizumab 4-weekly was also superior to placebo for ASAS40 in patients with nr-axSpA who were TNF-alpha inhibitor naïve at week 16 (COAST-X: 35% versus 19%). Secondary outcomes were supportive in all three studies with statistically significant improvements in outcomes measuring disease activity, objective signs of inflammation, function and quality of life. The favourable effects of ixekizumab were observed as early as week one and were maintained up to week 52. Results from the COAST studies were considered clinically relevant.[2-5]

There were some limitations associated with the COAST studies. In COAST-X, after week 16 patients with an investigator-assessed inadequate response could receive rescue treatment with open-label ixekizumab every 2 weeks. As a large proportion of patients switched to open-label rescue treatment (42% in the ixekizumab 4-weekly group and 59% in the placebo group), the 52 week results are likely to be less robust.[2, 5] The studies did not establish whether treatment with ixekizumab should continue long-term in responders, particularly those with nr-axSpA, or if dose tapering or treatment discontinuation should be considered. This has been assessed during the 40-week randomised withdrawal-retreatment period in COAST-Y; 83% (40/48) of patients in the ixekizumab 4-weekly group remained flare-free compared with 55% (29/53) who withdrew to placebo.[17] However the sample size is limited and results are descriptive, therefore these results should be interpreted with caution.

In the COAST studies, patients were permitted to continue treatment with methotrexate, sulfasalazine or hydroxychloroquine (use ranged from 27% in COAST-W to 40% in COAST-X) and most patients continued to receive NSAIDs (use ranged from 76% in COAST-W to 92% in COAST-V).[3-5] The studies did not analyse the efficacy of combinations of concomitant treatments which may differ from clinical practice in Scotland and affect the generalisability of results.

The COAST studies compared ixekizumab to placebo, which the submitting company considered a proxy for conventional care. COAST-V also included an active comparator, adalimumab however this is not a relevant comparator based on the proposed positioning. The submitting company considered that conventional care and secukinumab are the most relevant comparators. Clinical experts consulted by SMC considered that the most relevant comparator is secukinumab, which is an alternative IL-17A inhibitor.

In the absence of direct comparative evidence with secukinumab, the submitting company presented Bucher ITCs, which were associated with a number of limitations. No comparisons were conducted in a relevant subset of the proposed positioning, which is in nr-axSpA TNF-alpha

inhibitor experienced patients. There was heterogeneity across studies used in the ITC in terms of baseline disease severity, prior and concomitant treatment, placebo response rates and study duration. Outcomes in the ITC were assessed at 16 weeks and therefore longer-term comparable efficacy is uncertain and no safety outcomes were compared. Limited data availability in specific patient populations prevented comparisons of clinically relevant outcomes including BASDAI50 and Bath Ankylosing Spondylitis Functional Index (BASFI) change from baseline. The efficacy outcomes included in the economic model (BASDAI50 and change from baseline in BASDAI and BASFI score) could not be compared in this ITC due to the paucity of comparator data, thus the submitting company concluded that a comparative cost-effectiveness comparison of ixekizumab versus secukinumab was not possible. Despite these uncertainties, no significant differences in relative efficacy were identified between treatments for the outcomes assessed and feedback received from clinical experts suggested it was reasonable to assume that ixekizumab and secukinumab may have comparable efficacy.

Clinical experts consulted by SMC considered that the place in therapy of ixekizumab is after treatment failure with TNF-alpha inhibitors or when these medicines are contraindicated. Some indicated that depending on cost-effectiveness, secukinumab may be displaced in the treatment pathway. The service implications are likely to be minimal.

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

Summary of comparative health economic evidence

The company submitted cost-utility analyses for the comparison of ixekizumab with conventional care for the treatment of adult patients with r-axSpA who have had inadequate response (biologic-experienced) or are contraindicated (biologic-naïve) to TNF-alpha inhibitors, or nr-axSpA who are contraindicated (biologic-naïve) to TNF-alpha inhibitors**.** This positioning is narrower than the licensed indication. The analyses adopted monthly cycles and a life-time horizon of approximately 60 years. Additionally, the company submitted a cost-minimisation analysis versus secukinumab on request.

The economic analyses incorporated a Markov cohort model with a tunnel state to represent a trial period, a maintenance health state for responders to ixekizumab, a conventional care state for non-responders to ixekizumab who discontinued treatment and for patients allocated to the conventional care arm and an all-absorbing “dead” health state. Patients in the conventional care arm could only transition to the “dead” state.

All patients received ixekizumab at the licensed dose until discontinuation due to failed response to treatment measured by BASDAI50 response criteria at 16 weeks and at a constant annual rate (11% for radiographic disease and 5% for non-radiographic disease) in the maintenance stage. Although there was no separate state for non-responders to conventional therapy, response was measured at 12 weeks for the purposes of modelling associated disease management costs and effects.

Clinical efficacy data used in the economic models came from the relevant subgroups of the COAST-V,-W, and -X trials. Data used in the model were treatment response rates, measured by BASDAI50 and change from baseline BASDAI and BASFI scores, conditional on response. For responders to ixekizumab, long-term BASDAI scores, assigned at the time point of response measurement, were assumed to remain constant. Long-term BASFI scores were modelled as a function of constant bony progression, measured by Modified Stoke Ankylosing Spondylitis Spinal Score (mSASSS) (at annual rate of mSASSS change of 0.69 and 1.44 for non-radiographic and radiographic disease, respectively). A constant treatment effect (0.42) was assumed in the maintenance stage, based on published literature. Upon loss of response, BASDAI scores were assumed to revert back to baseline whereas BASFI scores were modelled to rebound to initial gain. In the conventional care arm, the BASDAI score reverted back to baseline and BASFI scores followed natural disease progression after 1 cycle following response measurement.

Health state utility data in the economic model came from the three COAST trials. Collected EQ-5D-5L data were mapped to EQ-5D-3L and valued according to UK societal preferences using a published algorithm.[18] An ordinary least-square utility regression model was developed between BASDAI/BASFI data and EQ-5D values for the biologic-experienced and biologic-naïve populations. No utility decrements associated with adverse events were included.

Aside from medicine acquisition and administration costs for ixekizumab, other costs included in the analysis were disease management costs, modelled as a function of BASFI score, based on a non-UK cohort study[19], medicine initiation and monitoring costs and costs of adverse events. Conventional care was associated with no cost of treatment and only disease management costs were included.

A Patient Access Scheme (PAS) was submitted by the company and assessed by the Patient Access Scheme Assessment Group (PASAG) as acceptable for implementation in NHSScotland. Under the PAS, a discount was offered on the list price for ixekizumab. Table 3 presents the results of the cost-utility analysis versus conventional care, accounting for the PAS associated with ixekizumab.

Table 3: Base case results: cost-utility analysis vs conventional care (with PAS)

Population	Incremental Cost-effectiveness ratio (ICER) (£/QALY)
Radiographic disease: biologic-naïve population	£18,987
Radiographic disease: biologic-experienced population	£19,168
Non-radiographic disease: biologic-naïve population	£24,926

Table 4 presents the results of the cost-minimisation analysis versus secukinumab. A PAS is also available for secukinumab. The cost-minimisation results presented below do not take account of the PAS for ixekizumab or secukinumab but these were considered in the results used for decision-making. SMC is unable to present the results provided by the company which used an estimate of the PAS price for secukinumab due to commercial confidentiality and competition law issues.

Table 4: Cost-minimisation results vs secukinumab (all medicines at list price)

	Biologic-naïve (radiographic)		Biologic-experienced (radiographic)		Biologic-naïve (non-radiographic)
	Sec 150 mg	Sec 300 mg	Sec 150 mg	Sec 300 mg	Sec 150 mg
1 year	+£2,726	+£750	+£1,779	+£749	+£2,251
2 years	+£5,319	+£749	+£3,130	+£749	+£4,332
5 years	+£11,080	+£749	+£6,127	+£749	+£9,580
Lifetime	+£20,696	+£749	+£11,065	+£749	+£25,865

Selected scenario analyses for the cost-utility analysis versus conventional care are presented in table 5 below. The ICERs appear stable, however, as discussed below, there are uncertainties around assumptions which are difficult to explore.

Table 5: Selected scenario analyses

		Biologic-naïve (radiographic)	Biologic-experienced (radiographic)	Biologic-naïve (non-radiographic)
0	Base case	£18,987	£19,168	£24,926
1	Time horizon: 10 years	£25,509	£25,569	£31,208
2	BASFI rebound: natural history	£23,238	£22,391	£26,512
3	Removal of treatment effect on BASFI for ixekizumab	£24,527	£23,486	£27,797
4	Assessment of response at 16 weeks for conventional care	Not provided	Not provided	Not provided
Abbreviations: BASFI, Bath Ankylosing Spondylitis Functional Index				

Key limitations with the analyses were:

- There are uncertainties around the cost-effectiveness of ixekizumab compared with secukinumab, which is the most relevant comparator. The company did not initially present an economic analysis vs secukinumab, stating lack of relevant comparative clinical efficacy data for most clinical outcomes needed for the economic model. However, Bucher ITCs including ASAS40 and change from baseline in BASDAI score, did not report statistically significant differences between ixekizumab and secukinumab. The similar clinical efficacy is also expected by Scottish clinical experts, consulted by SMC, due to similar mode of action. Results of a requested cost-minimisation analysis are presented in table 4, although do not include the use of a confidential PAS for ixekizumab or secukinumab.
- Clinical efficacy data for ixekizumab in the biologic-naïve population do not fully reflect the company proposed positioning, which only includes TNF-alpha contraindicated patients. However, as these patients are expected to be only a small proportion of the overall biologic-naïve population in Scotland, economic analyses using the biologic-naïve population data may be less relevant than the analysis in the biologic-experienced population. It should be noted that data were only available for biologic-experienced patients with radiographic disease.

- The structure and assumptions in the cost-utility analyses do not allow for modelling durable response to conventional care. Such response for a small proportion of patients is observed in the three COAST trials and failure to account for it in the economic model is likely to create a bias in the comparator arm. While the submitting company indicated that a durable response to conventional care was lacked clinical plausibility and was not in line with assumptions used in other models in this area, since quality of life data are modelled as a function of both BASDAI and BASFI scores, failure to account for any response to conventional care may result in an overestimation of the incremental quality of life gain associated with ixekizumab. Additionally, failure to account for the effect of treatment-related adverse events on quality of life in the ixekizumab arm may also add to the uncertainty around the quality of life benefit associated with ixekizumab.
- The biggest cost-driver in the cost-utility analyses were disease management costs associated with conventional care as a function of BASFI scores. The algorithm was based on the non-UK OASIS cohort study and was thus associated with uncertainties. The methods were not validated by Scottish clinical experts and it is unknown if reported resource use in the study aligns with clinical practice in Scotland.

Due to these limitations, the economic case has not been demonstrated.

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

Summary of patient and carer involvement

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

- We received a patient group submission from the National Axial Spondyloarthritis Society (NASS), which is a registered charity.

- NASS has received 34% pharmaceutical company funding in the past two years, including from the submitting company.

- Axial spondyloarthritis (axSpA) including ankylosing spondylitis, is a form of inflammatory arthritis that mainly affects the spine. It is a painful and progressive long-term condition for which there is no cure. In addition to the spinal pain, people with the condition can also have a range of complications and co-morbidities. Some of the less visible complications can be the most debilitating – many people will suffer from severe fatigue and most will have a flare at some point which can make socialising, work and exercising problematic. The invisibility of this condition means it is often difficult to communicate its impact to loved ones, leading to a profound effect on relationships. The burden of disease for those with non-radiographic axSpA is not less than those with radiographic progression.

- When the patient group conducted a survey of people with axSpA and their families and carers, only 45% believed currently available treatments are sufficient; 55% believed that they are not. This was due to a number of factors including: some individuals not having found any available treatment to be effective, some not being able to tolerate available treatments due to other health conditions, efficacy of a treatment wearing off over time, worries about side effects, and some people with severe symptoms but not meeting the criteria for biological treatment not being able to get an effective treatment.

- There is currently only one other IL-17A inhibitor available for the treatment of axSpA. If people are treated with the medicine that suits them the best then they may be more likely to be able to stay in work and contribute more fully to society. Having an alternative medicine available could ultimately help people live independent lives and remain economically active. This could have a hugely positive impact on the families of people with the condition.

Additional information: guidelines and protocols

The British Society of Rheumatology and the British Health Professionals in Rheumatology published the "BSR and BHPR guideline for the treatment of axial spondyloarthritis (including ankylosing spondylitis) with biologics" in 2017.[15] The guidance predates the availability of ixekizumab and therefore no specific recommendations are made, however the guidance makes the following relevant recommendations:

- Patients should be considered for anti-TNF therapy if they have active axSpA. Active disease is defined as a BASDAI and spinal pain visual analogue scale (VAS) score ≥4 despite standard therapy.

- Patients with active disease who do not meet modified New York criteria for AS (radiographic axSpA) should also have had a positive MRI and/or raised CRP before starting treatment in a patient with nr-axSpA.

- Extra-articular manifestations and patient choice should be considered when selecting an anti-TNF agent. In the absence of head-to-head studies, systematic reviews have shown no statistical difference in efficacy between infliximab, golimumab, etanercept and adalimumab in the treatment of AS (certolizumab data were not included in these comparative reviews, but its efficacy has been established in clinical trials). There are insufficient data to comment on relative efficacy in nr-axSpA. However, not all biologics are licensed for or effective in the treatment of extra-articular disease, so treatment choice should take into account co-morbidities and the preferred route and frequency of administration.

- Initial efficacy response should be assessed following 3 to 6 months of therapy and responders should then be reassessed every 6 months.

- Response is defined as a reduction in the BASDAI and spinal pain VAS of ≥2U from baseline.

- In the absence of an initial clinical response by 6 months, or failure to maintain response at two consecutive assessments, withdrawal of that anti-TNF agent should be considered.

- In the event of anti-TNF failure due to inefficacy or adverse events, an alternative anti-TNF agent should be offered if clinically appropriate.

The National Institute for Health and Care Excellence (NICE) "Spondyloarthritis in over 16s: diagnosis and management (NG65)" was updated in 2017.[16] The guidance recommends the use of adalimumab, certolizumab pegol, etanercept, golimumab and infliximab, within their marketing authorisations, as options for treating severe active AS and severe nr-axSpA in adults whose disease has responded inadequately to, or who cannot tolerate, NSAIDs. The guideline also advises that the choice of treatment should be made after discussion between the clinician and the patient and recommends that if more than one treatment is suitable, the least expensive (taking into account administration costs and patient access schemes) should be chosen. The guidance recommends that people who cannot tolerate, or whose disease has not responded to, treatment with a first TNF-alpha inhibitor, or whose disease has stopped responding after an initial response, be treated with another TNF-alpha inhibitor.

The Assessment of SpondyloArthritis international Society (ASAS) in collaboration with the European League Against Rheumatism (EULAR) published a guidance in 2006 (ASAS-EULAR) which was last updated in 2016.[14] The guideline predates the availability of ixekizumab and therefore no specific recommendations are made, however the guidance makes the following relevant recommendations:

- Patients suffering from pain and stiffness should use an NSAID as first-line treatment up to the maximum dose, taking risks and benefits into account. For patients who respond well to NSAIDs continuous use is preferred if symptomatic otherwise.

- Patients with purely axial disease should normally not be treated with conventional synthetic DMARDs (csDMARDs); sulfasalazine may be considered in patients with peripheral arthritis.

- Biologic DMARDS should be considered in patients with persistently high disease activity despite conventional treatments; current practice is to start with TNF-alpha inhibitor therapy.

- If TNF-alpha inhibitor therapy fails, switching to another TNF-alpha inhibitor or an anti-IL-17 therapy should be considered.

Additional information: comparators

Secukinumab and conventional care.

Additional information: list price of medicine under review

Medicine	Dose Regimen	Cost per year (£)
Ixekizumab	**160mg by subcutaneous injection at week 0, followed by 80mg every 4 weeks.**	**Year 1: 16,875** **Subsequent years: 14,625**

Costs from BNF online on 07/03/22. Costs do not take patient access schemes into consideration.

Additional information: budget impact

SMC is unable to publish the estimated budget impact due to commercial in confidence issues.

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

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This assessment is based on data submitted by the applicant company up to and including 14 April 2022.

**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 NHSScotland 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 NHSScotland 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.