

Roflumilast for the management of severe chronic obstructive pulmonary disease

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1 Guidance

- 1.1 Roflumilast is recommended only in the context of research as part of a clinical trial for adults with severe chronic obstructive pulmonary disease (COPD) (for the purposes of this guidance defined as forced expiratory volume in 1 second [FEV₁] post-bronchodilator less than 50% predicted) associated with chronic bronchitis with a history of frequent exacerbations as an add-on to bronchodilator treatment.
- 1.2 Such research should be designed to generate robust evidence about the benefits of roflumilast as an add-on to long-acting muscarinic antagonists (LAMA) plus long-acting beta₂ agonists (LABA) plus inhaled corticosteroids (ICS), or LAMA plus LABA for people who are intolerant to ICS.
- 1.3 People receiving roflumilast should have the option to continue treatment until they and their clinicians consider it appropriate to stop.

2 The technology

- 2.1 Roflumilast (Daxas, Merck Sharp & Dohme) has a marketing authorisation for maintenance treatment of severe COPD (FEV₁ post-bronchodilator less than 50% predicted) associated with chronic bronchitis in adult patients with a history of frequent exacerbations as an add-on to bronchodilator treatment. The recommended dose is one tablet of 500 micrograms roflumilast daily.
- 2.2 According to the summary of product characteristics, in clinical COPD studies approximately 16% of participants treated with roflumilast experienced adverse reactions (compared with 5% treated with placebo). The most commonly reported adverse reactions were diarrhoea (5.9%), weight decrease (3.4%), nausea (2.9%), abdominal pain (1.9%) and headache (1.7%). Most of the adverse reactions were mild or moderate. Adverse reactions occurred mainly in the first weeks of treatment and mostly resolved on continued treatment. Roflumilast was associated with an increased risk of psychiatric disorders such as insomnia, anxiety, nervousness and depression. Suicidal thinking and behaviour (including completed suicide) were also reported, although rarely. As part of the conditions of the marketing authorisation for roflumilast, all healthcare professionals expected to prescribe roflumilast should be given an educational pack, including a summary of product characteristics, patient information leaflet, educational material and patient cards. For full details of side effects and contraindications, see the summary of product characteristics.
- 2.3 Roflumilast is priced at £37.71 for a 30-tablet pack and £113.14 for a 90-tablet pack (excluding VAT; 'British national formulary' [BNF] edition 61). Costs may vary in different settings because of negotiated procurement discounts.

3 The manufacturer's submission

The Appraisal Committee ([appendix A](#)) considered evidence submitted by the manufacturer of roflumilast and a review of this submission by the Evidence Review Group (ERG; [appendix B](#)).

- 3.1 In the manufacturer's submission, roflumilast was positioned as an add-on to LAMA plus LABA/ICS (triple therapy) for people who are ICS tolerant, and as an add-on to LAMA plus LABA (dual therapy) for people who are ICS intolerant. The manufacturer stated that 'roflumilast would most typically be used as an add-on to triple therapy (LAMA plus LABA/ICS) [...] and in addition to LAMA plus LABA for patients who do not tolerate or decline, ICS'.

Clinical effectiveness

- 3.2 The main evidence for the clinical effectiveness of roflumilast was from six clinical trials: M2-124, M2-125, M2-127, M2-128, M2-111 and M2-112. The trials were double-blind, multicentre, randomised, placebo-controlled studies. Trials M2-124 and M2-125 were 1 year studies that compared roflumilast (500 micrograms once daily) with placebo in people with severe or very severe COPD (FEV₁ 50% predicted or less) with associated chronic bronchitis and a history of moderate or severe exacerbations (defined as having at least one recorded COPD exacerbation needing systemic corticosteroids or treatment in hospital, or both, in the previous year). M2-124 recruited 1523 people and M2-125 recruited 1568 people. Approximately 50% of the participants received concomitant LABA therapy. The use of ICS and LAMA was prohibited. For reporting, the results from trials M2-124 and M2-125 were pooled.

- 3.3 Trials M2-127 and M2-128 were each 6 months long and recruited people with moderate to severe COPD (post-bronchodilator FEV₁ 40–70% predicted). People enrolled in the M2-127 study (n = 933) did not need to have chronic bronchitis or a history of exacerbations. Of the study population, 78% had chronic cough and sputum. Study M2-127 compared roflumilast (500 micrograms once a day) plus LABA (salmeterol, 50 micrograms twice a day) with LABA plus placebo. People enrolled in trial M2-128 (n = 743) had associated chronic bronchitis and frequent use of as-needed short-acting beta₂ agonists (at least 28 puffs per week) during run-in. The study compared roflumilast (500 micrograms once daily) plus LAMA (tiotropium, 18 micrograms once daily) with LAMA plus placebo. In the M2-111 and M2-112 trials, which were both 1 year long and compared roflumilast (500 micrograms once daily) with placebo, people were recruited who had severe or very severe COPD (post-bronchodilator FEV₁ 50% predicted or less). Participants did not need to have chronic bronchitis or a history of frequent exacerbations. M2-111 recruited 1173 participants and M2-112 recruited 1513 participants. Results were reported from the intention-to-treat populations for the six trials.
- 3.4 From the pooled results of studies M2-124 and M2-125, a statistically significant improvement in the rate of moderate or severe exacerbations was observed for roflumilast compared with placebo (rate ratio [RR] 0.83, 95% confidence interval [CI] 0.75 to 0.92, p = 0.0003). The results from the individual trials were consistent with those of the pooled results. A statistically significant difference was also observed for moderate exacerbations in the M2-112 trial (RR 0.82, standard error [SE] = 0.09).
- 3.5 The results from the 'overall exacerbation' outcome showed that in trials M2-127, M2-128, M2-111 and M2-112, although the rate of exacerbations was lower in the roflumilast arm than in the comparator arm, the difference was not statistically significant. For example, comparing roflumilast with placebo gave:
- a RR of 0.79, 95% CI 0.58 to 1.08, p = 0.1408 in M2-127
 - a RR of 0.84, 95% CI 0.57 to 1.23, p = 0.3573 in M2-128
 - a RR of 0.86, 95% CI 0.72 to 1.06, p = 0.1279 in M2-111.

In studies M2-127 and M2-111, roflumilast was found to reduce the proportion of participants who experienced a moderate or severe exacerbation (M2-127: RR 0.60, 95% CI 0.43 to 0.82, $p = 0.002$; M2-111: odds ratio 0.74, 95% CI 0.58 to 0.95, $p = 0.015$).

- 3.6 Roflumilast was shown to statistically significantly improve pre- and post-bronchodilator FEV₁ compared with the comparator arm in all trials. In trials M2-124 and M2-125, lung function improved in the roflumilast arm. A difference of 55 ml in lung function was reported between people in the two treatment arms at 1 year. The greatest improvement in post-bronchodilator FEV₁ was demonstrated in the M2-128 trial, with a relative change of 81 ml (95% CI 51 to 110) over the 6 months of the study, and the lowest improvement in lung function was seen in the M2-111 study, with a relative change of 38 ml (SE = 10) for roflumilast compared with placebo over the 1year study.
- 3.7 For other outcomes: the manufacturer's submission stated that 'no significant differences were observed in the health-related quality of life measures (St Georges Respiratory Questionnaire and EQ-5D) with roflumilast compared to placebo'; statistically significant improvements in Transition Dyspnoea Index focal score ($p < 0.05$), a measure of symptom control, were observed with roflumilast compared with the comparator in studies M2-124, M2-125, M2-128 and M2-111, but not in study M2-127; and no statistically significant difference was observed in time to mortality from any cause between roflumilast and placebo in the trials that recorded this outcome (M2-124 and M2-125).

- 3.8 In a pooled analysis of the adverse event data from 14 trials (n = 12,054) the incidence of adverse events (62.8% and 67.2%, RR = 1.07) and serious adverse events (14.2% and 13.5%, RR = 0.95) was similar for placebo and roflumilast 500 micrograms, respectively. Of the people on roflumilast 500 micrograms, 6.8% lost weight compared with 1.8% on placebo (RR = 3.71). More people taking roflumilast 500 micrograms (22%) than placebo (10.7%) experienced a gastrointestinal adverse event (RR = 2.06) and the incidence of cardiac adverse events was lower in the roflumilast 500 micrograms group (5.7%) than in the placebo group (5.9%) (RR = 0.95). Completed suicide/suicidal ideation/attempt was infrequent but seen in three roflumilast-treated people (two more completed suicides occurred 3 weeks after treatment) and in one placebo-treated person (rate: 0.793 versus 0.284 per 1000 patient-years of exposure, p = 0.6327).
- 3.9 The manufacturer carried out a mixed treatment comparison so that comparisons could be made with all the comparators (except theophylline) listed in the scope. The manufacturer justified not comparing roflumilast with theophylline on the grounds that it was not thought to be an appropriate comparator for roflumilast because in 'Chronic obstructive pulmonary disease: management of chronic obstructive pulmonary disease in adults in primary and secondary care (partial update)' (NICE clinical guideline 101), theophylline is positioned very late in the treatment pathway, largely because of its side-effect profile and the need for additional monitoring. A systematic literature search identified relevant papers. Studies were included if they were randomised controlled trials longer than 6 months; included people with moderate to severe COPD (FEV₁ 80% predicted or less); included exacerbations of COPD as an outcome; and studied any of the following interventions: LABA (formoterol or salmeterol), LAMA (tiotropium), ICS (fluticasone or budesonide) and roflumilast. These inclusion criteria meant that data from people with both moderate and severe COPD were included. This resulted in 26 studies from 29 trials to inform the mixed treatment comparison. The manufacturer explained that if the inclusion criteria had restricted the studies to people with FEV₁ 50% predicted or less, only people with severe COPD would be included, as in the marketing authorisation, but would have resulted in only eight eligible studies. The manufacturer stated that a mixed treatment comparison derived from this dataset (eight studies) would not have been informative.

- 3.10 To demonstrate the effects of missing combinations including roflumilast (LABA plus ICS plus roflumilast, LABA plus LAMA plus ICS plus roflumilast, and LABA plus LAMA plus roflumilast) an additive mixed treatment comparison analysis was conducted. This analysis used an additive main effects model, in which each of the single treatments (placebo, LABA, LAMA, ICS and roflumilast) were assigned a mean treatment effect. The effect of each combination of two or more agents was expressed as the sum of the relevant active components (by addition on the log scale).
- 3.11 The results of the primary analysis, using the additive approach, suggested that adding roflumilast to other therapies reduces exacerbations. For example:
- adding roflumilast to LAMA compared with LAMA alone gave a RR 0.84, 95% CI 0.61 to 1.14
 - adding roflumilast to LAMA plus LABA compared with LAMA plus LABA alone gave a RR 0.84, 95% CI 0.74 to 0.95
 - adding roflumilast to LAMA plus LABA/ICS versus LAMA plus LABA/ICS alone gave a RR 0.84, 95% CI 0.74 to 0.95.

Cost effectiveness

- 3.12 The manufacturer developed a de novo model, which was designed to assess the cost effectiveness of roflumilast as an add-on to bronchodilator therapies, compared with standard care, in people who have severe COPD associated with chronic bronchitis and who continue to have exacerbations despite prior treatment.

- 3.13 The economic model is a Markov model with five states: severe COPD, defined as a post-bronchodilator score of 30–49% FEV₁ predicted (one state for first-line treatment, one state for second-line treatment), very severe COPD, defined as FEV₁ less than 30% predicted (one state for first-line treatment, one state for second-line treatment), and death. First-line treatment comprises ten possible treatment options, followed by second-line treatment with LAMA plus LABA/ICS. For people who are ICS intolerant there are six possible first-line treatment options, followed by LAMA plus LABA as second-line treatment. In the model a treatment effect that reduces the risk of exacerbations, including severe exacerbations that may need admission to hospital, has an impact on cost, utility and mortality.
- 3.14 All people start in the severe COPD state. In each 1month cycle of the model they can: stay in the same state; have an exacerbation; switch to a second-line treatment; progress to very severe COPD (if already in a severe COPD state); or die because of background mortality or an exacerbation. Progression from the severe to the very severe health state is determined by the decline in lung function in the COPD population relative to that in the general population (0.052 litres per year). All participants were assumed to start with a lung function of FEV₁ 40% predicted. The transition from first-line to second-line treatment was assumed to be 12 months. The time horizon was 30 years (which is assumed to be a lifetime).
- 3.15 For people who have an exacerbation in the severe health state, it was assumed that 16% of the time it would be a severe exacerbation, rather than a moderate exacerbation, which compares with 24% in the very severe group. The background exacerbation rate was assumed to be two exacerbations per year for treatment with LAMA plus LABA/ICS. Relative rates of exacerbations for the different treatment options were based on this number. The relative rate ratio of exacerbations for people treated with LAMA plus LABA/ICS plus roflumilast compared with LAMA plus LABA/ICS was 0.84, which was used in the model and informed by the additive mixed treatment comparison.

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- 3.16 Utilities for the health states in the model were derived from the LABA subgroup of the pooled analysis of studies M2-124 and M2125 roflumilast clinical trials, which used the EQ-5D. A utility of 0.751 was applied to the severe COPD state and a utility of 0.657 to the very severe COPD state. A utility decrement of -0.01 per year adjusted to a 1month value (-0.12) was applied to the model for one cycle if a moderate exacerbation occurred and -0.042 per year adjusted to a 1month value (-0.504) was applied to the model for one cycle for a severe exacerbation.
- 3.17 Total cost comprised cost of COPD regimens, cost of maintenance of people with COPD and cost of exacerbations. The monthly cost for maintenance in the severe state was £48.33 and £150.05 in the very severe state. The monthly cost of a moderate exacerbation was £73.56 and a severe exacerbation was £1346.63.
- 3.18 After the exclusion of treatment options that were dominated (more expensive and less effective than the comparator) or extendedly dominated (had an incremental cost-effectiveness ratio [ICER] that was higher than that of a comparator treatment which was at least as effective), the analysis showed that roflumilast added to LAMA plus LABA/ICS, compared with LAMA plus LABA/ICS alone, gave an ICER of £16,567 per quality-adjusted life year (QALY) gained. For people who are intolerant of ICS, it showed that roflumilast added to LAMA plus LABA had an ICER of £13,764 per QALY gained.

3.19 In sensitivity analyses, the most influential factor affecting cost effectiveness was the relative risk of exacerbations in people taking LAMA plus LABA/ICS plus roflumilast compared with those taking LAMA plus LABA/ICS. A relative risk of 0.73 (lower boundary of relative risk confidence interval) yielded an ICER of £10,027 per QALY gained, whereas a relative risk of 0.94 (upper boundary of relative risk confidence interval) yielded an ICER of £48,000 per QALY gained. All other one-way sensitivity analyses gave ICERs that ranged from £13,613 to £19,811 per QALY gained. Sensitivity analyses in the ICS-intolerant population were consistent with these results, with the ICER ranging from £6389 to £26,913 per QALY gained when the relative risk of exacerbation ranged from 0.69 to 0.93. For all other one-way sensitivity analyses, the ICER ranged from £11,403 to £16,361 per QALY gained. In the probabilistic sensitivity analysis, at willingness to pay thresholds of £20,000 and £30,000, the probability that LAMA plus LABA/ICS plus roflumilast represents a cost-effective treatment option compared with LAMA plus LABA/ICS was approximately 55% and 81% respectively for the ICS-tolerant population and approximately 73% and 89% respectively for the ICS-intolerant population.

3.20 The following scenario analyses were conducted in the ICS-tolerant and ICS-intolerant populations:

A The number of exacerbations per year in the severe COPD state was set to one and three (the base case was two) for the common comparator (LAMA plus LABA/ICS).

B Incorporation of a lung function benefit. The lung function benefit was assumed to be for 1 year.

C Time on first-line therapy was adjusted to 0.5 years, 1.5 years, 2 years and lifetime (the base case was 1 year).

D Estimates of disutilities of exacerbations based on the relative reduction of baseline utilities: 15% because of moderate exacerbation and 50% because of severe exacerbation.

E People who start on first-line LAMA plus LABA/ICS plus roflumilast (ICS tolerant) and LAMA plus LABA plus roflumilast (ICS intolerant) stay on this therapy for their lifetime (in the base case

people were assumed to receive a second-line treatment that was common to all comparator regimens).

F People start treatment in the very severe COPD health state.

3.21 ICERs from these analyses ranged from £7552 per QALY gained (incorporating a lung function benefit [scenario B]) to £29,581 per QALY gained (one exacerbation [scenario A]). The scenario analyses showed that the ICER was most sensitive to the number of exacerbations assumed for the common comparator.

Evidence review group comments

3.22 The ERG found substantial differences in baseline characteristics between the clinical studies used in the manufacturer's analysis. In terms of reporting, the ERG found that in most trials it was not clear how many participants had a history of frequent exacerbations, and none of the roflumilast trials had inclusion criteria that specified a history of two or more exacerbations in the previous year. In the clarification response, the manufacturer explained that it had focused its submission on people who experience at least two exacerbations per year, which should be interpreted as the manufacturer's definition of 'frequent exacerbations'. The ERG found that the severity of COPD at baseline was clearly reported in all trials.

3.23 The ERG found that roflumilast alone reduced the annual rate of exacerbations when compared with placebo across the three studies (M2-111, M2-112 and the pooled studies, M2-124 and M2125). However, only one result from the pooled M2-124 and M2125 studies was statistically significant (RR 0.854, 95% CI 0.736 to 0.992). Most other treatments also showed mainly nonstatistically significant results for exacerbations when compared with placebo.

- 3.24 The ERG considered that the standard mixed treatment comparison model used by the manufacturer was methodologically correct. However, the ERG thought the patient population was inappropriate, because it included data from a wider patient population than was specified in the scope. The ERG explained that the population for the mixed treatment comparison was described as people with moderate to severe COPD, defined by the Global Initiative for Chronic Obstructive Lung Disease and the criteria in NICE clinical guideline 101 as FEV₁ 80% predicted or less. However, the decision problem refers to a more severely affected patient population – adults with severe COPD (postbronchodilator FEV₁ less than 50% predicted) associated with chronic bronchitis and a history of frequent exacerbations – which matches the population specified in the scope and corresponds with the licensed population.
- 3.25 The ERG considered that the additive mixed treatment comparison analysis was invalid and should not be used to estimate the effect of the combination treatments (roflumilast plus LABA plus LAMA; roflumilast plus LABA/ICS plus LAMA; roflumilast plus ICS; roflumilast plus LABA/ICS; and LAMA plus ICS). The ERG believed that there is an interaction between the treatments, such that it is not independent of the drug to which it is added, and so the additive approach was inappropriate. The ERG concluded that it was not possible to obtain reliable relative rates of exacerbations for the following treatment combinations: LAMA plus roflumilast; LABA/ICS plus roflumilast; LABA plus LAMA plus roflumilast; and LABA plus LABA/ICS plus roflumilast, because they were derived from the additive analysis.

- 3.26 The ERG conducted its own mixed treatment comparison, which was more restrictive than the manufacturer's. It sought to provide evidence for the population that was defined in the scope by restricting the evidence base to only those studies that included participants with FEV₁ 50% predicted or less. Nine trials covering seven treatments were included in the ERG's mixed treatment comparison, as opposed to the 29 trials in the manufacturer's submission. The ERG also conducted another mixed treatment comparison with wider inclusion criteria (FEV₁ less than 65% predicted), the results from which are referred to as the 'ERG-alternative analysis'. This mixed treatment comparison used results from 16 trials and nine treatments. Because the ERG did not consider the additive analysis to be valid, the comparisons the ERG carried out were restricted to those for which data were available. The only combinations including roflumilast that the ERG assessed in its additional analyses were roflumilast by itself and roflumilast plus LABA.
- 3.27 The results from the ERG's mixed treatment comparison showed that for the mean annual rate of exacerbations roflumilast alone was likely to be superior to placebo (RR 0.89, 95% CI 0.82 to 0.97). The ERG commented that when compared with other active treatments, roflumilast monotherapy did not show a high likelihood of superiority. The ERG found that for the mean annual rate of exacerbations, roflumilast plus LABA was likely to be superior to placebo (RR 0.81, 95% CI 0.69 to 0.95). When compared with other active treatments roflumilast plus LABA was likely to be superior to LABA alone (RR 0.78, 95% CI 0.69 to 0.89).
- 3.28 The ERG considered that the model structure in general was adequate, but that the economic model lacked transparency and documentation. In addition, the model set-up had some inconsistencies in data handling and mistakes in the technical details. Because of the lack of transparency, the ERG indicated that it was not possible to check whether the model was truly reliable. The ERG questioned the following assumptions used in the model:
- The fixed 12month duration of first-line treatment and whether this duration is independent of treatment options. In the literature, the ERG found that, based on observational data, people still use first-line drugs after 1, 2 and 3 years.

- People switching to second-line treatment as a function of time on first-line treatment. The manufacturer explained that 'sensitivity analyses showed varying the time to switch did not have a substantial effect on the results'.
- Second-line therapy being the same for all people (LAMA plus LABA/ICS for the ICS-tolerant population, LAMA plus LABA for the ICS-intolerant population) and lasting for the rest of the time horizon (29 years). The ERG did not consider this likely in reality. This implies that a difference between strategies can only be made in the first year, and the difference established in the first year will be extrapolated for 29 years.
- People continue treatment for the rest of their lives irrespective of whether the treatment is beneficial. The ERG considered it unlikely that clinicians would continue to prescribe treatment to people who gained no benefit. Therefore, the ERG considered that a continuation rule should have been part of the cost-effectiveness analysis.
- The use of two exacerbations as the baseline average given that, in the manufacturer's clarification response, the manufacturer explained that its submission focused 'on a group of people who experience at least two exacerbations per year', which implies that the average number of exacerbations would be higher than two. The ERG found the rate of two exacerbations per year was not based on published evidence. It cited a paper in which the annual rate of exacerbations was reported as 1.83 for severe COPD and 2.38 for very severe COPD, and another paper in which the weighted average number of exacerbations was found to be 1.97 per year. The ERG considered that two exacerbations per year is conservative and estimated a rate of 2.86 for people with severe COPD on placebo. The ERG noted that the manufacturer varied the number of exacerbations in the scenario analysis to three exacerbations per year.

3.29 The ERG identified from the literature alternative estimates for the proportion of severe exacerbations experienced in the severe and the very severe health states and applied these in its analysis. The rates were changed from those assumed in the model (from 0.155 and 0.224 to 0.12 and 0.117 for severe and very severe COPD respectively).

- 3.30 The manufacturer obtained the utility decrements for the model from a different population than the utility values for the model health states (a preference-based study of Dutch adults rather than the clinical trial). The ERG found that lower utility values for the same severe and very severe health states were obtained if the preference-based study (instead of the trial data) was used to derive utilities. Because of this, the ERG considered that the utility values used may not match the decrements because the decrements were obtained from a different population, which showed a tendency towards lower utility values compared with the people with COPD from the clinical trial. The ERG also highlighted that adverse events are not accounted for in the utility scores.
- 3.31 The ERG's calculations found that for people who are ICS tolerant, the ICER for LAMA plus LABA/ICS plus roflumilast compared with LAMA plus LABA/ICS was the same as in the manufacturer's base case, at £16,560 per QALY gained. For the ICS-intolerant population for LAMA plus LABA plus roflumilast compared with LAMA plus LABA, the ERG calculated the ICER to be £13,784 per QALY gained, compared with the manufacturer's base-case ICER of £13,764 per QALY gained.
- 3.32 The ERG's scenario analysis assumed that participants switch to the second-line regimen on disease progression (instead of after a period of time) with disease progression independently modelled from a possible treatment effect on FEV₁% predicted. The ICER for LAMA plus LABA/ICS plus roflumilast compared with LAMA plus LABA/ICS was £19,186 per QALY gained. For the ICS-intolerant population, the ICER for LAMA plus LABA plus roflumilast compared with LAMA plus LABA was £15,736 per QALY gained.
- 3.33 The ERG explained that, given the problems identified with both the additive mixed treatment comparison and the choice of studies included in the mixed treatment comparison, it considered the manufacturer's incremental analysis to be invalid and the results should be ignored. Instead the ERG conducted its own analyses.

- 3.34 The ERG carried out its own mixed treatment comparison to investigate the cost effectiveness of roflumilast compared with a list of comparators for which evidence was available, as previously described in section 3.26. In these additional analyses only roflumilast alone and roflumilast plus LABA were included. The results for the ICS-tolerant and ICS-intolerant people show that these treatment options were dominated by other available treatment options.
- 3.35 Full details of all the evidence are in the manufacturer's submission and the ERG report, which are available from the [NICE website](#).

4 Consideration of the evidence

- 4.1 The Appraisal Committee reviewed the data available on the clinical and cost effectiveness of roflumilast, having considered evidence on the nature of COPD and the value placed on the benefits of roflumilast by people with the condition, those who represent them, and clinical specialists. It also took into account the effective use of NHS resources.
- 4.2 The Committee discussed the clinical pathway of care for COPD. The Committee noted that according to the NICE guidance on COPD (NICE clinical guideline 101), people with severe COPD with a FEV₁ less than 50% predicted experiencing persistent exacerbations or breathlessness would normally be treated with LAMA plus LABA/ICS (triple therapy). People who are intolerant to ICS can be offered LAMA plus LABA (dual therapy). The guideline also states that 'theophylline should only be used after a trial of short-acting bronchodilators and long-acting bronchodilators, or in patients who are unable to use inhaled therapy'. The Committee heard from the clinical specialists that people who have recurrent exacerbations may also be treated with a continuous antibiotic regimen or theophylline. 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. The clinical specialists stated that smoking cessation strategies and pulmonary rehabilitation are also used for people with severe COPD.

- 4.3 The Committee considered the nature of the condition, and noted evidence submitted and presented by the patient expert and clinical specialists on the clinical symptoms associated with COPD. The Committee heard from the clinical specialists and patient expert that exacerbations are a feature of the disease. It heard that a severe COPD exacerbation, particularly one that means the person has to be admitted to hospital, has a major impact on quality of life, and that severe exacerbations have an associated mortality risk. The Committee also heard from the patient expert that for people who have severe disease, who are already on many treatments for COPD, there are few other treatment options if they have a severe exacerbation needing admission to hospital, other than oxygen and antibiotics. The patient expert indicated that even a moderate exacerbation may be very debilitating and can limit the ability to carry out everyday activities such as shaving or leaving the house. An exacerbation may also make the person feel depressed and it can take 10 to 14 days to recover. The Committee recognised the debilitating nature of the condition, particularly exacerbations, and the potential benefit of additional effective treatments for people with severe COPD who have frequent exacerbations.
- 4.4 The Committee discussed the manufacturer's submission of clinical evidence, noting that the evidence in the submission came from six trials in which roflumilast was compared with placebo. The Committee discussed the likely position of roflumilast in clinical practice. The Committee noted that in clinical practice people with severe COPD with a history of frequent exacerbations would generally be on triple therapy (LAMA plus LABA/ICS), or dual therapy (LAMA plus LABA) if they were intolerant to ICS. The Committee heard from the clinical specialists that some people already on triple therapy would benefit from further treatment and that it may be reasonable to add roflumilast to triple therapy. In a small minority of people roflumilast may be considered earlier in the treatment pathway, for example in addition to a LABA or LAMA. The Committee noted the lack of clinical trial evidence to show the clinical effectiveness of roflumilast as an add-on to triple or dual therapy. The Committee concluded that roflumilast was most likely to be used in addition to triple therapy, but that there was no direct clinical trial evidence related to roflumilast in this position.

- 4.5 The Committee discussed whether the trials were conducted against an appropriate comparator and whether theophylline should be considered a comparator. The Committee heard from the manufacturer that there was no trial evidence for theophylline relating to exacerbation rates and that data it had studied showed limited prescribing of theophylline in clinical practice. The clinical specialists explained that theophylline can be used in people with severe COPD and that limited evidence did not mean it should be excluded as a comparator. The Committee heard from the patient expert that it would be difficult for people who are currently on theophylline to make an informed decision about whether or not to switch from theophylline to roflumilast without relevant effectiveness data. The Committee concluded that theophylline is an appropriate comparator for a subgroup of people in this patient population.
- 4.6 The Committee discussed whether the participants in the trials were representative of people with 'frequent exacerbations'. The Committee heard from the clinical specialists that having frequent exacerbations is generally regarded as having two exacerbations or more in 1 year. The Committee noted the inclusion criterion used in the M2-124 and M2-125 trials, which was that the participants must have had at least one recorded COPD exacerbation needing systemic corticosteroids or hospital treatment, or both, in the previous year. The Committee heard from the clinical specialists that most exacerbations would be treated with antibiotics rather than corticosteroids, and that because of this it is highly likely that the people in the two studies would have had more than one exacerbation in the previous year, had a broader definition of an exacerbation been applied. The Committee also noted that none of the four trials (M2-111, M2-112, M2-127 and M2128) had, as an inclusion criterion, experiencing an exacerbation in the previous year. The Committee concluded that there was some trial evidence for people with frequent exacerbations but that there was uncertainty about how many exacerbations people in the trials had experienced and whether, as a whole, the body of evidence accurately represented the patient population of interest.

- 4.7 The Committee discussed the primary and secondary outcomes in the trials. It noted that in some of the trials there was a statistically significant reduction in exacerbation rate with roflumilast. It also noted a small and statistically significant improvement in lung function in the trials, although this effect was not considered to be clinically significant by the clinical specialists. The clinical specialists said that the improved lung function was likely to be explained by the anti-inflammatory effect of the treatment and that there was no evidence to show that roflumilast has an effect on the rate of FEV₁ decline or disease progression. The Committee was satisfied that there was evidence from the trials that treatment with roflumilast reduced exacerbations and that the trials also showed a small, although not clinically significant, improvement in lung function.
- 4.8 The Committee considered the evidence for the effect of roflumilast on health-related quality of life. The Committee noted that the combined analysis of trial data for M2-111 and M2-112 showed that roflumilast compared with placebo did not statistically significantly improve health-related quality of life and symptom control. It noted there was a small, statistically significant difference in health-related quality of life favouring roflumilast in one trial (M2-111) but the clinical specialists said that when analysed individually the difference of 1.5 units on the St George's Respiratory Questionnaire did not reach the minimally important difference for this questionnaire, which is a change of 4 units. The Committee also noted that the combined analysis of trial data for M2-124 and M2-125 showed no statistically significant difference in EQ-5D total score between the roflumilast group compared with the placebo group, although it noted a statistically significant difference in favour of roflumilast for the Transition Dyspnoea Index focal score. The Committee heard from the clinical specialists that they would have expected greater differences in quality of life for the roflumilast group compared with placebo. The Committee concluded that no meaningful effect of roflumilast on health-related quality of life was demonstrated in the trial populations.

4.9 The Committee considered the adverse events associated with treatment with roflumilast. The Committee noted that adverse events were likely to be an important factor in the high rate of withdrawals (approximately 30%) from the clinical trials with roflumilast. The Committee noted that roflumilast can cause weight loss, and heard from the clinical specialists that this was a concern because many people with COPD were already underweight and that weight loss was a poor prognostic feature. The Committee also noted that roflumilast was associated with an increased risk of psychiatric disorders (including depression and suicide) and insomnia. The Committee concluded that the adverse events associated with roflumilast could be a concern for people with COPD and clinicians, and that follow-up to address this concern may be needed. It noted that the summary of product characteristics stated that all people for whom roflumilast was prescribed should be informed about the risks of roflumilast and the precautions for safe use, and that they should be given a patient card before starting treatment. The Committee noted that checking for weight loss could be carried out routinely at clinical visits. The Committee heard from the clinical specialists that monitoring the mental status of people with COPD taking roflumilast would be challenging because there is no established method for this. The Committee heard from the manufacturer that the onus is on the patient to report any changes in mood and/or weight to the clinician and, if deemed necessary, to stop taking the treatment. The manufacturer also said that the additional burden on the prescriber would probably be minimal, with only one or two extra questions during routine clinical visits. The Committee concluded that, although there was likely to be some additional workload associated with following up people treated with roflumilast, the scale of this increase was unclear.

4.10 The Committee discussed the manufacturer's mixed treatment comparison, which used data from trials including people with moderate and severe COPD. The Committee discussed whether it could infer anything about how effective roflumilast was in severe disease, for which it was licensed, from data from people with moderate and severe disease. The Committee heard from the clinical specialists that the classification of COPD severity is based on lung function. The Committee also heard that although symptoms tend to worsen as disease severity worsens, people with COPD have a range of symptoms such as exacerbations, irrespective of disease severity. The clinical specialists said that, from trial evidence, they anticipated that the relative effect of roflumilast was likely to be similar in moderate and in severe disease. Conversely, the Committee heard from the ERG that evidence from COPD trials showed roflumilast to be more effective in people with moderate disease than in people with severe disease. The Committee noted the manufacturer's response to consultation, which showed that there was no interaction between disease severity and treatment effectiveness. The Committee accepted that treatment response in people with moderate disease was likely to be similar to that for severe disease. However, a trial of roflumilast as an add-on to triple therapy, in the same population as defined in the marketing authorisation, would provide robust evidence for efficacy in the proposed place in the treatment pathway and for the population for whom roflumilast is licensed.

4.11 The Committee considered the validity of the additive approach used by the manufacturer in the mixed treatment comparison, which was used to determine the exacerbation rate for treatment comparisons where no trial data were available (for example for triple therapy plus roflumilast compared with triple therapy alone). The additive mixed treatment comparison assumes that all treatments have the same treatment effect, independent of whether used alone or in combination with one or more agents. The Committee discussed the biological plausibility of this assumption. The Committee heard from one of the clinical specialists that roflumilast was likely to have an additive effect on top of triple therapy because its mechanism of action was different to the drugs used in triple and dual therapy. However, another clinical specialist said that roflumilast added to triple therapy would probably have a lesser effect than in combination with a single agent. The Committee thought that for some agents a consistent additive effect was unlikely. The Committee heard from one of the clinical specialists there is a maximum degree of dilatation that can be achieved anatomically (ceiling effect). Although a second bronchodilator (LABA or LAMA) added to a first could have an additive effect, and this was assumed in NICE clinical guideline 101, it may be less than additive if the maximum dilatation was, or was close to already being achieved with the first agent. The Committee heard from the clinical specialist that roflumilast has a different mechanism of action to LABA and LAMA, and that data showing a 15–20% reduction in exacerbation rate for roflumilast when added to a LABA, or a LAMA support an additive effect. The Committee did not accept that this proved the effect would be the same if roflumilast was added to LABA, LAMA and ICS.

- 4.12 The Committee noted that an additive effect was assumed when roflumilast was added to ICS, which has an anti-inflammatory action and could overlap with roflumilast. The Committee considered that the effect of roflumilast may be less than additive when added to ICS and noted the European Medicines Agency's request that the manufacturer conduct a trial to assess the efficacy of roflumilast as add-on therapy to LABA plus ICS because of the lack of data for this treatment comparison (see 4.23 for further information). The Committee concluded that although roflumilast could be postulated to have the same additive effect when given as monotherapy or in combination with one or more other agents, there was considerable doubt about whether its effect as demonstrated as monotherapy, and in combination with LABA alone and LAMA alone, would be the same when combined with maximal standard care comprising LABA/ICS plus LAMA. The Committee noted that only direct trial evidence could show this.
- 4.13 The Committee further considered the results in the manufacturer's submission. This indicated that the relative risks for roflumilast from the mixed treatment comparison as monotherapy, in combination with LABA alone and with LAMA alone, and the estimate from the additive mixed treatment comparison were all closely aligned. The Committee noted the wide confidence intervals for the point estimates, which in the cases of roflumilast in combination with LABA alone and with LAMA alone, both crossed one. They considered that this demonstrated uncertainty about the size of the benefit of roflumilast with LABA alone or with LAMA alone, which cast further doubt on the additive estimate of the efficacy of roflumilast in combination with two or more agents. The Committee concluded that the figures presented did not confirm the validity of the additive approach and that the additive mixed treatment comparison did not provide a sufficiently robust estimate of the clinical effectiveness of roflumilast in the proposed place in the treatment pathway.

4.14 The Committee considered evidence on the cost effectiveness of roflumilast for the treatment of adults with severe COPD associated with chronic bronchitis with a history of frequent exacerbations as an add-on to bronchodilator treatment. The Committee noted that the model was driven by the effect of treatment on reducing exacerbations and the corresponding disutility and associated cost, and the resultant effect on exacerbation-related mortality. The Committee also noted that a lung function benefit was only considered in a scenario analysis, although there was evidence of an improvement in lung function in the clinical trials, which considerably reduced the ICER. The Committee further discussed the design of the economic model in the base case, noting that people have first-line treatment lasting 1 year followed by second-line treatment for their remaining lifetime (up to 29 years). The Committee heard from the clinical specialists that once a person with COPD starts treatment with a particular drug it is difficult for them to stop treatment because of concerns that their condition may deteriorate as a result. The clinical specialists said that in COPD, individual patient outcomes for exacerbations are not routinely and objectively measured. They said that, importantly, there was no way to know how many exacerbations the person they are treating would have experienced without that treatment. They said that the decision to prescribe and to continue prescribing was based largely on patient reports of their health and efficacy results from clinical trials. The Committee discussed the finding in the scenario analysis of triple therapy plus roflumilast continuing unchanged over a lifetime rather than defaulting to triple therapy without roflumilast after 1 year as in the base case, and heard that this alternative scenario did not substantially affect the ICER. The Committee heard from the manufacturer that in this scenario, it had assumed that both costs and benefits of treatment occurred for a lifetime. The Committee noted that no evidence had been presented to show how long the benefits of roflumilast would last, and that if the effect diminished over time, the ICER could increase substantially. The Committee considered that the design of the model was generally appropriate. The Committee concluded that the scenario in which treatment with roflumilast continued for the lifetime of the person with COPD was more likely to reflect clinical practice than the base case, in which people stopped treatment with roflumilast after a year and then remained on triple therapy alone. However there remained uncertainty about the size of the ICER when lifetime benefits of roflumilast are not assumed.

- 4.15 The Committee discussed the fact that the model did not take account of adverse effects associated with treatment. The Committee was concerned that adverse events were likely to be an important contributor to the high withdrawal rate in the roflumilast trials, and that because the effect of adverse events was not modelled, the associated costs and disutilities would not be captured in the model's outcomes. The Committee concluded that it would have been appropriate to include adverse events in the model because these were potentially significant and could be associated with additional costs and an impact on health-related quality of life, which would affect the ICER.
- 4.16 The Committee noted that the manufacturer's base-case ICER was £16,600 per QALY gained in the ICS-tolerant population and £13,800 in the ICS-intolerant population. The Committee considered that because of the lack of relevant data there was much uncertainty around these ICERs. In addition, many assumptions had to be accepted in both the derivation of the clinical effect of roflumilast and in the modelling in order to accept these ICERs. The Committee concluded that these ICERs were highly uncertain and it was not satisfied that they accurately represent the cost effectiveness of treatment with roflumilast in addition to triple therapy.
- 4.17 The Committee then considered the advice in the technology appraisals methods guide that, when evidence of effectiveness is either absent or weak, the Committee may recommend that particular interventions are used within the NHS only in the context of research, noting that the following factors will be considered before issuing such a recommendation:
- 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 guidance.
 - The broad balance of the benefits and costs of conducting the research are favourable.

- 4.18 The Committee discussed the ICERs in the manufacturer's sensitivity analysis around the rate ratio for exacerbations, which ranged from £10,000 (RR 0.73) to £48,000 (RR 0.94) per QALY gained. The Committee noted that the threshold normally considered by NICE as a cost-effective use of NHS resources is in this range, but that at lower estimates of clinical effectiveness, the ICER was higher than would be considered cost effective. The Committee concluded that, although there was a reasonable prospect of providing benefits to people with COPD in a cost-effective way, there was considerable uncertainty about the size of the treatment effect of roflumilast as an add-on to triple therapy or dual therapy (if the person is intolerant to ICS) and on the rate of exacerbations. The Committee noted that the relative risk of 0.84 for reduction in exacerbations for roflumilast, when it is added to other treatments, was associated with considerable uncertainty and that many of the results from the six roflumilast trials had confidence intervals for the relative risks that crossed one, indicating a statistically non-significant result. It concluded that further data were needed so the Committee could be more certain about the cost effectiveness of roflumilast.
- 4.19 The Committee discussed the proposed positioning by the manufacturer of roflumilast as an add-on to triple therapy. The Committee noted the lack of trial evidence for this position. The Committee discussed the probability that roflumilast was cost effective when used in addition to triple therapy as in the manufacturer's model. It noted that in the manufacturer's submission, at a threshold of £20,000 per QALY gained, there was a 55% probability that roflumilast would be cost effective. It considered that many assumptions had to be accepted, in both the derivation of the clinical effect of roflumilast and in the modelling, in order to accept the manufacturer's estimate of cost effectiveness. The Committee concluded that there was much uncertainty about whether roflumilast was a cost-effective use of NHS resources and that, to produce a recommendation for the licensed population, it would need more robust evidence about the benefits of roflumilast as an add-on to LAMA plus LABA/ICS or LAMA plus LABA for people who are intolerant to ICS.

- 4.20 The Committee discussed the feasibility of setting up a trial to assess the clinical effectiveness of roflumilast as an add-on to triple therapy or dual therapy. The Committee considered a number of aspects including: trial duration, sample size needed, alternative study design and presence of other trials already underway. The Committee considered the likely duration of a clinical trial to assess the clinical effectiveness of roflumilast as an add-on to triple therapy or dual therapy. The Committee heard from the clinical specialists that a 12month trial would provide useful results, bearing in mind potential problems with participant dropout. The Committee noted comments from the manufacturer that the likely time frame from design to completion would be at least 4 years for a trial of 12 months' duration. The Committee noted that in other disease areas, for example in cardiology, trials with a much larger sample size are conducted in a shorter time frame and that a 4year time frame could be an overestimate. The Committee concluded that it would be feasible to set up a trial to assess the clinical effectiveness of roflumilast as an add-on to triple therapy or dual therapy, and that the value of obtaining further information on the treatment effect was such that a trial was necessary.
- 4.21 The Committee considered the sample size needed for a clinical trial to assess the clinical effectiveness of roflumilast as an add-on to triple therapy or dual therapy. The Committee noted comments received in consultation from the manufacturer that the expected sample size for such a trial would be between 2500 and 4500 people, accounting for attrition. The Committee was aware of the sample sizes in the six roflumilast trials reported in the manufacturer's submission, which were between 743 and 1568 patients per trial and noted that these numbers were significantly lower than the estimates provided by the manufacturer. The Committee noted that the potential population eligible for treatment with roflumilast in the UK is large, and the clinical specialist reported that recruiting participants to a trial comparing roflumilast as an add-on to triple therapy with triple therapy alone would be relatively straightforward. The Committee concluded that the sample size needed for obtaining reliable information on roflumilast compared with triple therapy was not unreasonably large and was likely to be achievable.

- 4.22 The Committee discussed one consultee's comments that an observational study of roflumilast in combination with triple therapy could allow data to be accumulated more quickly. The Committee noted a comment from a clinical specialist that one difficulty with such a trial design is that it would be impossible to know what would have happened to a person's health if they were not on roflumilast. Therefore, only a properly designed randomised controlled trial would provide robust evidence on the effectiveness of roflumilast in combination with other agents. The Committee concluded that a randomised controlled trial was a more preferable study design than an observational study for generating the evidence needed.
- 4.23 The Committee noted that the manufacturer is conducting a study (REACT) to assess the effect of roflumilast on exacerbation rates when added to LABA/ICS. The trial is being undertaken because the European Medicines Agency's Committee for Medicinal Products for Human Use (CHMP) found in its assessment of the evidence that the current first-line treatment (LABA/ICS) was not used in the trials, either as concomitant medication or as a comparator. At the CHMP's request, the manufacturer committed to conduct a controlled study to evaluate the use of roflumilast as an add-on therapy to LABA and ICS in the population defined in the indication of the current summary of product characteristics. The CHMP requested that the design of the study should be appropriate to demonstrate a clinically relevant effect of roflumilast as add-on therapy. The Committee noted that it may be possible to gain information on the effectiveness of roflumilast as an add-on to triple therapy if patients on this treatment combination were included in the trial. In addition, from the evidence generated from this trial, it should be possible to generate robust cost-effectiveness estimates of roflumilast in combination with LABA/ICS. The Committee agreed with the European Medicines Agency that additional evidence of the efficacy of roflumilast in combinations not previously studied is necessary.

4.24 The Committee considered the feasibility of a trial comparing roflumilast with theophylline. 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 Committee also noted that theophylline is used in only about 5% of people with severe or very severe COPD. The Committee concluded that theophylline is an appropriate comparator for a subgroup of people in this patient population, and although the generation of trial data to show evidence of a treatment of roflumilast compared with theophylline would be desirable, the Committee accepted that such a trial would be challenging to conduct. As such the Committee accepted that a recommendation for a comparison with theophylline would not meet the criteria outlined in 4.17.

4.25 The Committee considered whether the broad balance of the benefits and costs of conducting the research are favourable. The Committee discussed the costs of conducting further research. It recognised that there would be costs to the manufacturer in setting up a trial to assess the benefits of roflumilast as an add-on to LAMA plus LABA/ICS or LAMA plus LABA for those people who are intolerant to ICS. It appreciated that roflumilast would not be routinely recommended for patients outside a trial for several years and that during that time there was a chance that exacerbations could occur that might otherwise have been avoided, with consequent effects on health-related quality of life and a risk of mortality. The Committee also considered the additional costs to the NHS as a result of exacerbations, which could have otherwise been avoided. The Committee agreed that because no clinical trial data were presented on the effectiveness of roflumilast in the place in the treatment pathway in which the manufacturer positioned roflumilast, it was not possible to know the size of the treatment effect in this position. It was therefore not possible to know whether roflumilast represented a cost-effective use of NHS resources. The Committee considered the potential number of people with COPD who would be eligible to receive roflumilast. The Committee noted that in England and Wales approximately one million people have COPD. It also noted the manufacturer's expectation that almost 200,000 would be eligible for treatment with roflumilast by 2015, and the revised estimate of 88,000 in the manufacturer's response to consultation. The Committee also noted that people were likely to be treated with roflumilast on a long-term or lifetime basis. Therefore, if roflumilast was recommended despite the uncertainty about its clinical and cost effectiveness and then found not to be cost effective, the opportunity cost to the NHS would be substantial (that is, the loss of potential gain from other treatments or services that are displaced if this one treatment is chosen, given the fixed NHS budget). The Committee reflected on the complexity of, and time involved in, setting up a trial to assess the size of the treatment effect of roflumilast on the rate of exacerbations when added to triple therapy. On balance the Committee concluded that the benefits and costs of conducting the research would be favourable to the NHS.

4.26 The Committee therefore agreed that the conditions for allowing a recommendation of 'only in the context of research' had been met. It concluded that roflumilast should be recommended only in the context of research as part of a clinical trial for adults with severe COPD (FEV₁ post-bronchodilator less than 50% predicted) associated with chronic bronchitis with a history of frequent exacerbations as an add-on to bronchodilator treatment. The Committee requested that the research should be designed to generate robust evidence about the benefits of roflumilast as an add-on to LAMA plus LABA/ICS or LAMA plus LABA for those people who are intolerant to ICS.

Summary of Appraisal Committee's key conclusions

TA244	Appraisal title: Roflumilast for the management of chronic obstructive pulmonary disease	Section
Key conclusion		

<p>Roflumilast is recommended only in the context of research as part of a clinical trial for adults with severe COPD (for the purposes of this guidance defined as FEV₁ post-bronchodilator less than 50% predicted) associated with chronic bronchitis with a history of frequent exacerbations as an add-on to bronchodilator treatment.</p>		<p>1.1</p>
<p>The Committee concluded that although roflumilast could be postulated to have an additive effect, there was considerable doubt about whether its effect as demonstrated as monotherapy, and in combination with LABA alone and LAMA alone would be the same when combined with LABA/ICS plus LAMA. The Committee noted that only direct trial evidence could show this.</p>		<p>4.12</p>
<p>The Committee considered that because of the lack of relevant data there was much uncertainty around the manufacturer's ICERs. In addition, many assumptions had to be accepted, in both the derivation of the clinical effect of roflumilast and in the modelling, in order to accept these ICERs. The Committee concluded that these ICERs were highly uncertain and it was not satisfied that they accurately represent the cost effectiveness of treatment with roflumilast in addition to triple therapy.</p>		<p>4.16</p>
<p>The Committee agreed that the conditions for allowing a recommendation of 'only in the context of research' had been met. It concluded that the research should be designed to generate robust evidence about the benefits of roflumilast as an add-on to LAMA plus LABA/ICS or LAMA plus LABA for those people who are intolerant to ICS.</p>		<p>4.26</p>
<p>Current practice</p>		
<p>Clinical need of patients, including the availability of alternative treatments</p>	<p>For people with COPD a severe exacerbation, particularly one that means the person has to be admitted to hospital, has a major impact on quality of life. In addition, severe exacerbations have an associated mortality risk. For people who have severe disease, who are already on many treatments for COPD, there are few other treatment options if they have a severe exacerbation needing admission to hospital, other than oxygen and antibiotics. A moderate exacerbation may also be very debilitating and can limit the ability to carry out everyday activities such as shaving or leaving the house. An exacerbation may also make the person feel depressed and it can take 10 to 14 days to recover.</p>	<p>4.3</p>

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?	In some of the trials there was a statistically significant reduction in exacerbation rate with roflumilast. A small and statistically significant improvement in lung function in the trials was also reported, although this effect was not considered to be clinically significant by the clinical specialists.	4.7
What is the position of the treatment in the pathway of care for the condition?	Some people already on triple therapy were likely to benefit from further treatment and for these people it may be reasonable to add roflumilast to triple therapy of LAMA plus LABA/ICS.	4.4
Adverse effects	Adverse events were likely to be an important factor in the high rate of withdrawals (approximately 30%) from the clinical trials with roflumilast. Roflumilast can cause weight loss and is associated with an increased risk of psychiatric disorders (including depression and suicide) and insomnia.	4.9
Evidence for clinical effectiveness		
Availability, nature and quality of evidence	The evidence in the manufacturer's submission came from six trials in which roflumilast was compared with placebo. The Committee concluded that roflumilast was most likely to be used in addition to triple therapy, but there was no direct clinical trial evidence related to roflumilast in this position.	4.4

Relevance to general clinical practice in the NHS	Theophylline can be used in people with severe COPD and so the Committee thought that theophylline is an appropriate comparator for a subgroup of people in this patient population. No data were available comparing roflumilast with theophylline.	4.5
Uncertainties generated by the evidence	There was uncertainty about how many exacerbations people in the trials had experienced and whether, as a whole, the body of evidence accurately represented the patient population of interest. Although roflumilast could be postulated to have an additive effect, there was considerable doubt about whether its effect as demonstrated as monotherapy, and in combination with LABA alone and LAMA alone would be the same when combined with LABA/ICS plus LAMA. The Committee noted that only direct trial evidence could show this.	4.6 4.12
Are there any clinically relevant subgroups for which there is evidence of differential effectiveness?	The Committee accepted that treatment response in people with moderate disease was likely to be similar to that for severe disease, but that a trial in the same population as defined in the marketing authorisation would provide robust evidence for the population for whom roflumilast is licensed.	4.10
Estimate of the size of the clinical effectiveness including strength of supporting evidence	There was evidence from the trials that treatment with roflumilast reduced exacerbations. The trials also showed a small, although not clinically significant, improvement in lung function. No meaningful effect of roflumilast on health-related quality of life was demonstrated in the trial populations.	4.7 4.8
Evidence for cost effectiveness		

<p>Availability and nature of evidence</p>	<p>The manufacturer submitted an economic model on the cost effectiveness of roflumilast for the treatment of adults with severe COPD associated with chronic bronchitis with a history of frequent exacerbations as an add-on to bronchodilator treatment. In the base case model people have first-line treatment lasting 1 year followed by second-line treatment for their remaining lifetime (up to 29 years).</p>	<p>4.14</p>
<p>Uncertainties around and plausibility of assumptions and inputs in the economic model</p>	<p>The scenario in which treatment with roflumilast continued for the lifetime of the person with COPD was more likely to reflect clinical practice than the base case, in which people stopped treatment with roflumilast after a year and then remained on triple therapy alone.</p>	<p>4.14</p>
<p>Incorporation of health-related quality-of-life benefits and utility values</p> <p>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?</p>	<p>Adverse events were likely to be an important contributor to the high withdrawal rate in the roflumilast trials, and because the effect of adverse events was not modelled, the associated costs and disutilities of adverse events would not be captured in the model's outcomes.</p>	<p>4.15</p>

Are there specific groups of people for whom the technology is particularly cost effective?	No specific groups were identified in which roflumilast was particularly cost effective.	
What are the key drivers of cost effectiveness?	The model was driven by the effect of treatment on reducing exacerbations and the corresponding disutility and associated cost, and the resultant effect on exacerbation-related mortality.	4.14
Most likely cost-effectiveness estimate (given as an ICER)	Because of the lack of relevant data, there was much uncertainty around the manufacturer's ICERs. In addition, many assumptions had to be accepted in both the derivation of the clinical effect of roflumilast and in the modelling, in order to accept these ICERs. The Committee concluded that these ICERs were highly uncertain and it was not satisfied that they accurately represent the cost effectiveness of treatment with roflumilast in addition to triple therapy.	4.16
Additional factors taken into account		
Patient access schemes (PPRS)	No patient access scheme was submitted.	
End-of-life considerations	End-of-life considerations were not discussed.	
Equalities considerations and social value judgements	There were no relevant equalities issues.	

5 Implementation

- 5.1 The Secretary of State and the Welsh Minister for Health and Social Services have issued directions to the NHS in England and Wales on implementing NICE technology appraisal guidance. When a NICE technology appraisal recommends use of a drug or treatment, or other technology, the NHS must usually provide funding and resources for it within 3 months of the guidance being published. If the Department of Health issues a variation to the 3month funding direction, details will be available on the NICE website. When there is no NICE technology appraisal guidance on a drug, treatment or other technology, decisions on funding should be made locally.
- 5.2 NICE has developed a tool to help organisations put this guidance into practice (listed below). This is available on our [website](#).
- A costing statement explaining the resource impact of this guidance.

6 Recommendations for further research

- 6.1 Nycomed is conducting a 52-week, randomised, double-blind study (REACT) to assess the effect of roflumilast on exacerbation rates when added to LABA/ICS.
- 6.2 The Committee recommends that a study is conducted to generate robust evidence about the benefits of roflumilast as an add-on to LAMA plus LABA/ICS or LAMA plus LABA for those people who are intolerant to ICS.
- 6.3 Ideally roflumilast should be compared with theophylline in those people for whom theophylline would be suitable.

7 Related NICE guidance

[Chronic obstructive pulmonary disease: management of chronic obstructive pulmonary disease in adults in primary and secondary care \(partial update\)](#). NICE clinical guideline 101 (2010).

8 Review of guidance

- 8.1 The guidance on this technology will be considered for review once the relevant trial data are available.

Andrew Dillon
Chief Executive
January 2012

Appendix A: Appraisal Committee members, guideline representatives and NICE project team

A Appraisal Committee members

The Appraisal Committees are standing advisory committees of NICE. Members are appointed for a 3-year term. A list of the Committee members who took part in the discussions for this appraisal appears below. There are four Appraisal Committees, each with a chair and vice chair. Each Appraisal Committee meets once a month, except in December when there are no meetings. Each Committee considers its own list of technologies, and ongoing topics are not moved between Committees.

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.

Dr Jane Adam (Chair)

Department of Diagnostic Radiology, St George's Hospital

Professor Iain Squire (Vice-Chair)

Consultant Physician, University Hospitals of Leicester

Professor A E Ades

Professor of Public Health Science, Department of Community Based Medicine, University of Bristol

Dr Jeremy Braybrooke

Consultant Medical Oncologist, University Hospitals Bristol NHS Foundation Trust

Dr Fiona Duncan

Clinical Nurse Specialist, Anaesthetic Department, Blackpool Victoria Hospital, Blackpool

Mr Christopher Earl

Surgical Care Practitioner, Renal Transplant Unit, Manchester Royal Infirmary

Mr Adrian Griffin

Vice President, HTA & International Policy, Johnson & Johnson

Professor Jonathan Grigg

Professor of Paediatric Respiratory and Environmental Medicine, Barts and the London School of Medicine and Dentistry, Queen Mary University London

Dr Peter Heywood

Consultant Neurologist, Frenchay Hospital

Dr Sharon Saint Lamont

Head of Quality and Innovation, North East Strategic Health Authority

Dr Ian Lewin

Consultant Endocrinologist, North Devon District Hospital

Dr Louise Longworth

Reader in Health Economics, HERG, Brunel University

Dr Anne McCune

Consultant Hepatologist, University Hospitals Bristol NHS Foundation Trust

Dr David Newsham

Lecturer (Orthoptics), University of Liverpool

Ms Pamela Rees

Lay Member

Dr Ann Richardson

Lay Member

Mr Stephen Sharp

Senior Statistician, MRC Epidemiology Unit

Dr Eldon Spackman

Research Fellow, Centre for Health Economics, University of York

Mr Mike Spencer

Assistant Director Patient Experience, Cardiff and Vale University Health Board

Mr David Thomson

Lay Member

Dr John Watkins

Clinical Senior Lecturer / Consultant in Public Health Medicine, Cardiff University and National Public Health Service Wales

Mr William Turner

Consultant Urologist, Addenbrooke's Hospital

Dr Anthony S Wierzbicki

Consultant in Metabolic Medicine/Chemical Pathology, Guy's and St Thomas' Hospitals NHS Trust

Dr Olivia Wu

Reader in Health Economics, University of Glasgow

B NICE project team

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

Dr Helen Starkie

Technical Lead

Joanna Richardson

Technical Adviser

Bijal Joshi
Project Manager

Appendix B: Sources of evidence considered by the Committee

The Evidence Review Group (ERG) report for this appraisal was prepared by Kleijnen Systematic Reviews.

- Riemsma R, Lhachimi SK, Armstrong N et al. Roflumilast for the management of severe chronic obstructive pulmonary disease: a Single Technology Appraisal. York: Kleijnen Systematic Reviews Ltd (2011)

The following organisations accepted the invitation to participate in this appraisal as consultees and commentators. They were invited to comment on the draft scope, the ERG report and the appraisal consultation document (ACD). Organisations listed in I were also invited to make written submissions. Organisations listed in II and III had the opportunity to give their expert views. Organisations listed in I, II and III also have the opportunity to appeal against the final appraisal determination.

I Manufacturer/sponsor:

- Merck Sharp & Dohme

II Professional/specialist and patient/carer groups:

- British Thoracic Society
- Primary Care Respiratory Society UK
- Royal College of Nursing
- Royal College of Physicians

III Other consultees:

- Department of Health
- Welsh Government

IV Commentator organisations (did not provide written evidence and without the right of appeal):

-
- AstraZeneca
 - Boehringer Ingelheim
 - Chiesi Ltd
 - Commissioning Support Appraisals Service
 - Department of Health, Social Services and Public Safety for Northern Ireland
 - GlaxoSmithKline
 - Health Care Improvement Scotland
 - Kleijnen Systematic Reviews Ltd
 - Medicines and Healthcare products Regulatory Agency
 - National Institute for Health Research Health Technology Assessment Programme

A The following individuals were selected from clinical specialist and patient expert nominations from the non-manufacturer/sponsor consultees and commentators. They gave their expert personal view on roflumilast by attending the initial Committee discussion and providing written evidence to the Committee. They were also invited to comment on the ACD.

- Dr Craig Davidson, Consultant Physician, nominated by organisation representing British Thoracic Society – clinical specialist
- Dr David Halpin, Consultant Physician, nominated by organisation representing British Thoracic Society – clinical specialist
- Dr Nicholas Hopkinson, Senior Lecturer and Honorary Consultant Chest Physician, nominated by organisation representing British Thoracic Society – clinical specialist
- Mr John Price, nominated by organisation representing Breathe Easy Group (British Lung Foundation) – patient expert

Representatives from the following manufacturer/sponsor attended Committee meetings. They contributed only when asked by the Committee chair to clarify specific issues and comment on factual accuracy.

- Merck Sharp & Dohme

About this guidance

NICE technology appraisal guidance is about the use of new and existing medicines and treatments in the NHS in England and Wales.

This guidance was developed using the NICE [single technology appraisal](#) process.

We have produced a [summary of this guidance for patients and carers](#). Tools to help you put the guidance into practice and information about the evidence it is based on are also [available](#).

Your responsibility

This guidance represents the views of NICE and was arrived at after careful consideration of the evidence available. Healthcare professionals are expected to take it fully into account when exercising their clinical judgement. However, the guidance does not override the individual responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.

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