National Institute for Health and Care Excellence

Single Technology Appraisal (STA/MTA)

Dupilumab for treating severe asthma [ID1213]

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	Sanofi	We believe it is timely and appropriate to refer this topic for NICE appraisal.	Comment noted.
	NHS England Specialised Respiratory CRG	Yes it would be appropriate	Comment noted.
	Asthma UK	No comment	
	Royal College of Physicians	Yes	Comment noted.
Wording	Sanofi	The current wording of the remit is *To appraise the clinical and cost effectiveness of dupilumab within its marketing authorisation for treating **severe** asthma inadequately controlled with inhaled corticosteroids.*	Thank you for your comment. The wording of the remit has been updated to be in line

Section	Consultee/ Commentator	Comments [sic]	Action
		We anticipate that the wording of the marketing authorisation will be for **moderate-to-severe asthma** and request that the wording of the remit and the title of the scoping document be amended to reflect the likely marketing authorisation wording. The current draft marketing authorisation is: [redacted] Please note that this wording is subject to change. [redacted]	with the final marketing authorisation for severe asthma.
	NHS England Specialised Respiratory CRG	See comments below	Comment noted.
	Asthma UK	No comment	Comment noted.
	Royal College of Physicians	Yes	Comment noted.
Timing Issues	Sanofi	We believe that it is timely to refer this product for appraisal and that there is unmet need in asthma that dupilumab may help to address.	Comment noted. No change to the scope required.

Section	Consultee/ Commentator	Comments [sic]	Action
		The UK has one of the highest prevalence and mortality rates of asthma in Western Europe. [2] The disease accounts for 60,000 hospital admissions and 200,000 bed days a year. [3] In 2016, 1224 teenagers and adults died due to asthma. [1] Currently patients with severe asthma may be treated with add-on oral corticosteroids (OCS) or a biologic agent (omalizumab, mepolizumab and reslizumab). Current recommendations by NICE restrict biologic treatments to populations that meet certain criteria based on age, blood eosinophil (EOS) level or blood immunoglobulin E (IgE) level, number of previous exacerbations in the previous 12 months and/or use of maintenance OCS. It should be noted that for adolescents with severe asthma high dose inhaled corticosteroids (ICS) with maintenance OCS or omalizumab (for allergic asthma only) are the only available treatments. Based on the trial inclusion criteria and anticipated marketing authorisation, dupilumab may be appropriate for a broader population (moderate-to-severe Type 2 asthma) than any of the currently recommended biologics. For patients uncontrolled with moderate ICS, dupilumab may reduce the need for higher doses of steroids. There is a need for treatments that minimise the use of maintenance OCS. Results from a clinical trial studying the impact of dupilumab on OCS use have demonstrated that most patients receiving dupilumab are able to decrease or discontinue maintenance OCS whilst also experiencing a reduction in exacerbations and increased lung function. [4]	
	NHS England Specialised	No particular urgency as other products are available	Comment noted.

Section	Consultee/ Commentator	Comments [sic]	Action
	Respiratory CRG		
	Asthma UK	No comment	Comment noted.
	Royal college of Physicians	This is urgent as this is a potentially more effective therapy than other biologics available for asthma and has a different mode of action	Comment noted.
Additional comments on the draft remit	NHS England Specialised Respiratory CRG	Without access to the phase III pivotal exacerbation studies and OCS sparing study it is not possible to comment with certainty on the draft remit. However, the population suggested appears to be very broad and technically incorrect. Most definitions of severe asthma are predicated on Global Initiative for Asthma (GINA) step IV/V treatment, which is always more than inhaled corticosteroids alone.	Thank you for your comments. NICE can only consider a drug within the remit of its marketing authorisation. The remit has been updated to reflect the final marketing authorisation for severe asthma.

Comment 2: the draft scope

Section	Consultee/ Commentator	Comments [sic]	Action
Background information	Sanofi	The information provided is accurate. We suggest adding the following information:	Thank you for your comment. The background section provides only a general overview of the disease

Section	Consultee/ Commentator	Comments [sic]	Action
		One pivotal phase 2b and one phase 3 trial evaluated the efficacy and safety of dupilumab with moderate to severe asthma. In addition, another clinical trial evaluated maintenance OCS reduction in severe asthma. [5] [4] [6]	area. No change to the scope required
	NHS England Specialised Respiratory CRG	We would suggest referencing GINA guidelines, which include omalizumab and mepolizumab at step V and are clearly more up to date than the BTS/SIGN equivalent.	Thank you for your comment. The scope has been updated to include recommendations from the recent NICE guideline NG80: asthma: diagnosis, monitoring and chronic asthma management and the updated GINA guidelines.
	Asthma UK	Asthma UK would recommend updating the deaths to the total recorded in 2016. There are 5.4 million people living with asthma across the UK. In England and Wales it is approximately 4.8 million people. Given that the NICE guidelines are now published we would suggest that the scope refers to these guidelines as well as or instead of the BTS/SIGN guidelines. Additionally, the relevant NICE guidelines section should be updated to reflect the published guidelines.	Thank you for your comment. The scope has been updated to include recent asthma statistics and recommendations from the recent NICE guideline NG80: asthma: diagnosis, monitoring and chronic asthma management and the updated GINA guidelines

Section	Consultee/ Commentator	Comments [sic]	Action
	Royal College of Physicians	Dupilumab targets T2 asthma ie asthma that has both an allergic or an eosinophilic mechanism of action	Comment noted. No change to the scope required
The technology/ intervention	Sanofi	The description of the technology and the mode of action is accurate. However, we suggest also incorporating the wording below. Type 2 inflammation is an important underlying pathophysiological feature of asthma that encompasses a range of biomarkers and phenotypes. IL-4,IL-5 and IL-13 are cytokines that are key drivers of type 2 inflammation. IL-4 mediates the production of IL-5 and IL-13. IL-5 promotes the activation survival, and recruitment of eosinophils and IL-13 causes an overexpression of globlet cell hyperplasia and drives increased mucus secretion. IL-4 also plays an important role in Th2 differentiation, mast cell recruitment, the production of IgE and in the recruitment of eosinophils. Currently available biologic therapies are either anti-IL-5 or anti-IgE which target only some of the signalling pathway involved in type 2 asthma. Dupilumab targets IL-4 and IL-13. As such, dupilumab could be effective in Type 2 asthma, including but not limited to allergic and eosinophilic subtypes. [5] - [9]	Thank you for your comment. The intervention section provides only a general overview of the technology. No change to the scope required
	NHS England Specialised Respiratory CRG	No, Dupilumab is an IL-4 receptor alpha antagonist.	Comment noted.
	Asthma UK	No comment.	Comment noted.

Section	Consultee/ Commentator	Comments [sic]	Action
	Royal College of Physicians	Yes	Comment noted.
Population	Sanofi	The expected license for dupilumab in asthma is: [redacted] It is therefore anticipated that dupilumab will be used for treatment of moderate-to-severe asthma in patients aged 12 years and older who are inadequately controlled with medium-to-high dose ICS plus another medicinal product (e.g. long-acting beta agonist [LABA], leukotriene receptor antagonist [LTRA], methylxanthines, slow-release theophylline or long-acting muscarinic agents). We will consider subgroups that facilitate a comparison within the NICE recommended populations for relevant comparators (see next section).	Thank you for your comment. The population in the scope has been updated to be in line with the final marketing authorisation for severe asthma.
	NHS England Specialised Respiratory CRG	No, should be people on high dose ICS and or OCS, i.e. GINA IV/V	NICE can only consider a drug within the remit of its marketing authorisation. The population in the scope has been updated to be in line with the final marketing authorisation for severe asthma.

Section	Consultee/ Commentator	Comments [sic]	Action
	Royal College of Pathologists	As far as I am aware, there is no subdivision of patients in relation to efficacy that relates to a histological or cytological parameter in routine clinical practice, so I do not think that this would affect RCPath members. However, if the scoping consultation identifies patient subsets that require histologic/cytologic assessment, then we should be involved in further stages.	Comment noted. No change to scope required.
	Asthma UK	No comment.	Comment noted.
	Royal College of Physicians	Yes	Comment noted.
Comparators	Sanofi	Standard of care in the dupilumab clinical trials was broadly defined as medium-to-high dose ICS with or without OCS plus a second controller medication. We believe this is reflective of the treatment that patients would receive in the NHS. As described above, dupilumab is likely to be effective in type 2 asthma, which includes both eosinophilic and allergic asthma populations. As such, some patients may be eligible for treatment with either dupilumab or an existing biologic. We believe the following are therefore relevant comparators in their recommended populations. - Mepolizumab in the NICE recommended population: Patients with severe refractory eosinophilic asthma who have a blood eosinophil count is 300 cells/microlitre in the previous 12 months and either have had 4 or more exacerbations needing systemic corticosteroids in the previous 12 months or had continuous oral corticosteroids of at least the equivalent of prednisolone 5 mg per day over the previous 6 months.	Thank you for your comment. The scope has been amended to include these comparators.

Section	Consultee/ Commentator	Comments [sic]	Action
		- Reslizumab in the NICE recommended population: Patients with severe eosinophilic asthma in whom the blood eosinophil count has been recorded as 400 cells per microlitre or more and have had 3 or more severe asthma exacerbations needing systemic corticosteroids in the past 12 months. - Omalizumab in the NICE recommended population: Patients with confirmed allergic IgE-mediated asthma who need continuous or frequent treatment with oral corticosteroids (defined as 4 or more courses in the previous year)	
	GSK	The draft scope would benefit from greater clarity on what exactly comprises and is deemed 'established clinical management without dupilumab'.	Thank you for your comment. This aspect will be covered in the company's evidence submission for the technology appraisal. The scope has been updated to include step up treatment (high dose inhaled corticosteroid as a fixed-dose regimen in combination with a short-acting beta-2 agonist to be used as reliever therapy) as a comparator for people with moderate asthma and to include biologics

Section	Consultee/ Commentator	Comments [sic]	Action
			recommended by NICE (mepolizumab, reslizumab, omalizumab and potentially benralizumab) as comparators for people with severe asthma for whom biologics are indicated and suitable.
	NHS England Specialised Respiratory CRG	No, this will likely be the 4th biologic in people with severe asthma and an eosinophilic signal. The true comparators are omalizumab, mepolizumab, reslizumab and potentially benralizumab.	Thank you for your comment. Following the scoping workshop the scope has been amended to include these comparators.
	Asthma UK	Agree.	Comment noted.
	Royal College of Physicians	Comparison can be made with all existing biologics currently approved for asthma as dupilumab appears effective in both allergic and eosinophilic asthma.	Thank you for your comment. Following the scoping workshop the scope has been amended to include biologics as comparators.
Outcomes	Sanofi	The outcomes presented in the draft scope are appropriate.	Comment noted.

Section	Consultee/ Commentator	Comments [sic]	Action
	NHS England Specialised Respiratory CRG	Yes	Comment noted.
	Asthma UK	For people with severe asthma the most important outcomes and impacts are the reduction in use of oral corticosteroids (OCS) and reduction in asthma attacks. These two outcomes should be the most important outcomes in the assessment of the technology. In early 2017 Asthma UK surveyed over 1100 people with severe asthma about the impact and side effects of OCS. Frequent concerns were: • I put on weight - 56.4% • I have more difficulty falling asleep at night - 54.7% • I eat more - 53.3% • I am hungrier - 52.4% • I get upset and tearful more easily - 43.4% • I am more irritable - 43.3% • I bruise more easily - 42.2% • I feel more anxious - 37.2% • I have less energy - 37.0% • My face feels puffy/swollen - 36.9% • I am hotter/sweatier - 34.4% • I have stomach irritation (e.g indigestion, stomach upset) - 33.7% • My joints and muscles ache/are crampy - 33.4%	Comment noted. No changes to the scope required.

Section	Consultee/ Commentator	Comments [sic]	Action
		• I get angry more easily - 29.4% • I have more difficulty paying attention - 28.7% • My body feels swollen - 27.7% • I am unhappier - 22.1% I am more forgetful - 20.6%	
	Royal College of Physicians	Yes	Comment noted.
Economic analysis	Sanofi	The economic analysis will be carried out in line with the NICE reference case.	Comment noted.
	NHS England Specialised Respiratory CRG	Modelling should suppose between 5-10 years of treatment. An early stopping rule would be of benefit. Clarification on home administration would be useful.	Thank you for your comment. These aspects were discussed at the scoping workshop. No changes to the scope required
	Asthma UK	No comment	Comment noted.
	Royal College of Physicians	The economic analysis should follow a similar path to TA for omalizumab, mepolizimab and reslizumab with similar criteria for use ie steroid sparing and reduction in exacerbations	Comment noted. No changes to scope required
Equality and Diversity	Sanofi	We have not identified any equity or equality issues within the draft scope.	Comment noted.
	NHS England Specialised	No concerns	Comment noted.

Section	Consultee/ Commentator	Comments [sic]	Action
	Respiratory CRG		
	Asthma UK	No comment	Comment noted.
	Royal College Physicians	None noted	Comment noted.
	Sanofi	None	Comment noted.
	Asthma UK	No comment	Comment noted.
Innovation	Sanofi	Dupilumab offers an alternative treatment for patients with moderate-to-severe asthma with a novel mechanism of action which may be effective in a broader patient population than existing biologics and may reduce the use of maintenance OCS. Productivity is not captured in the QALY. In a recently published cross-sectional survey of 2613 working-age adults with asthma, the authors found that having more severe asthma symptoms was increased with the risk of unemployment and an increased risk of work disability. [5] By reducing exacerbations we anticipate patients treated with dupilumab will have fewer work days lost due to illness. Dupilumab may also provide a benefit to carers which may not be captured in the QALY. A number of diseases are mediated by the IL-4 IL-13 pathway, including nasal polyps and atopic dermatitis. Dupilumab has a marketing authorisation	Thank you for your comments. No changes to the scope required.

Section	Consultee/ Commentator	Comments [sic]	Action
		for patients with moderate-to-severe Atopic Dermatitis and Sanofi intends to file for marketing authorisation in other atopic conditions.	
	NHS England Specialised Respiratory CRG	Innovative technology, but should be assessed in comparison with anti-IgE and anti-eosinophilic monoclonal antibodies.	Thank you for your comment. The scope has been amended to include comparisons with these technologies.
	Asthma UK	Dupilumab would be the first treatment for severe asthma to target interleukin 13 and therefore it is our understanding that it will further reduce the unmet need for severe asthma treatments.	Comment noted. No change to the scope required.
	Royal College of Physicians	First in class inhibitor of IL4 and IL13 so novel and innovative	Comment noted. No change to the scope required
Questions for consultation	GSK	*Have all relevant comparators for dupilumab been included in the scope? Could dupilimumab be used in people with IgE mediated or eosinophilic asthma? Should reslizumab, mepolizumab and omalizumab be included as a comparators?* It is unclear from the current draft scope which treatments are considered established clinical management without dupilumab. There are now a number of targeted treatments available for severe asthma (associated NICE guidance is referred to in the draft scope), such as add-on therapy with mepolizumab. It is therefore important that NICE consider each of these as potential comparators; there is likely to be an overlap of eligible patients. This is with	Thank you for your comment. The scope has been amended to include comparisons with these technologies.

Section	Consultee/ Commentator	Comments [sic]	Action
		the intention that subsequent guidance ensures each patient receives the most appropriate targeted therapy for their individual needs.	
	Royal College of Physicians	This drug is also likely to be effective in severe atopic dermatitis which sometimes accompanies T2 asthma	Comment noted. No changes to the scope required.
Additional comments on the draft scope	NHS England Specialised Respiratory CRG	Dupilumab is likely to be clinically and cost effective in the same patient cohort as the other biologics, i.e. people with severe asthma on continuous OCS or having at least 3 to 4 exacerbations per year requiring OCS, despite optimised standard therapy at GINA step IV.	Comment noted. No changes to the scope required.

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

Department of Health