National Institute for Health and Care Excellence

Single Technology Appraisal (STA)

Ixekizumab for treating moderate to severe plaque psoriasis

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	*Would it be appropriate to refer this topic to NICE for appraisal?*		
	British Association of Dermatologists	Yes	Comment noted.
	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 its licensed indication.	Comment noted.
	Napp Pharmaceuticals	Yes	Comment noted.
	Novartis Pharmaceuticals	No comment	Noted.
Wording	*Does the wording of the remit reflect the issues of clinical and cost effectiveness about this technology that NICE should consider?*		

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	Eli Lilly	Agree	Comment noted.
	Napp Pharmaceuticals	Yes	Comment noted.
	Novartis Pharmaceuticals	No comment	Noted.
Timing Issues	Eli Lilly	Advice to the NHS should be as close to marketing authorisation as is feasible within the NICE appraisal programme	Comment noted. NICE aims to provide draft guidance to the NHS within 6 months of the date when the marketing authorisation for a technology is granted.
	Napp Pharmaceuticals	Other treatments are available for the group of patients defined in the remit. Therefore this appraisal should follow the normal prioritisation process used by NICE taking into account regulatory timelines.	Comment noted. NICE aims to provide draft guidance to the NHS within 6 months of the date when the marketing authorisation for a technology is granted.
	Novartis Pharmaceuticals	No comment	Noted.
Additional comments on the	Eli Lilly	No further comments	Noted.

Section	Consultee/ Commentator	Comments [sic]	Action
draft remit			

Comment 2: the draft scope

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Background information	Eli Lilly	This section provides comprehensive background information, although the following points should be considered with respect to the current understanding of psoriasis: Psoriasis is now known to be primarily an immunologic T-cell driven disease that leads to accumulation of inflammatory cells, angiogenesis and epidermal hyperproliferation. This underlying pathology gives rise to the typical clinical features of psoriasis of red elevated scaly plaques. Activation of T-cells is dependent on innate immune mechanisms involving specific series of cytokines including IL-12 & IL-23.These trigger a cascade of events resulting in increased expression of IL-17A and keratinocyte hyperproliferation. Although clinical studies and treatment goals are essentially based on addressing the skin manifestations of the disease, psoriasis is associated with a range of co-morbid conditions including inflammatory arthritis in the form of psoriatic arthritis, increased risk of cardiovascular co-morbidities; including myocardial infarction and stroke, and metabolic syndrome, diabetes, chronic renal insufficiency and occasionally liver abnormalities. Gelfand and colleagues demonstrated psoriasis may shorten life expectancy by up to 5 years due to associated co-morbidities[1]. Psoriasis can have a significant impact on patients QOL with itch, or involvement of face, hands, scalp, genitals, palms or soles having a further debilitating effect. Patients with psoriasis are at increased risk of the developing psychological	Comments noted. This section of the scope aims to provide a brief overview of the background for the appraisal; additional details may be considered by the Committee, if appropriate, at the time of the appraisal. The prevalence of psoriasis has been updated. NICE Technology Appraisal 368 (TA368) has been added to the list of related NICE recommendations.

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		disorders including depression, anxiety and suicidalilty[2,3] with the risk being greatest in younger patients[2].1More than 10,400 diagnoses of depression, 7,100 diagnoses of anxiety and 350 diagnoses of suicidality are attributable to psoriasis each year in the UK[2]. We would suggest that the prevalence of psoriasis in England is updated to 1.75% as utilised in the costing template for NICE Clinical Guideline 153 *Psoriasis: assessment and management*[4] and subsequently used in the costing template for secukinumab (TA350)[5] With respect to the information provided on published NICE guidelines and technology appraisals, it should be updated to include TA368- apremilast for moderate to severe plaque psoriasis (even though this appraisal resulted in a 'not recommended' outcome). <u>References</u> 1. Gelfand JM, et al. The risk of mortality in patients with psoriasis: results from a population-based study. Arch Dermatol. 2007;143:1493–1499 2. Kurd SK et al. The risk of depression, anxiety, and suicidality in patients with psoriasis: a population-based cohort study. Arch Dermatol. 2010; 146: 891–5. 3. Dowlatshahi EA et al. The prevalence and odds of depressive symptoms and clinical depression in psoriasis patients: a systematic review and meta-analysis. J Invest Dermatol. 2013; 134: 1542–51. 4 http://www.nice.org.uk/guidance/cg153 5 http://www.nice.org.uk/guidance/TA350/costing	
	Novartis Pharmaceuticals	No comment	Noted.
The technology/	British	*Is the description of the technology or technologies accurate?*	Comment noted.

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intervention	Association of Dermatologists	Yes	
	Eli Lilly	Ixekizumab has been studied in three phase 3 clinical trials in comparison with placebo or etanercept in people with moderate-to-severe plaque psoriasis who **were candidates for phototherapy and/or systemic therapy**.	Comment noted. No changes to the scope are needed.
	Novartis Pharmaceuticals	No comment	Noted.
Population	British Association of Dermatologists	See below	Noted.
	Eli Lilly	It should be noted that the population stated in the draft scope could be considered different to the population in which biologics are currently approved by NICE and used by the NHS- please see further comments in the comparator section.	Comment noted. No changes to the scope are needed.
	Novartis Pharmaceuticals	No comment	Noted
Comparators	British Association of Dermatologists	Apremilast (licensed but not NICE approved) and fumaric acid esters (unlicensed but used in the psoriasis population with moderate severity) should both be considered in the comparator group. As indicated in the NICE guideline, ciclosporin should only be used for a maximum of a year. It is therefore only ever a relatively 'short-term' option. Psoriasis is a long-term condition and no treatments so far are 'curative'. Thus in any economic modelling, inclusion of ciclosporin is problematic. In addition, PUVA (i.e. phototherapy with psoralen), whilst effective, is no longer	Comments noted. Apremilast was not recommended in NICE TA368, so is not considered established practice in the NHS. It is therefore not included as a comparator.

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		used routinely in people with psoriasis because of its propensity to cause skin cancer, particularly when followed by immunosuppression. In the NICE guideline certain groups are specified as 'DO NOT USE" populations; When considering PUVA this should only be when other options – including biologic therapies – have been offered and can't be used or are inappropriate. Established clinical practice is very much in line with CG153 – i.e. topicals for limited psoriasis only (not in the population being considered). Phototherapy – specifically UVB, and then systemic (non-biologic) therapy – particularly methotrexate. Where psoriatic arthritis is present, methotrexate may be used before phototherapy. Acitretin is not considered cost effective for patients who meet NICE criteria for biologic therapy and has limited utility due to poor tolerability and teratogenicity (a risk that persists for 3 years after treatment cessation). Ciclosporin is not used long term. In view of the high prevalence of metabolic syndrome (up to 40% in some studies), methotrexate is often contraindicated or is poorly tolerated due to abnormal LFTs. The population of patients with moderate disease (i.e. PASI<10) may still have significant disease with major impact (DLQI>10) and treatment options for this group are profoundly limited if methotrexate is ineffective or not tolerated, and ciclosporin cannot be used long term. Treatments used include acitretin, fumaric acid esters, apremilast, biologic drugs (but only if funded under IFR route).	Fumaric acid esters have been added to the list of systemic non-biological therapies. The description of phototherapy has been amended to refer to UVB specifically.
	Eli Lilly	As highlighted above, the biologic treatments for plaque psoriasis currently approved by NICE are for use in a defined population where the disease has failed to respond to standard systemic therapies, for example, ciclosporin, methotrexate and PUVA (psoralen and long-wave ultraviolet radiation), or where these treatments are contraindicated or not tolerated (as well as restrictions regarding the severity of disease). Therefore, should ixekizumab be compared against systemic non-biological therapies, the available biologic therapies should NOT be included as	Comments noted. The comparators have been amended to reflect the populations for whom they would be considered. The Committee will normally be guided by

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		comparators as NICE guidance precludes use of biologics in that population. Additionally, it should be noted that methotrexate is only licensed for severe psoriasis, and acitretin for extensive and severe refractory forms of psoriasis and pustulous psoriasis of the hands and feet. The biologic treatments listed are valid comparators in the population in which biologics are currently used in the NHS, as per current NICE guidance. TA368 (apremilast) was highlighted previously- it should be confirmed that this is not a relevant comparator as it is not currently recommended by NICE guidance.	established practice in the NHS when identifying the appropriate comparator(s), and can consider technologies outside their marketing authorisations; methotrexate and acitretin are therefore included as comparators. Apremilast was not recommended in NICE TA368, so is not considered established practice in the NHS. It is therefore not included as a comparator.
	Napp Pharmaceuticals	When considering infliximab as a comparator the actual acquisition prices charged to the NHS, rather than the list price should be included in any health economic models. For example NHS list prices would not be appropriate for biosimilar infliximab when these products are subject to the NHS procurement tender process.	Comment noted. Comparator technologies may include biosimilar products, and the availability and cost of biosimilars should be taken into account. This has been added to the scope. When there are

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			nationally available price reductions, the reduced price should be used in the reference-case analysis.
	Novartis Pharmaceuticals	biosimiliar biologic agents should be included	Comment noted. Comparator technologies may include biosimilar products and the availability and cost of biosimilars should be taken into account. This has been added to the scope.
Outcomes	Eli Lilly	Please consider the following: • **Severity of psoriasis**- the primary measure for this will be the PASI score • **Other complications of psoriasis**: Please note that nail and scalp outcomes are strictly speaking areas of involvement rather than complications of the disease as such and that there may be limited comparative data for these outcomes. Symptoms of the face may also be a consideration. Some aspects of these areas of involvement will likely be captured by the overall PASI measure. **Joint outcomes**- [redacted]	Comments noted. The outcomes have been amended to reflect manifestations of psoriasis on the face, scalp and nails as symptoms of psoriasis, rather than complications. Mortality is included as an outcome for consistency with previous psoriasis scopes and to allow

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		[redacted] • **Mortality**: please note that no biologic treatment for plaque psoriasis has demonstrated an effect on mortality outcomes in the context of a clinical trial. • **Response rate**: the key outcome here will be PASI response as measured by the percentage improvement in PASI score from baseline • **Relapse rate**: relapse rates are captured by all-cause discontinuation rates in the economic model	calculation of health outcomes in terms of quality-adjusted life years (QALYs).
	Novartis Pharmaceuticals	No comment	Noted.
Economic analysis	Eli Lilly	An economic analysis that addresses the requirements of the NICE reference case will be submitted.	Comment noted. No changes to the scope are needed.
	Napp Pharmaceuticals	Please see above, the sensitivity analysis could take into account a range of prices to take into account the tender process prices in order to produce more realistic ICERS for ixekizumab vs infliximab biosimilars.	Comment noted. The availability and cost of biosimilars should be taken into account. This has been added to the scope. When there are nationally available price reductions, the reduced price should be used in the reference-case analysis.

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	Novartis Pharmaceuticals	No comment	Noted.
Equality and Diversity	Eli Lilly	No comment	Noted.
	Novartis Pharmaceuticals	No comment	Noted.
Innovation	British Association of Dermatologists	*Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how it might improve the way that current need is met (is this a 'step-change' in the management of the condition)?* Yes – inhibitors of the IL17 pathway are a major step change in terms of ability to achieve clearance of disease (PASI90). Genetic and immunopathogenic studies strongly implicate the IL17 pathway to be of major relevance in psoriasis (and ps arthritis). *Do you consider that the use of the technology can result in any potential significant and substantial health-related benefits that are unlikely to be included in the QALY calculation?* Yes Neither the DLQI – the commonly used tool for impact in skin disease, or the EQ5D – encompass distress or low mood. These are extremely common in people with moderate-to-severe psoriasis and are known to improve with disease control.	Comments noted. No changes to the scope are needed.
	Eli Lilly	Ixekizumab has the potential to be considered innovative as the phase III clinical studies have demonstrated that a significant proportion of patients achieve complete clearance of their skin symptoms (represented by a PASI100 response). A treatment option that offers a real possibility of this outcome for patients should be considered an innovative evolution in the treatment of plaque psoriasis. The outcomes demonstrated in the phase III	Comments noted. No changes to the scope are needed.

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		studies for ixekizumab may be associated with its mode of action- it 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. There is a need for additional, innovative treatments for psoriasis as evidenced by data examining the real-world effectiveness of the currently available biologics. For example, Warren et al[1] showed that drug survival fell to 53% by the 3rd year of biologic treatment, indicating a need for additional, effective treatment options. The QALY calculation has the potential to underestimate the benefits of the treatment in that it is known that generic preference based HRQOL measures such as EQ-5D may not be the most appropriate tool for some disease areas, including dermatological conditions. An attempt to explore this aspect will be undertaken with the available data from a modified EQ-5D tool. Additionally, it was noted by the committee in the appraisal of secukinumab (TA350) that it is likely that the treatment benefit of best supportive care would be impacted by a treatment-related disutility- it should be acknowledged that there is limited data in this area so this will continue to be an aspect of the cost-effectiveness assessment that will not be taken into account by the QALY calculation. <u>References</u> 1.Warren et al Differential Drug Survival of Biologic Therapies for the Treatment of Psoriasis: A Prospective Observational Cohort Study from the British Association of Dermatologists Biologic Interventions Register (BADBIR)Journal of Investigative Dermatology (2015) 135, 2632–2640	
Other considerations	Eli Lilly	**Severity of psoriasis:** Please note that, in common with all recent clinical trials for biologic agents in the treatment of psoriasis, the phase III studies for ixekizumab specified a	Comment noted. No changes to the scope are needed.

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		baseline PASI score of 12 or more in the inclusion criteria.	
Questions for consultation	British Association of Dermatologists	Are the subgroups suggested in 'other considerations' appropriate? - Yes. Are there any other subgroups of people in whom the technology is expected to be more clinically effective and cost effective or other groups that should be examined separately? - Consider those with/without psoriatic arthritis. - Consider including consideration of weight – obesity is common in people with severe disease (40% prevalence of metabolic syndrome) and weight is an important predictor of outcome Where do you consider ixekizumab will fit into the existing NICE pathway for psoriasis? - As an option for people with moderate to severe disease requiring biologic therapy. Whilst the PASI is embedded in the criteria for consideration of biologic therapy it remains a very limited tool for proper, holistic disease severity assessment. As indicated in the NICE guideline – assessment needs to encompass all aspects of disease severity (including high need sites, impact, joint disease). It would be an advance to include these elements in the criteria so that patients who may have severe disease at high need sites with major impact but do not have a PASI >10 may still be considered for treatment. Whilst there is always concern about 'downward' drift of use to 'milder' cases (and thus cost) the evidence from the UK registry suggests that the majority of patients treated with biologics more than exceed the current disease severity bar (e.g. of 5069 registered on BADBIR, the mean PASI and DLQI (± SD) were 16·4 ± 8·3 and 17·4 ± 7·5, respectively. Br J Dermatol 2015 Aug;173(2):510-8. doi: 10.1111/bjd.13908. Epub 2015 Jul 6).	Comments noted. No changes to the scope are needed.

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	Eli Lilly	Our comments on comparators have been captured above. All biologic treatments have been approved by NICE and are used to varying degrees in clinical practice. Our comments on sub-groups have been captured above. Ixekizumab will likely fit into the treatment pathway where psoriasis patients are currently being treated with biologic agents in the NHS with the potential option of being available as an option for patients currently being treated with standard systemic agents before being possible candidates for biologic treatment. Aspects of innovation have been noted above, together with the potential issues with the QALY calculation. 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	Comments noted. No further changes to the scope are needed.
	Novartis Pharmaceuticals	Have all relevant comparators for ixekizumab been included in the scope? Novartis: biosimiliar agents should be considered Are the subgroups suggested in 'other considerations' appropriate? Novartis: Are there any other subgroups of people in whom the technology is expected to be more clinically effective and cost effective or other groups that should be examined separately? Novartis: The UNCOVER trials include approximately 50% of patients who have received a non-biologic systemic therapy and approximately 25% of patients who have received a biologi treatment. It will be important to demonatrate subgroup analyses for both of these patient groups. Where do you consider ixekizumab will fit into the existing NICE pathway for psoriasis? Novartis: We would expect ixekizumab to be positioned alongside the other biologics reimbursed for treating moderate to severe psoriasis.	Comments noted. Comparator technologies may include biosimilar products, and the availability and cost of biosimilars should be taken into account. This has been added to the scope. If the evidence allows, consideration will be given to subgroups based on previous use of non-biological or

Section	Consultee/ Commentator	Comments [sic]	Action
			biological therapy. No change to the scope is needed.
Additional comments on the draft scope	Eli Lilly	No further comments	Noted
	Novartis Pharmaceuticals	No	Noted

The Royal College of Physicians endorsed the comments from the British Association of Dermatologists.

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

Allergy UK
Department of Health