NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Appraisal consultation document

Roflumilast for treating chronic obstructive pulmonary disease

The Department of Health has asked the National Institute for Health and Care Excellence (NICE) to produce guidance on using roflumilast in the NHS in England. The appraisal committee has considered the evidence submitted by the company and the views of non-company consultees and commentators, clinical experts and patient experts.

This document has been prepared for consultation with the consultees. It summarises the evidence and views that have been considered, and sets out the recommendations made by the committee. NICE invites comments from the consultees and commentators for this appraisal and the public. This document should be read along with the evidence (see the committee papers).

The appraisal committee is interested in receiving comments on the following:

- Has all of the relevant evidence been taken into account?
- Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?
- Are the recommendations sound and a suitable basis for guidance to the NHS?
- Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?

Note that this document is not NICE's final guidance on this technology. The recommendations in section 1 may change after consultation.

After consultation:

- The appraisal committee will meet again to consider the evidence, this appraisal consultation document and comments from the consultees.
- At that meeting, the committee will also consider comments made by people who are not consultees.
- After considering these comments, the committee will prepare the final appraisal determination (FAD).
- Subject to any appeal by consultees, the FAD may be used as the basis for NICE's guidance on using roflumilast in the NHS in England.

For further details, see NICE's guide to the processes of technology appraisal.

The key dates for this appraisal are:

Closing date for comments: 28 February 2017

Second appraisal committee meeting: 8 August 2017

Details of membership of the appraisal committee are given in section 6.

1 Recommendations

1.1 Roflumilast is not recommended, within its marketing authorisation, as an add-on to bronchodilator treatment for severe chronic obstructive pulmonary disease in adults with chronic bronchitis and frequent exacerbations.

1.2 This guidance is not intended to affect the position of patients whose treatment with roflumilast was started within the NHS before this guidance was published. Treatment of those patients may continue without change to whatever funding arrangements were in place for them before this guidance was published until they and their NHS clinician consider it appropriate to stop.

2 The technology

Description of the technology	Roflumilast (Daxas, AstraZeneca) is an orally administered long-acting selective phosphodiesterase-4 enzyme inhibitor. It targets cells and mediators believed to be important in chronic obstructive pulmonary disease (COPD).
Marketing authorisation	Roflumilast has a marketing authorisation in the UK for maintenance treatment of severe COPD (forced expiratory volume in the first second [FEV_1] 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.
Adverse reactions	The most common adverse reactions associated with roflumilast include diarrhoea, weight loss, nausea, abdominal pain and headache. For full details of adverse reactions and contraindications, see the summary of product characteristics.
Recommended dose and schedule	The recommended dose is 500 micrograms (1 tablet) of roflumilast once daily.
Price	£37.71 for 30 tablets and £113.14 for 90 tablets (excluding VAT; 'British national formulary' [BNF] edition 72). Costs may vary in different settings because of negotiated procurement discounts.

3 Evidence

The appraisal committee (section 6) considered evidence submitted by AstraZeneca and a review of this submission by the evidence review group (ERG). See the committee papers for full details of the evidence.

4 Committee discussion

The appraisal committee reviewed the data available on the clinical and cost effectiveness of roflumilast, having considered evidence on the nature of chronic obstructive pulmonary disease (COPD) and the value placed on the benefits of roflumilast by clinical experts. No evidence was submitted by patient groups and no patient experts attended the committee meeting. The committee also took into account the effective use of NHS resources.

Clinical need of people with COPD

4.1 The committee heard that COPD is a chronic and progressive disease characterised by obstruction of the airways, breathlessness and cough. Airflow limitation becomes worse over time, with periodic acute exacerbations. The clinical expert advised that despite treatment with optimal inhaled therapy many people with severe COPD have several exacerbations each year, which is a huge burden on patients and the NHS. Exacerbations worsen a patient's health status, reduce their quality of life, accelerate decline in lung function, lead to hospitalisation and increase mortality. The committee was disappointed that no evidence was submitted by patient groups and that no patient experts attended the committee meeting. However, it recognised that a new treatment that reduced exacerbations in people with severe COPD would be highly valued by patients and their carers and address an unmet need.

Clinical management of COPD

4.2 The committee heard from the clinical expert that COPD is treated according to NICE's clinical guideline on chronic obstructive pulmonary disease in over 16s: diagnosis and management. For severe COPD (defined as forced expiratory volume in the first second [FEV_1] less than 50% predicted) the guideline recommends using either an inhaled long-acting muscarinic antagonist alone, a fixed combination of an inhaled corticosteroid and a long-acting beta-2 agonist (dual inhaled therapy), or a combination of all these treatments (triple inhaled therapy). The committee understood that triple inhaled therapy is the standard treatment for people who continue to have exacerbations despite treatment with monotherapy or dual therapy. It noted that the company was seeking a recommendation for the use of roflumilast as an add-on treatment to triple inhaled therapy but not for monotherapy or dual therapy, which were included in the NICE scope. The committee considered whether this was appropriate. It heard from the clinical expert that the 2017 update of the

Global Initiative for Chronic Obstructive Lung Disease (GOLD) report recommended roflumilast as an add-on therapy for people with severe COPD who continue to have exacerbations despite treatment with triple therapy, particularly if they had at least 1 hospitalisation for an exacerbation in the previous year. The committee also heard from the clinical expert that the company's proposed placement of roflumilast in the treatment pathway is consistent with clinical practice, and that around 90% of people having roflumilast will be on triple therapy. The committee concluded that the company's proposed positioning of roflumilast as an add-on to triple inhaled therapy is appropriate.

Comparators

4.3 The committee understood that the comparators in the appraisal scope included monotherapy (a long-acting muscarinic or beta-2 agonist), dual therapy (the above treatments combined with each other or with inhaled corticosteroids), triple therapy (all of the above treatments) and theophylline in combination with inhaled maintenance bronchodilator treatment. The committee noted that the company did not consider monotherapy and dual therapy to be appropriate comparators because it intended to position roflumilast as an add-on treatment to triple inhaled therapy (see section 4.2). The committee accepted that this approach is appropriate. It also noted that the company does not consider theophylline to be an appropriate comparator. The committee heard from the clinical expert that theophylline is not generally used in clinical practice because of the high risk of toxicity, lack of evidence for clinical effectiveness, and associated side effects (such as seizures and cardiac arrhythmias).The committee accepted the company's rationale for excluding theophylline and concluded that triple inhaled therapy is the appropriate comparator for this appraisal.

Clinical effectiveness

Source of clinical evidence

4.4 The evidence for roflumilast submitted by the company came from REACT, a multicentre double-blind randomised controlled trial with 1,935 patients. It compared roflumilast plus inhaled combination therapy (a long-acting beta-2 agonist plus inhaled corticosteroids, with or without a long-acting muscarinic antagonist) with placebo plus inhaled combination therapy. The committee noted that the evidence review group (ERG) presented a pooled analysis of REACT plus another multicentre double-blind trial of roflumilast that included 2,352 patients (RE^2SPOND). It understood that the company did not include detailed information on RE^2SPOND in its submission because it believed that the people in the trial do not accurately reflect the target population. The company stated that fewer than half of patients in RE^2SPOND were on triple therapy (47% compared with 70% in REACT), 0.5% were from Western Europe (compared with 29.5% in REACT) and pre-treatment with inhaled therapies was for a minimum of 3 months rather than 12 months as in REACT. The committee heard from the clinical expert that the duration of background inhaled therapies is an important difference between the 2 trials. Patients in REACT were more likely to have well controlled COPD because they had optimal inhaled therapy for 12 months, whereas patients in RE^2SPOND were not appropriately pre-treated with inhaled therapies. The clinical expert suggested that the population in RE^2SPOND had a higher risk of exacerbations compared with the population in REACT. The committee also heard from the company that RE^2SPOND did not reflect current clinical practice in the UK because it used lower doses of long-acting beta-2 agonists and inhaled corticosteroids and an alternative formulation of roflumilast. The committee discussed the characteristics of the people included in both trials and considered that there were many similarities between the trial populations. The committee

also decided that any heterogeneity between the studies, including the difference in the duration of background inhaled therapy, is unlikely to have systematically biased the relative treatment estimates for roflumilast. The committee concluded that it had not heard adequate justification for not including RE^{2}SPOND and therefore that both REACT and RE^{2}SPOND are relevant for this appraisal.

Intention-to-treat or per-protocol population

4.5 The committee noted that the pre-specified primary analyses in both REACT and RE^{2}SPOND were in the intention-to-treat population. It understood that the company preferred to use clinical data from the per-protocol population because this excluded patients with major protocol violations (such as people who had a post-bronchodilator FEV_1 of 50% or higher than predicted, those not pre-treated with inhaled therapy for 12 months or those who had fewer than 2 exacerbations in the previous year). However, the committee noted that the ERG favoured the intention-to-treat analysis because this included all randomised patients and was therefore more robust and at lower risk of bias. The ERG also suggested that protocol violations are likely to occur in routine clinical practice because FEV_1 values and sputum counts will vary and patients may forget medication changes. The committee considered both populations and agreed with the ERG that the per-protocol population would be at higher risk of bias, because the reasons why participants do not comply with the treatment protocol may be related to their allocated treatment. The committee decided that it had not heard adequate justification from the company for using the per-protocol population. It therefore concluded that the clinical-effectiveness results from the intention-to-treat population are the most appropriate for decision-making.

Clinical-effectiveness results

4.6 The committee noted that both REACT and RE^{2}SPOND reported the rate of moderate to severe exacerbations as the primary outcome. The

committee acknowledged that there was no statistically significant difference in the rate of moderate to severe exacerbations in the overall population of patients randomised to roflumilast plus inhaled combination therapy compared with placebo plus inhaled combination therapy, when using the pre-specified analysis for the primary outcome (REACT: rate ratio [RR] 0.87, 95% confidence interval [CI] 0.75 to 1.00; RE^{2}SPOND: RR 0.92, 95% CI 0.81 to 1.04). It noted however that there was a statistically significantly lower rate of severe exacerbations in REACT in the roflumilast group compared with the placebo group in the pre-specified intention-to-treat analysis (RR 0.76, 95% CI 0.60 to 0.95). These findings were not observed in RE^{2}SPOND (RR 0.95, 95% CI 0.75 to 1.19 for severe exacerbations). The committee concluded that there is some evidence that roflumilast added-on to inhaled combination therapy may reduce severe exacerbations, but that roflumilast did not reduce moderate to severe exacerbations in the overall populations in REACT and RE^{2}SPOND.

4.7 The committee noted that the company had presented clinical-effectiveness results for the subgroup of patients in REACT who were taking a concomitant long-acting muscarinic antagonist as part of their inhaled combination therapy (1,346 [70%] patients). It also noted that the ERG presented results for the same subgroup from RE^{2}SPOND (1,094 [47%] patients) and a pooled analysis of the 2 studies. The committee considered that it was reasonable to consider the results for this subgroup given the company's intention to position roflumilast as an add-on treatment to triple inhaled therapy (see section 4.2). It noted that there was no statistically significant difference in the rate of moderate to severe exacerbations in this subgroup of patients, when using the intention-to-treat analysis (REACT: RR 0.87, 95% CI 0.74 to 1.02; RE^{2}SPOND: RR 0.94, 95% CI 0.79 to 1.11; pooled result: RR 0.90, 95% CI 0.80 to 1.02). However, it noted that in the intention-to-treat analysis of REACT there was a statistically significant reduction in severe

exacerbations in this subgroup of patients (RR 0.77, 95% CI 0.60 to 0.99). This finding was not observed in the same subgroup of RE^{2}SPOND (RR 1.04, 95% CI 0.76 to 1.43) or the pooled analysis of both trials done by the ERG (RR 0.88 95% CI 0.65 to 1.18). The committee concluded that in the pooled analysis of the relevant subgroup, roflumilast added-on to triple therapy was not associated with a statistically significant reduction in the rate of moderate to severe exacerbations or severe exacerbations compared to placebo plus triple therapy.

Cost effectiveness

4.8 The committee noted that the company had developed a Markov model with 3 health states (severe COPD, very severe COPD and death) and monthly cycles. It understood that exacerbations led to additional costs, a temporary decrease in quality of life and, in the case of a severe exacerbation, an increased risk of death. The committee agreed with the ERG that the model structure excluded some important aspects of COPD progression. For example, health states were defined by FEV_1 values alone rather than incorporating other prognostic information. The model also assumed that exacerbations did not affect FEV_1, previous exacerbations did not affect future risk of exacerbations and baseline characteristics such as smoking status did not affect disease progression and risk of exacerbation. The committee noted the limitations of the model but concluded that it is adequate for decision-making.

Modelling rates of exacerbation

4.9 The committee noted that in each cycle of the model, patients were at risk of moderate or severe exacerbations and that these rates were incorporated separately in the model. It also noted that the company's base-case model used exacerbation rate ratios from the subgroup of patients in REACT who were taking a concomitant long-acting muscarinic antagonist, in the per-protocol population. By contrast, the ERG's preferred analysis used pooled exacerbation rate ratios for the subgroup

from the intention-to-treat populations of REACT and RE^{2}SPOND. The committee recalled its earlier conclusions that both REACT and RE^{2}SPOND are relevant for this appraisal (see section 4.4) and that the results from the intention-to-treat populations are most appropriate (see section 4.5). It also recalled that a relatively large subgroup of patients in RE^{2}SPOND (47%) were treated with background triple therapy (see section 4.7). The committee was therefore not persuaded that the data from RE^{2}SPOND should not be considered and concluded that pooled exacerbation rates from REACT and RE^{2}SPOND are the most appropriate for use in the cost-effectiveness model.

Incorporation of health-related quality of life data in the model

4.10 The committee noted that in its base case, the company derived the utility values in the model from 2 studies: Rutten van Molken (2006) for COPD severity and Rutten van Molken (2009) for disutilities for exacerbation. Rutten van Molken (2006) estimated utilities in 1,235 patients, including patients with COPD from the UK, using the UK tariff of the EQ-5D. Utility values from Rutten van Molken (2009) were from valuations of COPD health profiles (presented as vignettes) by the Dutch general public rather than EQ-5D. The committee noted that the ERG's analysis used disutilities for exacerbation from Hoogendoorn et al. (2011), because these were based on patient-reported EQ-5D values and used the UK tariff. The committee compared the ERG's incremental cost-effectiveness ratio (ICER) estimated using Hoogendoorn with the company's base-case ICER. It concluded that using a different data source for disutilities did not have a large impact on the ICER.

Most plausible incremental cost-effectiveness ratio

4.11 The committee noted that the company's base case ICER was £18,774 per QALY gained. It understood that the ERG amended several components of the company's base-case model including the number of GP visits for moderate and severe exacerbations, the costs of

hospitalisation for a severe exacerbation, the cost of pneumonia, and the rate ratios used for exacerbations. The committee recognised that the main driver of the cost-effectiveness results was the rate ratios used for exacerbations. It noted that when the ERG used exacerbation rates from the intention-to-treat population of REACT, which is the committee's preferred approach (see section 4.5), rather than the per-protocol population used in the company's model, the ICER increased to £35,814 per QALY gained. The committee considered that this is more plausible than the company's base-case ICER of £18,774. However, the committee preferred the ERG's use of pooled exacerbation rates from the intention-to-treat populations of REACT and RE^{2}SPOND (see sections 4.4 and 4.9). It noted that this increased the ICER substantially to £71,365 per QALY gained, and concluded that this is the most plausible ICER. The committee agreed that this ICER is substantially above the range normally considered a cost-effective use of NHS resources (that is, between £20,000 and £30,000 per QALY gained) and therefore it concluded that roflumilast could not be recommended for treating COPD.

Pharmaceutical Price Regulation Scheme (PPRS) 2014

4.12 The committee was aware of NICE's position statement on the Pharmaceutical Price Regulation Scheme (PPRS) 2014, and in particular the PPRS payment mechanism. It accepted the conclusion 'that the 2014 PPRS payment mechanism should not, as a matter of course, be regarded as a relevant consideration in its assessment of the cost effectiveness of branded medicines'. The committee heard nothing to suggest that there is any basis for taking a different view about the relevance of the PPRS to this appraisal. It therefore concluded that the PPRS payment mechanism was not relevant in considering the cost effectiveness of the technology in this appraisal.

Summary of appraisal committee's key conclusions

TAXXX	Appraisal title: Roflumilast for treating chronic obstructive pulmonary disease	Section
Key conclusion		
Roflumilast is not recommended, within its marketing authorisation, as an add-on to bronchodilator treatment for severe chronic obstructive pulmonary disease in adults with chronic bronchitis and frequent exacerbations. The committee considered that the most plausible incremental cost-effectiveness ratio (ICER) is £71,365 per quality-adjusted life year (QALY) gained, because this includes the committee's preferred pooled rate ratios for exacerbation using the intention-to-treat populations from both REACT and RE^{2}SPOND. It agreed that this ICER was substantially above the range normally considered a cost-effective use of NHS resources (that is, between £20,000 and £30,000 per QALY gained) and therefore that roflumilast could not be recommended for treating chronic obstructive pulmonary disease (COPD).		1.1 4.11
Current practice		

Clinical need of patients, including the availability of alternative treatments	The committee heard from the clinical expert that despite treatment with optimal inhaled therapy many people with severe COPD have several exacerbations each year, which is a huge burden on patients and the NHS. The committee was disappointed that no evidence had been submitted by patient groups and that no patient experts attended the committee meeting.	4.1
The technology		
Proposed benefits of the technology How innovative is the technology in its potential to make a significant and substantial impact on health-related benefits?	The committee recognised that a new treatment that reduces exacerbations in people with severe COPD would be highly valued by patients and their carers and address an unmet need.	4.1
What is the position of the treatment in the pathway of care for the condition?	The committee understood that triple inhaled therapy is the standard treatment for people who continue to have exacerbations despite treatment with monotherapy or dual therapy. It concluded that the company's proposed positioning of roflumilast as an add-on to triple inhaled therapy is appropriate.	4.2

Adverse reactions	The most common adverse reaction with roflumilast are diarrhoea, weight decrease and nausea.	2
Evidence for clinical effectiveness		
Availability, nature and quality of evidence	The committee noted that the evidence for roflumilast submitted by the company came from REACT, a multicentre double-blind randomised controlled trial with 1,935 patients, which compared roflumilast plus inhaled combination therapy with placebo plus inhaled combination therapy. It also noted that the evidence review group (ERG) reported a pooled analysis of REACT with another multicentre double-blind trial of roflumilast that included 2,352 patients (RE^{2}SPOND). The committee concluded that it had not heard adequate justification from the company for not including RE^{2}SPOND.	4.4
Relevance to general clinical practice in the NHS	The committee concluded that both REACT and RE^{2}SPOND are relevant for this appraisal.	4.4

Uncertainties generated by the evidence	The committee considered uncertainties in the clinical evidence and acknowledged the difference in duration of background inhaled therapies in REACT and RE^{2}SPOND, but concluded that it had not heard adequate justification for not including RE^{2}SPOND. The committee considered results from the intention-to-treat and per-protocol populations. It agreed with the ERG that the per-protocol population would be at higher risk of bias because the reasons that participants may not comply with the treatment protocol may be related to their allocated treatment. The committee did not consider that it had heard adequate justification from the company to use the per-protocol population and therefore concluded that the clinical-effectiveness results from the intention-to-treat population are the most appropriate for decision-making.	4.4, 4.5
Are there any clinically relevant subgroups for which there is evidence of differential effectiveness?	The committee considered that it was reasonable to consider the results for the subgroup of patients who were taking a concomitant long-acting muscarinic antagonist as part of their inhaled combination therapy, given the company's intention to position roflumilast as an add-on treatment to triple inhaled therapy.	4.7

Estimate of the size of the clinical effectiveness including strength of supporting evidence	The committee concluded that there is some evidence that roflumilast added-on to inhaled combination therapy may reduce severe exacerbations, but that roflumilast did not reduce moderate to severe exacerbations in the overall populations in REACT and RE^{2}SPOND. In the subgroup of patients who were taking a concomitant long-acting muscarinic antagonist as part of their inhaled combination therapy, the committee concluded that roflumilast added-on to triple therapy was not associated with a statistically significant reduction in the rate of moderate-to-severe or severe exacerbations compared to placebo plus triple therapy in the pooled analysis of REACT and RE^{2}SPOND.	4.66, 4.7
For reviews (except rapid reviews): How has the new clinical evidence that has emerged since the original appraisal (TA244) influenced the current recommendations?	TA244 recommended that roflumilast should only be used as part of a clinical trial for adults with severe COPD. Since TA244 was published, 2 multicentre double-blind randomised controlled trials have been published and the results of both trials have informed the recommendations in this appraisal.	4.4
Evidence for cost effectiveness		

Availability and nature of evidence	The committee noted that the company had developed a Markov model with 3 health states (severe COPD, very severe COPD and death) and monthly cycles. The committee noted the limitations of the model but concluded that it is adequate for decision-making.	4.8
Uncertainties around and plausibility of assumptions and inputs in the economic model	The committee noted that the company's base-case model used exacerbation rate ratios from the subgroup of patients in REACT who were taking a concomitant long-acting muscarinic antagonist, in the per-protocol population. By contrast, the ERG's preferred analysis used pooled exacerbation rate ratios for the subgroup from the intention-to-treat populations of REACT and RE^{2}SPOND. The committee was not persuaded that the data from RE^{2}SPOND should not be considered, and concluded that pooled exacerbation rates from REACT and RE^{2}SPOND are the most appropriate for use in the cost-effectiveness model.	4.4, 4.5, 4.9

Incorporation of health-related quality-of-life benefits and utility values Have any potential significant and substantial health-related benefits been identified that were not included in the economic model, and how have they been considered?	The committee noted that in its base case, the company derived the utility values in the model from 2 studies: Rutten van Molken (2006) for COPD severity and Rutten van Molken (2009) for disutilities for exacerbation. The committee noted that the ERG's analysis used disutilities for exacerbation from Hoogendoorn et al. (2011) because these were based on patient-reported EQ-5D valued and used the UK tariff. The committee concluded that using a different data source for disutilities did not have a large impact on the ICER.	4.10
Are there specific groups of people for whom the technology is particularly cost effective?	The committee made no specific recommendations for any subgroups but accepted that the company's proposed positioning of roflumilast as an add-on to triple inhaled therapy is appropriate.	4.2
What are the key drivers of cost effectiveness?	The committee concluded that the main driver of the cost-effectiveness results was the rate ratios used for exacerbations.	4.11

Most likely cost-effectiveness estimate (given as an ICER)	The committee concluded that the most plausible ICER is the ERG's estimate of £71,365 per QALY gained, because this included the committee's preferred pooled rate ratios for exacerbation using the intention-to-treat populations from both REACT and RE^{2}SPOND.	4.11
For reviews (except rapid reviews): How has the new cost-effectiveness evidence that has emerged since the original appraisal (TA244) influenced the current recommendations?	The current appraisal used clinical evidence from 2 randomised controlled trials (REACT and RE^{2}SPOND) to re-model the cost effectiveness of roflumilast and this has led to a change in the recommendations.	4.9
Additional factors taken into account		
Patient access schemes (PPRS)	The company did not submit a patient access scheme.	
End-of-life considerations	Not applicable.	
Equalities considerations and social value judgements	The committee did not note any specific equalities considerations.	

5 Proposed date for review of guidance

5.1 NICE proposes that the guidance on this technology is considered for review by the guidance executive 3 years after publication of the guidance. NICE welcomes comment on this proposed date. The guidance executive will decide whether the technology should be reviewed based on information gathered by NICE, and in consultation with consultees and commentators.

Iain Squire
Chair, appraisal committee
January 2017

6 Appraisal committee members and NICE project team

Appraisal committee members

The 4 technology appraisal committees are standing advisory committees of NICE. This topic was considered by committee A.

Committee members are asked to declare any interests in the technology to be appraised. If it is considered there is a conflict of interest, the member is excluded from participating further in that appraisal.

The minutes of each appraisal committee meeting, which include the names of the members who attended and their declarations of interests, are posted on the NICE website.

NICE project team

Each technology appraisal is assigned to a team consisting of 1 or more health technology analysts (who act as technical leads for the appraisal), a technical adviser and a project manager.

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