# Roflumilast (Daxas): a novel approach to treating COPD

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## KEY POINTS


- Roflumilast (Daxas) is a PDE-4 inhibitor indicated for the maintenance treatment of severe COPD ($FEV_1$ postbronchodilator less than 50 per cent predicted) associated with chronic bronchitis in adult patients with a history of frequent exacerbations as an add-on to bronchodilator treatment
- available as 500µg tablets taken once daily; 30 tablets £37.71, 90 tablets £113.14
- in trials of patients with severe airflow limitation, bronchitic symptoms and a history of exacerbations and who were also taking bronchodilators, but not inhaled corticosteroids, once-daily roflumilast improved lung function and reduced moderate or severe exacerbations compared with placebo
- common adverse effects include diarrhoea, nausea, headache, insomnia, weight loss and decreased appetite
- roflumilast may have a role in the management of patients with COPD and bronchitic symptoms already on guideline-recommended treatment

**Roflumilast (Daxas) is the first in a new class of treatment for COPD that targets the underlying inflammation. In our New products review, Dr Iain Small presents the clinical trial evidence for its efficacy and side-effects and discusses its place in COPD management.**

The practice list of an average general practice in the UK is likely to include about 200 people with COPD.[1] Many of these cases will be undiagnosed. Of the three million people estimated to have COPD in the UK, only about 900 000 have been diagnosed;[1] most of the undiagnosed cases are likely to have relatively mild disease. Patients with COPD will make about 1.4 million consultations with their GP each year and account for 130 000 emergency admissions to hospital, making COPD the second largest cause of emergency admissions in the UK.[1]

COPD is defined as a progressive airflow obstruction that is not fully reversible and that does not change markedly over several months. The damage is the result of chronic inflammation that differs from that seen in asthma and which is usually caused by smoking.

COPD is an umbrella term that includes patients suffering from different phenotypes of progressive destructive lung disease, such as those with predominantly airway damage (chronic bronchitis) and those with more peripheral/alveolar destruction (emphysema). Airflow obstruction is defined as a postbronchodilator $FEV_1$/FVC ratio of less than 0.7.

Much of COPD management can be provided in primary care by a multidisciplinary team comprising respiratory nurse specialists, physiotherapists, GPs, health visitors and practice nurses. Effective management involves pharmacological and nonpharmacological treatments.[2]

Regarding drug treatment of COPD, short-acting bronchodilators and short-acting muscarinic antagonists (SAMAs) are recommended for initial COPD therapy.[2]

For moderate and severe disease, long-acting $beta_2$-agonists (LABAs) or long-acting muscarinic antagonists (LAMAs) are advised, with additional treatments such as theophylline and inhaled corticosteroids added if symptoms persist or if a patient has exacerbations in spite of maintenance therapy.[2]

The National Institute for Health and Clinical Excellence (NICE) is currently appraising

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CPD questions available for this article.
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roflumilast and is expected to publish guidance in January 2012. The key recommendations of its clinical guideline on the management of COPD (updated June 2010) are:

In people with stable COPD who remain breathless or who have exacerbations despite use of short-acting bronchodilators as required, the following should be offered as maintenance therapy:

– if $FEV_1$ ≥50 per cent predicted either a LABA or LAMA

– if $FEV_1$ ≤50 per cent predicted give either a LABA with an inhaled corticosteroid (ICS) in a combination inhaler or give a LAMA

– offer a LAMA in addition to LABA + ICS to people with COPD who remain breathless or have exacerbations despite taking LABA + ICS irrespective of their $FEV_1$.

The novel anti-inflammatory oral drug roflumilast (Daxas) was approved by the European Medicines Agency for use in patients with severe COPD in July 2010.[3] The drug is indicated for maintenance treatment of severe COPD associated with symptoms of chronic bronchitis in patients at risk of exacerbations as an add-on therapy to bronchodilator treatment.

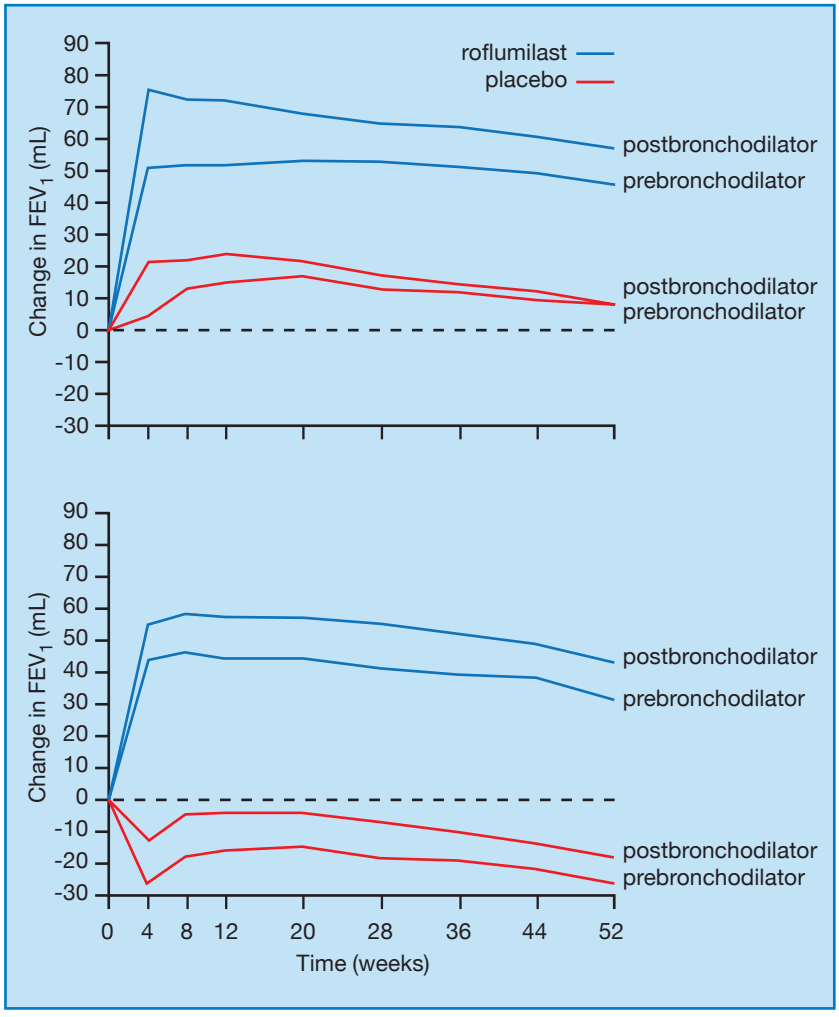


**Figure 1.** Changes in pre- and postbronchodilator $FEV_1$ in the two 12-month pivotal trials comparing roflumilast and placebo, giving a pooled difference in prebronchodilator $FEV_1$ (a primary end-point) of 48ml (roflumilast 40ml *vs* placebo -9ml); after reference 5

## A new class of COPD treatment

Although the drugs used to treat COPD are effective, the size of the benefit from each therapeutic agent is small and no drug has been shown conclusively to reduce the accelerated decline in lung function seen in COPD patients. New treatments for COPD are thus of great interest to respiratory physicians and their patients.

Roflumilast is a phosphodiesterase-4 (PDE-4) inhibitor. Phosphodiesterases are a superfamily of enzymes that inactivate the intracellular second messengers cyclic adenosine monophosphate (cAMP) and cyclic guanosine monophosphate (cGMP). There are 11 enzymes in this family that are distributed at different sites in the body and have specific substrates.[4]

PDE-4 is the main cAMP metabolising enzyme in airway smooth muscle cells, immune and inflammatory cells and pulmonary nerves. The PDE-4 inhibitor roflumilast exhibits an anti-inflammatory effect by inhibiting the production of inflammatory mediators including leukotrienes, reactive oxygen species, TNF-alpha and interferon-gamma.

Roflumilast is the first new class of treatment for COPD in over a decade and represents a new approach to targeting the inflammatory processes in COPD.

## Clinical trials

Two placebo-controlled, double-blind, one-year trials provide the pivotal data for roflumilast; these have been reported in a pooled analysis.[5] Two six-month trials have evaluated roflumilast in patients also using an inhaled LABA or LAMA.[6]

In the pivotal trials,[5] 3091 patients with severe or very severe

COPD (postbronchodilator: mean $FEV_1$/FVC 42 per cent, mean $FEV_1$ 36 per cent predicted) and chronic bronchitis, and at least one recorded COPD exacerbation requiring systemic steroids and/or treatment in hospital in the previous year, were randomised to treatment with roflumilast 500µg per day or placebo. Almost all were also using a short-acting $beta_2$-agonist (SABA) and about one-third were using a SAMA; half were using a LABA. Inhaled steroids and a LAMA were not permitted.

The primary end-points were the change in prebronchodilator $FEV_1$ and the rate of COPD exacerbations (defined as moderate if they required oral or parenteral corticosteroids or severe if associated with admission or death).

Approximately one-third of patients in each group withdrew from the study, mainly due to adverse events (roflumilast 16 per cent *vs* placebo 10 per cent) and exacerbations (5.6 *vs* 9.1 per cent).

Compared with placebo, roflumilast significantly increased prebronchodilator $FEV_1$ (+40 *vs* -9ml; $p<0.0001$, see Figure 1). The mean rate of moderate or severe exacerbations per year was 1.14 with roflumilast and 1.37 with placebo (rate ratio 0.83, CI 95% 0.75–0.92). The number of patients needed to treat with roflumilast to prevent one moderate or severe exacerbation per year was 5.3 in one study and 3.6 in the other, irrespective of concurrent treatment with a LABA.

Roflumilast also significantly prolonged the median time to the first or second exacerbations (by 9–80 days and 29–177 days respectively). In patients taking roflumilast, fewer exacerbations required treatment with antibiotics and/or systemic steroids. Small improvements in breathlessness with roflumilast were not clinically important and there was no difference in quality-of-life scores or mortality.

In the six-month trials, patients with moderate to severe COPD (postbronchodilator: mean $FEV_1$/FVC 50–53 per cent, mean $FEV_1$ 55–56 per cent predicted) were ran-

domised to receive roflumilast 500µg per day or placebo, plus salmeterol (n=933) or tiotropium (n=743).[6] Patients in the tiotropium trial were more symptomatic because the recruitment criteria included chronic bronchitis. SABAs, but no other drugs, were permitted. The primary end-point in both studies was change in mean prebronchodilator $FEV_1$.

Twenty-three per cent of patients taking roflumilast and 18 per cent assigned to placebo withdrew from the study due to adverse events (roflumilast 17 per cent *vs* placebo 10 per cent) and exacerbation (3.4 *vs* 5.8 per cent).

Roflumilast significantly increased $FEV_1$ compared with placebo in patients taking salmeterol (+39 *vs* -10ml; $p<0.0001$) or tiotropium (+65 *vs* -16 ml; $p<0.0001$). It reduced mild but not moderate or severe exacerbations but few such events were recorded. In patients taking tiotropium, there was a small improvement in breathlessness and a reduction in the use of rescue SABA (mean 0.5 puffs per day).

*Adverse effects*

In an analysis of data pooled from all clinical trials (>5766 patients exposed to treatment), roflumilast was associated with a higher frequency than placebo of diarrhoea (10.1 *vs* 2.6 per cent), nausea (5.2 *vs* 1.4 per cent), weight loss (6.8 *vs* 1.8 per cent), decreased appetite (2.2 *vs* 0.4 per cent), nervous system disorders (10.7 *vs* 5.5 per cent) and insomnia (2.6 *vs* 0.9 per cent).[7]

Three cases of suicide occurred during treatment with roflumilast (none with placebo).[7] Patients should inform their physician of changes in behaviour or mood and of any suicidal ideation. Roflumilast is not recommended in patients with a history of depression associated with suicidal ideation or behaviour.

Patients should be given a card when prescribed roflumilast.[8] This advises them to tell their doctor if they have a history of cancer, CNS disorders (insomnia, anxiety, depression, suicidal ideation or

behaviour), multiple sclerosis or systemic lupus erythematosus or serious infection (tuberculosis, herpes, hepatitis, HIV). They are advised to inform their doctor if they develop insomnia, anxiety, depression or suicidal ideation or behaviour. Patients should weigh themselves regularly and record this on the card, which they should bring to consultations.

### Implications for practice

The results of these well-controlled studies suggest that roflumilast is beneficial as assessed by improvements in lung function, even when added to long-acting bronchodilators. There was a reduction in the combined endpoint of moderate to severe COPD exacerbations in the pivotal 12-month (versus placebo) studies, although studies powered to monitor severe exacerbations would need to be carried out to demonstrate whether this effect is universal for all patient groups and degrees of exacerbation.

The shorter six-month studies of adding roflumilast to long-acting agents were too small and too short to provide useful information on exacerbations. Moreover, these studies did not provide any evidence of the effect on exacerbations in patients on ICS.

One key feature that can be taken away from these data is that the number needed to treat to prevent one moderate to severe COPD exacerbation per year is three to five patients, which is a modest number to gain clinical benefit.

**Roflumilast resources**

The following materials designed to support prescribers are available from MSD at www.daxaseducationalmaterials.co.uk:

- educational material for prescribers
- Summary of Product Characteristics (SmPC)
- Patient Information Leaflet (PIL)
- copies of a patient card to be given to patients before they receive roflumilast

The patient cards are intended to prompt for certain potential adverse events; patients should be given a patient card before they receive roflumilast.

Another key implication of the trials is that benefit should be considered as applicable only to the subset of patients recruited in the trials.

Moreover, these studies did not give us any information about the efficacy of roflumilast when added to ICS/long-acting bronchodilator combinations bearing in mind that roflumilast is thought to act mainly as an anti-inflammatory agent, so whether its benefit in reducing COPD exacerbations persists in the presence of ICS in these patients has yet to be shown.

A *post-hoc* analysis[9] of a trial involving patients with a lower risk of exacerbations than those in the pivotal trials found that roflumilast significantly reduced moderate to severe exacerbations by 30.2 per cent in the subgroup of patients with chronic bronchitis using ICS ($p$=0.01), whereas in those not using an ICS the reduction was 15.5 per cent ($p$=0.55).

Interestingly, the most frequent side-effects of roflumilast were diarrhoea, nausea and weight loss, but these were not the main reasons why patients discontinued treatment. It goes without saying that these side-effects still need to be borne in mind when considering the risk:benefit ratio for an individual patient.

The precise place of roflumilast in the treatment of patients with COPD is therefore uncertain. The four studies reviewed provide insufficient evidence to justify its use ahead of or instead of ICS for those people who remain symptomatic or suffer exacerbations on optimal bronchodilator therapy (LABAs and/or tiotropium).

However, they do provide good evidence that, in the subgroup of COPD patients with chronic bronchitis, adding roflumilast to standard guideline treatment, in accordance with its licence, will improve lung function and reduce the risk of exacerbations. Another treatment option in patients with COPD is welcome.

### References

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## Forum

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# CPD: Roflumilast

Answer these questions online at Prescriber.co.uk and receive a certificate of completion for your CPD portfolio. Utilise the Learning into Practice form to record how your learning has contributed to your professional development.

Learning Central

**1. One of these statements about COPD and its management is false – which one?**
a. COPD is defined as a progressive airflow obstruction that is not fully reversible and that does not change markedly over several months
b. Patients with COPD account for 130 000 emergency admissions to hospital annually, making COPD the second largest cause of emergency admissions in the UK
c. Airflow obstruction is defined as a postbronchodilator $FEV_1$/FVC ratio of less than 0.5
d. Airways damage in people with COPD is the result of chronic inflammation

**2. Which one of these statements about NICE guidance on the management of COPD (in people with stable COPD who remain breathless or who have exacerbations despite use of as-required short-acting bronchodilators) is false?**
a. An inhaled corticosteroid (ICS) should be offered to all patients to reduce exacerbations
b. If $FEV_1$ ≤50 per cent predicted give either a long-acting beta-agonist (LABA) with an ICS in a combination inhaler or give a long-acting muscarinic antagonist (LAMA)
c. Offer a LAMA in addition to LABA + ICS to people with COPD who remain breathless or have exacerbations despite taking LABA + ICS irrespective of their $FEV_1$
d. If $FEV_1$ ≥50 per cent predicted, give either a LABA or LAMA

**3. Which one of these statements about the mechanism of action of roflumilast is false?**
a. Phosphodiesterases inactivate the intracellular second messengers cyclic adenosine monophosphate (cAMP) and cyclic guanosine monophosphate (cGMP)
b. PDE-4, one of 11 phosphodiesterases in the body, is the main cAMP-metabolising enzyme in airway smooth muscle cells, immune and inflammatory cells and pulmonary nerves
c. Roflumilast inhibits the production of inflammatory mediators including leukotrienes and reactive oxygen species
d. Roflumilast does not inhibit the production of TNF-alpha and interferon-gamma

**4. Regarding the pivotal clinical trials of roflumilast, which one of these statements is false?**
a. Roflumilast significantly reduced mortality compared with placebo
b. Roflumilast significantly increased $FEV_1$ compared with placebo
c. Patients in the trials had severe to very severe COPD
d. The number of patients needed to treat with roflumilast to prevent one moderate or severe exacerbation per year was approximately three to five, irrespective of concurrent treatment with a LABA

**5. One of these statements about the two six-month trials of roflumilast is false – which one?**
a. Roflumilast significantly increased $FEV_1$ compared with placebo in patients taking salmeterol or tiotropium
b. Few moderate or severe exacerbations were recorded
c. Roflumilast did not alter the frequency of use of rescue medication
d. Patients in the tiotropium trial were more symptomatic because the recruitment criteria included chronic bronchitis

**6. Which one of these statements about the adverse effects of roflumilast in clinical trials is false?**
a. The frequency of diarrhoea in patients taking roflumilast was about 10 per cent
b. Roflumilast was associated with increased appetite
c. Patients prescribed roflumilast should be given a card in which they should record their weight
d. Roflumilast is not recommended in patients with a history of depression associated with suicidal ideation or behaviour

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