National Institute for Health and Care Excellence

Single Technology Appraisal (STA)

Roflumilast for treating chronic obstructive pulmonary disease (review of technology appraisal guidance 244) [ID984]

Response to consultee and commentator comments on the draft remit and draft scope

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 this topic be appropriate for a NICE appraisal?*		
	AstraZeneca	AstraZeneca believes that it is important that NICE re-appraise roflumilast in a relevant and timely manner as it offers COPD patients who are exacerbating despite inhaled triple therapy a clinically appropriate and efficacious treatment option.	Comment noted.
	Association of Respiratory Nurse Specialists (ARNS)	Yes	Comment noted.
Wording	*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*		

Section	Consultee/ Commentator	Comments [sic]	Action
	AstraZeneca	Yes	Comment noted.
	ARNS	Yes	Comment noted.
Timing Issues	*What is the relative urgency of this appraisal to the NHS?*		
	ARNS	Routine	Comment noted.

Comment 2: the draft scope

Section	Consultee/ Commentator	Comments [sic]	Action
Background information	AstraZeneca	No corrections required	Comment noted.
	ARNS	Accurate and complete	Comment noted.
	British Thoracic Society (BTS)	Background: In terms of comparators the background should include pulmonary rehabilitation and smoking cessation as treatment for COPD.	Comment noted. Background section revised in the final scope.
The technology/ intervention	*Is the description of the technology or technologies accurate?*		
	AstraZeneca	No corrections required	Comment noted.
	ARNS	Yes	Comment noted.

Section	Consultee/ Commentator	Comments [sic]	Action
Population	*Is the population defined appropriately? Are there groups within this population that should be considered separately?*		
	AstraZeneca	Please add the following wording in italics to the population so that it matches the licensed indication: Adults with severe chronic obstructive pulmonary disease (FEV1 post bronchodilator less than 50% predicted) associated with chronic bronchitis in adult patients with a history of frequent exacerbations *as add-on to bronchodilator treatment.*	Comment noted. This is clear from the information about the intervention– no changes to the population considered necessary.
	ARNS	Yes Consideration for ACOS patients	The population is in line with the marketing authorisation
Comparators	*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'?*		
	AstraZeneca	Aligned with the roflumilast NICE TA guidance document, AstraZeneca believe the clinically appropriate positioning for roflumilast within the COPD treatment pathway is for patients who are still exacerbating despite LAMA + ICS/LABA inhaled therapy. AstraZeneca recommend theophylline not be considered an appropriate comparator, as it is not the UK standard of care in this setting. The previous roflumilast NICE TAG states "The Committee heard that theophylline is contraindicated in some people because of interactions with other drugs, that it has many side effects, and that it requires additional monitoring." and "The Committee also noted that theophylline is used in only about 5% of people with severe or very severe COPD." While roflumilast efficacy on reducing exacerbations is well established, theophylline has not been shown to have an effect on reducing exacerbations.	While noting the company's comment on deficiencies in the evidence-base, theophylline remains an option for treating chronic obstructive pulmonary disease and is therefore a relevant comparator.

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		In a recent study (Cosío et al. Chest 2016,) which concludes that oral low-dose theophylline added to ICS-LABA fails to prevent exacerbations in severe COPD patients (see attached). COPD exacerbations were not reduced by the combination of oral low-dose theophylline and ICS-LABA in patients with severe COPD, neither in the intention-to-treat or per protocol analysis. In fact, there was a trend of exacerbations being more frequent in the intervention group, although not statistically significant, probably due to the small sample size. The Global Initiative for Chronic Obstructive Lung Disease (GOLD) Guidelines state: *Theophylline has been associated with a wide range of serious treatment-limiting side-effects. The main side-effects of theophylline are gastrointestinal, cardiovascular (cardiac arrhythmias), and central nervous system- related (headache and seizures). The serum levels must be controlled due to a very narrow therapeutic range, in which most therapeutic benefit occurs only when near-toxic doses are given (GOLD 2015a). The use of theophylline is limited by the frequency of adverse effects.* In addition, the previous roflumilast appraisal investigated the ability to conduct a trial comparing roflumilast to theophylline and the TAG states "the Committee noted comments received during consultation, and agreed that such a trial could be difficult to recruit to because of contraindications, side effects, and additional monitoring needed for people on theophylline. These factors would also make it difficult to carry out a fully blinded study." The NICE committee for the previous appraisal concluded that the requirement for theophylline comparative data did not meet the following criteria for the NICE recommendation "in the context of clinical research": - The intervention should have a reasonable prospect of providing benefits to patients in a cost-effective way. - The research can realistically be set up, is already planned, or is already recruiting patients. - There is a real prospect that the research will inform future NICE	

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		guidance. - The broad balance of the benefits and costs of conducting the research are favourable.	
	ARNS	Yes	Comment noted.
	BTS	Effectiveness should be compared to regular azithromycin for frequent exacerbators	Azithromycin was not included as a comparator because it is used off-label and is not standard of care in treating chronic obstructive pulmonary disease
Outcomes	*Will these outcome measures capture the most important health related benefits (and harms) of the technology?*		
	ARNS	Yes	Comment noted.
Economic analysis	*Comments on aspects such as the appropriate time horizon.*		
	AstraZeneca	Life time horizon will be adopted as COPD is a chronic condition and benefits (prevention of future exacerbations)/costs accrue in the long-term	Comment noted.
	ARNS	Agreed	Comment noted.
Innovation	ARNS	Possibly an add on before an ICS is considered	Comment noted.

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Questions for consultation	AstraZeneca	**Where do you consider roflumilast will fit into the existing NICE pathway, 'Chronic Obstructive Pulmonary Disease'?** The NICE COPD Clinical Guidelines (CG101) are in the process of being updated and therefore AstraZeneca recommend that the recently updated GOLD COPD Guidelines should be utilised for this technology appraisal, whose authors include global COPD clinical experts based in the UK.	Comment noted. Question added to the "Questions for consultation".
Additional comments on the draft scope	Royal College of Physicians (RCP)	The RCP is grateful for the opportunity to comment on the draft scope consultation. We have liaised with the British Thoracic Society (BTS) and clinical leads for COPD audit programme. We wish to endorse the BTS response and highlight that experts believe that roflumilast is a useful technology which has a place in the management of repeated exacerbations in patients with severe, recalcitrant bronchitis-predominant COPD.	Comment noted.

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

- Boehringer Ingelheim
- Healthcare Improvement Scotland