National Institute for Health and Care Excellence

Single Technology Appraisal (STA/MTA)
Ixekizumab for treating active psoriatic arthritis following inadequate response to disease-modifying anti-rheumatic drugs

Response to consultee and commentator comments on the draft remit and draft scope (pre-referral)

Please note: Comments received in the course of consultations carried out by NICE are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the submissions that NICE has received, and are not endorsed by NICE, its officers or advisory committees.

Comment 1: the draft remit

Section	Consultee/ Commentator	Comments [sic]	Action
Appropriateness	Eli Lilly	Yes, this is an appropriate topic to refer to NICE for appraisal so appropriate advice can be given to the NHS in England and Wales regarding the use of ixekizumab within the anticipated licensed indication.	Thank you for your comment. No changes to the scope are needed.
	British Society for Rheumatology	Fully appropriate.	Thank you for your comment. No changes to the scope are needed.
	Merck Sharp & Dohme Limited	`It is important that appropriate topics are referred to NICE to ensure that NICE guidance is relevant, timely and addresses priority issues, which will help improve the health of the population. Would it be appropriate to refer this topic to NICE for appraisal?` - **Yes**	Thank you for your comment. No changes to the scope are needed.

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	Novartis Pharmaceuticals UK Ltd.	We consider the proposed appraisal appropriate.	Thank you for your comment. No changes to the scope are needed.
	Psoriasis and Psoriatic Arthritis Alliance	Yes, appropriate to refer for appraisal.	Thank you for your comment. No changes to the scope are needed.
Wording	Eli Lilly	In line with the anticipated marketing authorisation, the wording of the remit should be amended to 'To appraise the clinical and cost effectiveness of ixekizumab within its marketing authorisation for treating active psoriatic arthritis in adults whose disease has not responded adequately to previous disease-modifying anti-rheumatic drug therapy, or have not been able to tolerate or have a contraindication to previous DMARD therapy'.	Thank you for your comment. The scope has been amended for clarity.
	British Society for Rheumatology	`Does the wording of the remit reflect the issue(s) of clinical and cost effectiveness about this technology or technologies that NICE should consider? If not, please suggest alternative wording.` - **Yes**	Thank you for your comment. The scope has been amended for clarity.
	Merck Sharp & Dohme Limited	`Does the wording of the remit reflect the issue(s) of clinical and cost effectiveness about this technology or technologies that NICE should consider? If not, please suggest alternative wording.` - **Yes**	Thank you for your comment. The scope has been amended for clarity.

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	Novartis Pharmaceuticals UK Ltd.	We consider the proposed wording appropriate.	Thank you for your comment. The scope has been amended for clarity.
	Psoriasis and Psoriatic Arthritis Alliance	`Does the wording of the remit reflect the issue(s) of clinical and cost effectiveness about this technology or technologies that NICE should consider? If not, please suggest alternative wording.` - **Yes**	Thank you for your comment. The scope has been amended for clarity.
Timing Issues	Eli Llilly	Advice to the NHS should be as close to marketing authorisation as is feasible within the NICE appraisal programme.	Thank you for your comment. NICE aims to provide draft guidance to the NHS within 6 months of the date when the marketing authorisation for a technology is granted.
	British Society for Rheumatology	There are now a number of biologic and non-biologic medications available to patients with PsA but there are still patients who have failed multiple agents and those with side effects to other biologic drugs that would benefit from ixekizumab being available ASAP.	Thank you for your comment. No changes to the scope are needed.
	Psoriasis and Psoriatic Arthritis Alliance	No immediate urgency, given other similar class agents are available.	Thank you for your comment. No changes to the scope are needed.

Section	Consultee/ Commentator	Comments [sic]	Action
Additional comments on the draft remit			

Comment 2: the draft scope

Section	Consultee/ Commentator	Comments [sic]	Action
Background information	Eli Lilly	Certolizumab pegol and secukinumab, either alone or in combination with methotrexate, have recently been recommended by NICE for patients whose psoriatic arthritis has not responded to at least two standard DMARDs given on their own or together; or for patients who have had a TNF-alpha inhibitor but whose disease stopped responding after the first 12 weeks. Secukinumab, either alone or in combination with methotrexate, is also recommended by NICE for patients who have had a TNF-alpha inhibitor but whose disease has not responded within the first 12 weeks. It should be noted in this section that certolizumab pegol, secukinumab and apremilast are recommended only if the respective manufacturers provide the drugs to the NHS at confidential discounted prices under a patient access scheme.	Thank you for your comments. The background section is intended to provide a brief overview of the disease and its associated management. The scope has been amended for clarity.
	Abbvie	It is note that in relation to the last sentence in the paragraph at the top of page 2 that the certolizumab pegol and secukinumab NICE TAG has now been published.	Thank you for your comment. The scope has been amended for clarity.

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	British Society for Rheumatology	`Consider the accuracy and completeness of this information.` - **Accurate**	Thank you for your comment.
	Merck Sharp & Dohme Limited	`Consider the accuracy and completeness of this information.` - **Yes**	Thank you for your comment.
	Novartis Pharmaceuticals UK Ltd.	We would like to point out that the appraisal of secukinumab and certolizumab pegol for the treatment of psoriatic arthritis is no longer ongoing but was published on May 24th 2017.1	Thank you for your comment. The scope has been amended for clarity.
	Psoriasis and Psoriatic Arthritis Alliance	No mention of nail involvement, which is a significant issue for many people with psoriatic arthritis.	Thank you for your comments. The background section is intended to provide a brief overview of the disease and its associated management.
The technology/ intervention	Eli Lilly	Ixekizumab, alone or in combination with conventional disease-modifying anti-rheumatic drug (cDMARD), 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 DMARD therapies.	Thank you for your comment. No changes to the scope are needed.
	British Society for Rheumatology	`Is the description of the technology or technologies accurate?` - **Yes**	Thank you for your comment. No changes

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			to the scope are needed.
	Merck Sharp & Dohme Limited	`Is the description of the technology or technologies accurate?` - **Yes**	Thank you for your comment. No changes to the scope are needed.
	Psoriasis and Psoriatic Arthritis Alliance	Appears to match descriptions used elsewhere.	Thank you for your comment. No changes to the scope are needed.
Population	Eli Lilly	The wording of the population should be changed to 'Adults with active psoriatic arthritis whose disease has not responded adequately to previous disease-modifying anti-rheumatic drug therapy, or have not been able to tolerate or have a contraindication to previous DMARD therapy'. Subgroups that should be considered separately are: • Patients who have previously received one or more TNF-alpha inhibitor • Patients with concomitant moderate to severe psoriasis for whom [redacted]	Thank you for your comment. The scope has been amended for clarity.

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	British Society for Rheumatology	Yes – there are subgroups of PsA eg oligoarthritis and spondyloarthritis and predominant enthesitis that are not fully addressed by the trial evidence but represent a reasonable proportion of patients with PsA.	Thank you for your comments. The population section is intended to provide an overview of the population in line with the marketing authorisation.
	Merck Sharp & Dohme Limited	`Is the population defined appropriately? Are there groups within this population that should be considered separately?` - **Yes**	Thank you for your comment. No changes to the scope are needed.
	Psoriasis and Psoriatic Arthritis Alliance	`Is the population defined appropriately? Are there groups within this population that should be considered separately?` - **Yes**	Thank you for your comment. No changes to the scope are needed.
Comparators	Eli Lilly	The positioning of biologic therapy in patients with only one prior standard DMARD is not in line with current NICE pathways or BSR guidance (except in the case of adverse prognostic factors). As noted in the Final Appraisal Determination document for the multiple technology appraisal of secukinumab and certolizumab pegol, the committee questioned whether biologic therapy is established clinical practice in the NHS after failure on only one prior DMARD and which specific group of patients would use a biologic at this stage in the pathway. We would therefore suggest that this is not a relevant population or comparator set for the current decision problem.	Thank you for your comment. During the scoping stage of previous PSA topics, scoping workshop attendees agreed that in clinical practice, people would receive at least 2 DMARDs before

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		We believe that the comparator set is appropriate for the population who have failed on two prior DMARDs. We believe that 'people whose disease has not responded adequately to non-biological and biological DMARDs, or biological DMARDs are contraindicated' could be considered as two distinct groups with the following comparator set: • For people whose disease has not responded adequately to TNF-alpha inhibitors o Certolizumab pegol o Secukinumab o Ustekinumab o Apremilast o BSC • For people who are intolerant or contraindicated to TNF-alpha inhibitors o Secukinumab o Ustekinumab o Apremilast o BSC	receiving biological treatment. However, the comparator part in the scope is kept broad and inclusive so that it reflects the wording of the marketing authorisation in line with previous scopes for psoriatic arthritis. The comparator section have been amended to differentiate between inadequate response to DMARDs and intolerance/contraindication.
	Abbvie	Abbvie do not believe that best supportive care is an appropriate comparator. Patients who receive ixekizumab would in the absence of ixekizumab receive a different treatment rather than receive no treatment (ie. BSC). For this	Thank you for your comment. The comparator part in the

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		reason it would be appropriate in an incremental analysis to include BSC following failure of a comparator active treatment (ie. in a treatment sequence) but it would not be appropriate to compare ixekizumab in a pairwise analysis versus BSC. For this reason Abbvie believe that best supportive care should not be included as a comparator in people whose disease has not responded adequately to non-biological and biological DMARDs, or biological DMARDs are contraindicated as is presently the case in the scope. In addition, it is note that the certolizumab and secukinumab NICE TAG has now been published.	scope should remain broad and inclusive.
	British Society for Rheumatology	Accurate comparators. TNFi are first line biologics for most Rheumatologists but sekukinumab is also now approved for first line biologic use, ustekinumab only for TNFi failures.	Thank you for your comment. The scope has been amended for clarity.
	Merck Sharp & Dohme Limited	`Is this (are these) the standard treatment(s) currently used in the NHS with which the technology should be compared? Can this (one of these) be described as 'best alternative care?` - **Yes**	Thank you for your comment.
	Novartis Pharmaceuticals UK Ltd.	We agree that non-biological DMARDs should be the main comparator for this population. We suggest that the wording of the "1 prior DMARD" population should be aligned to that of the "2 prior DMARD population" i.e. "people whose disease has not responded adequately to 1 non-biological disease modifying anti-rheumatic drug" rather than "people who have only received" 1 prior non-biological DMARD. In relation to the population of "people whose disease has not responded adequately to non-biological and biological DMARDs, or biological DMARDs are contraindicated", see comment in "Background information" section above	Thank you for your comment. The scope has been amended for clarity.

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		regarding the appraisal of secukinumab and certolizumab pegol no longer being ongoing.	
	Psoriasis and Psoriatic Arthritis Alliance	Yes, these are the current range offered, although from those who speak to us etanercept appears to be offered less frequently than in the past.	Thank you for your comment.
	Pfizer Ltd	With recent publication of the guidance on Certolizumab pegol and secukinumab for treating active psoriatic arthritis after inadequate response to DMARDs [TA445], Pfizer would like to recommend the update of the comparator section within this draft scope to reflect current NICE guidance for the included populations.	Thank you for your comment. The scope has been amended for clarity.
Outcomes	Eli Lilly	Skin involvement (e.g. PASI response) is a relevant outcome to include in the scope. Please note that while excess mortality risk due to psoriatic arthritis has been applied to background mortality risk in previous economic analyses, no biologic treatment for psoriatic arthritis has demonstrated an effect on mortality outcomes in the context of a clinical trial. The following outcomes will be modelled in the economic analysis: - Disease activity, assessed by the PsARC - Functional capacity, measured by the HAQ-DI score - Health-related quality of life, measured by EQ-5D and mapped using PASI and HAQ-DI scores Please note that data on the impact of ixekizumab on periarticular disease and disease progression, and the adverse effects of treatment will be	Thank you for your comment. Scoping workshop attendees from recent PSA topics agreed that nail involvement was related to psoriasis rather than psoriatic arthritis so it was suggested this outcome be removed.

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		presented in the submission but there may not be enough comparative data on these outcomes to include these in the economic analysis.	
	Abbvie	Abbvie believe that an additional outcome that should be added is radiographic progression of disease.	Thank you for your comment. Disease progression is already included as an outcome in the scope
	British Society for Rheumatology	The outcome measures stated are based on those used in the clinical trials. PsARC, ACR 20/50/70, HAQ, radiographic progression and PASI response are the most important with added data on dactylitis and enthesitis.	Thank you for your comment. No changes to the scope are needed
	Merck Sharp & Dohme Limited	`Will these outcome measures capture the most important health related benefits (and harms) of the technology?` - **Yes**	Thank you for your comment. No changes to the scope are needed.
	Psoriasis and Psoriatic Arthritis Alliance	They generally cover what are important to patients, although patients are specifically interested in reduction in pain and fatigue, which as some people tell us, do not always improve in line with other disease activity improvements.	Thank you for your comment. During the scoping stage of previous PSA topics, scoping workshop attendees agreed that pain and fatigue were important outcomes and agreed that they were covered by the existing,

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			broader outcomes. No action required.
Economic analysis	Eli Lilly	An economic analysis that addresses the requirements of the NICE reference case will be submitted. As per the MTA for secukinumab and certolizumab pegol, a treatment sequencing approach would be relevant for the economic analysis, therefore a lifetime time horizon would be appropriate.	Thank you for your comment. No changes to the scope are needed.
	Novartis Pharmaceuticals UK Ltd.	Given the range of populations within the remit of the appraisal we consider the STA process will be more appropriate than a cost comparison.	Thank you for your comment. No changes to the scope are needed.
Equality and Diversity	Eli Lilly	No further comment	Thank you for your comment.
	British Society for Rheumatology	No issues of equality.	Thank you for your comment.
	Merck Sharp & Dohme Limited	No equality issues	Thank you for your comment.
	Psoriasis and Psoriatic Arthritis Alliance	The only issue that might cause some people issues is self-injection, if they lack hand dexterity due to the effects of the arthritis. Although, this could be overcome with assistance of a carer, but does therefore mean that they will be reliant on that assistance, which may need to be included as a cost somewhere.	Thank you for your comment. No changes to the scope are needed.

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Other considerations	Eli Lilly	The follow subgroups are relevant for consideration: • Biologic-naïve or prior biologic experience • Presence or severity of concomitant psoriasis (no psoriasis, mild to moderate psoriasis, moderate to severe psoriasis)	Thank you for your comment. The scope has been amended for clarity.
	Novartis Pharmaceuticals UK Ltd.	We suggest the specified potential subgroups may better be better described as being based on “the reason for previous treatment failure”. Since the licensed dose of secukinumab for psoriatic arthritis differs depending on presence of concomitant moderate to severe psoriasis,2 we suggest it may also be necessary to consider subgroups defined by the presence of concomitant psoriasis and its severity.	Thank you for your comment. The scope has been amended for clarity.
Innovation	Eli Lilly	Ixekizumab is the first monoclonal antibody to block both active forms of IL-17A (IL-17A is expressed in both homodimer and heterodimer forms). Furthermore, it has a high binding affinity to both forms of IL-17A. It is the second IL-17 (and third biologic therapy) to offer an alternative mechanism of action to TNF-alpha inhibitors. Ixekizumab could be considered to represent a step-change in the management of patients who have had a previous inadequate response to TNF-alpha inhibitor therapy or were intolerant to TNF-alpha inhibitors. Results from the SPIRIT-P2 trial (in which patients had previously received or were intolerant to TNF-alpha inhibitor therapy) suggested that the improvement in psoriatic arthritis disease activity and patient-reported quality of life was similar between patients receiving ixekizumab whether they had experienced an inadequate response to one TNF-alpha inhibitor, to two TNF-alpha inhibitors or were intolerant to TNF-alpha inhibitors. Efficacy and safety results at Week 24 in the SPIRIT-P2 trial were also consistent with results observed in the SPIRIT-P1 trial which recruited only biologic-naïve patients	Thank you for your comment. The innovative nature of the technology will be considered by the appraisal committee based on evidence presented to it, if the topic is referred for appraisal.

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		(1;2). In contrast, the Assessment group for the recent MTA of certolizumab pegol and secukinumab note that splitting the populations of the RAPID-PsA and FUTURE 2 trials resulted in low numbers of placebo patients and differences in placebo response rates between the biologic-naïve and biologic-experienced subgroups, making it difficult to interpret the relative risks for certolizumab pegol and secukinumab across these subgroups (3). Phase III clinical studies in psoriasis have demonstrated that a significant proportion of patients achieve complete clearance of their skin symptoms (represented by a PASI100 response), therefore ixekizumab may represent a significant change in the management of psoriatic arthritis with concomitant moderate–to-severe psoriasis. Please note that the QALY calculation may not capture the benefit of ixekizumab in the management of hard-to-treat symptoms such as nail psoriasis. (1) Nash P, Kirkham B, Okada M; et al. Ixekizumab for the treatment of patients with active psoriatic arthritis and an inadequate response to tumour necrosis factor inhibitors: results from the 24-week randomised, double-blind, placebo-controlled period of the SPIRIT-P2 phase 3 trial. Lancet. 2017 Jun 10;389(10086):2317-2327i (2) Mease PJ, van der Heijde D, Ritchlin CT; et al. Ixekizumab, an interleukin-17A specific monoclonal antibody, for the treatment of biologic-naive patients with active psoriatic arthritis: results from the 24-week randomised, double-blind, placebo-controlled and active (adalimumab)-controlled period of the phase III trial SPIRIT-P1. Ann Rheum Dis. 2017 Jan;76(1):79-87 (3) CRD and CHE Technology Assessment Group's report. Certolizumab pegol and secukinumab for treating active psoriatic arthritis following inadequate response to disease modifying anti-rheumatic drugs. 2016.	

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	British Society for Rheumatology	Yes – IL17A is a key inflammatory cytokine in PsA and Ps. Ixekizumab offers highly selective inhibition of IL17A that has not previously been available and may therefore offer a high level of efficacay with fewer associated side effects. It offers more selective inhibition than sekukinumab and is therefore a step change. The data in biologic naïve and exposed populations looks very exciting and offers further therapeutic options for patients in a more selective targeted setting.	Thank you for your comment. The innovative nature of the technology will be considered by the appraisal committee based on evidence presented to it, if the topic is referred for appraisal.
	Novartis Pharmaceuticals UK Ltd.	An IL-17A inhibitor is already licensed and NICE approved for the treatment of chronic plaque psoriasis. As the second IL-17A inhibitor to market, we do not consider ixekizumab to represent an innovative treatment option.	Thank you for your comment. The innovative nature of the technology will be considered by the appraisal committee based on evidence presented to it, if the topic is referred for appraisal.
NICE Pathways [Delete section if not relevant]	Novartis Pharmaceuticals UK Ltd.	We would expect ixekizumab to be positioned alongside the other biologics recommended by NICE for treating active psoriatic arthritis.	Thank you for your comment. No changes to the scope are needed.
Questions for consultation	Eli Lilly	Our comments on outcomes, comparators, sub-groups, innovation and capturing benefits in the QALY calculation have been noted above.	Thank you for your comment. No changes

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		Ixekizumab will likely fit into the treatment pathway: • where patients are currently being treated with biologic agents in the NHS after the failure of two conventional DMARDs, • or where a TNF-alpha inhibitor is not tolerated, or is associated with an inadequate response within the first 12 weeks (primary non-response) or after the first 12 weeks (secondary non-response), • or where patients are contraindicated to a TNF-alpha inhibitor. We agree that an appraisal of ixekizumab through the STA process is appropriate in order for NICE to be able to provide timely advice to the NHS.	to the scope are needed.
	British Society for Rheumatology	Ixekizumab should definitely be appraised as it offers huge potential benefits to patients with PsA and will widen the choice of agent and pathway to target and prevent irreversible joint damage and keep people with PsA functioning in society and improving their QoL.	Thank you for your comment. No changes to the scope are needed.
Additional comments on the draft scope	Novartis Pharmaceuticals UK Ltd.	We consider that the STA process is the appropriate route for this appraisal.	Thank you for your comment. No changes to the scope are needed.
	Novartis Pharmaceuticals UK Ltd.	Within the “Related NICE recommendations and NICE Pathways”: a) TA445 can now be included as a “Related Technology Appraisal” rather than an “Appraisal in development” (see comment in “Background information” section above) b) TA433; Apremilast for treating active psoriatic arthritis” should also be included as a “Related Technology Appraisal”	Thank you for your comment. The scope has been amended for clarity.

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		c) The Clinical Guideline “Spondyloarthritis in over 16s: diagnosis and management” (NG65) published in February 2017 should be included as a “Related Guideline”.	

The following consultees/commentators indicated that they had no comments on the draft remit and/or the draft scope

Jane Newton

Sanofi