

roflumilast 500 microgram tablets (Daxas®)

SMC No. (635/10)

Nycomed Ltd

06 August 2010 (*Issued 10 September 2010*)

The Scottish Medicines Consortium (SMC) has completed its assessment of the above product and advises NHS Boards and Area Drug and Therapeutic Committees (ADTCs) on its use in NHS Scotland. The advice is summarised as follows:

ADVICE: following a full submission

roflumilast (Daxas®) is not recommended for use within NHS Scotland.

Indication under review: maintenance treatment of severe chronic obstructive pulmonary disease (COPD) (forced expiratory volume in 1 second [FEV₁] post-bronchodilator <50% predicted) associated with chronic bronchitis in adult patients with a history of frequent exacerbations as add on to bronchodilator treatment.

Roflumilast has been associated with improved lung function and reduced the rate of moderate and severe COPD exacerbations compared to placebo in studies of patients representing the licensed population.

The manufacturer did not present a sufficiently robust economic analysis to gain acceptance by SMC.

Overleaf is the detailed advice on this product.

**Chairman,
Scottish Medicines Consortium**

Indication

For maintenance treatment of severe chronic obstructive pulmonary disease (COPD) (forced expiratory volume in 1 second [FEV₁] post-bronchodilator <50% predicted) associated with chronic bronchitis in adult patients with a history of frequent exacerbations as add on to bronchodilator treatment.

Dosing Information

Roflumilast 500 microgram tablet once daily

Product availability date

9 September 2010

Summary of evidence on comparative efficacy

Chronic obstructive pulmonary disease (COPD) is characterised by airflow obstruction that is usually progressive, not fully reversible and does not change markedly over several months. Roflumilast is an oral selective phosphodiesterase 4 (PDE4) inhibitor which has anti-inflammatory activity designed to target both the systemic and pulmonary inflammation associated with COPD.

The efficacy to support the use of roflumilast within its licensed indication comes from the results of two identically designed, double-blind, multi-centre studies. Eligible patients were ≥ 40 years of age with post-bronchodilator FEV₁ $\leq 50\%$ of predicted with a clinical diagnosis of COPD (confirmed with a post-bronchodilator FEV₁ /forced vital capacity [FVC] ratio $\leq 70\%$), former or current smokers (≥ 20 pack-year history) with chronic cough and sputum production and \geq one moderate (requiring systemic corticosteroids) or severe (requiring hospital treatment) COPD exacerbation in the previous year. Both studies included a 4-week (single-blinded to patients only) run-in period when all patients received placebo once daily. Patients recorded short-acting bronchodilator use and production of cough and sputum in daily diary cards and those with a total cough and sputum score of >14 during the week before randomisation, a negative faecal occult blood test, $\geq 80\%$ compliance with placebo tablets and who were clinically stable were randomised to roflumilast 500 micrograms or placebo once daily for 52 weeks. Randomisation was stratified according to use of long-acting $\beta 2$ -agonists (LABA) and smoking status. Patients were allowed to continue to use short-acting $\beta 2$ -agonists as needed or short-acting anticholinergics or LABA at stable doses. However patients were not allowed to use long-acting anticholinergics, theophylline or inhaled corticosteroids during the study period. Patients were assessed every 4 weeks up to 12 weeks then every 8 weeks thereafter.

The two primary outcomes were the mean change in pre-bronchodilator FEV₁ from baseline to each post-randomisation visit during the treatment period and the mean rate of moderate (requiring systemic corticosteroids) or severe (requiring hospitalisation or leading to death) COPD exacerbation per patient per year.

Primary outcome data were presented for the pooled study population (n=3,091) with key details included in the table below. There was a significantly greater increase in pre-bronchodilator FEV₁ from baseline in the roflumilast group than the placebo group (difference

48ml (95% confidence interval [CI]: 35 to 62). This increase was also significantly greater with roflumilast in the subgroup of patients who were also receiving LABA.

Table: Results for the primary outcomes in the pooled population of the two one-year studies

Outcome	Roflumilast	Placebo	Roflumilast versus placebo: difference or rate ratio (95% CI)
Lung function outcome			
Total pooled study population			
Mean change (SE) in pre-bronchodilator FEV ₁ (mL)	(n=1475) 40 (6)	(n=1511) -9 (5)	48 (35 to 62) p<0.0001
Exacerbation outcome			
Total pooled study population with ≥one exacerbation			
Mean rate (95% CI) of moderate or severe exacerbations per patient per year	(n=717) 1.14 (1.05 to 1.24)	(n=821) 1.37 (1.28 to 1.48)	0.83 (0.75 to 0.92) p=0.0003

(n= number of patients with data available)

In the pooled population, the relative risk reduction of the rate of moderate or severe exacerbations for roflumilast versus placebo was 16.9% (95% CI: 8.2% to 24.8%). Effects were similar, independent of previous treatment with inhaled corticosteroids or concomitant treatment with LABA. When severity of exacerbations was analysed separately, the reduction in exacerbation rate was only statistically significant between roflumilast and placebo for moderate but not severe exacerbations both in the total pooled population and in the subgroup on concomitant LABA. In the subgroup of patients with a history of frequent exacerbations (≥ two in previous year) the rate of exacerbations was 1.53 with roflumilast and 1.94 with placebo corresponding to a relative risk reduction of 21.3% (95% CI: 7.5% to 33.1%). The reduction of moderate to severe exacerbations in the subgroup of patients on concomitant LABA was on average 21% (p=0.0011), while in those not on concomitant LABA was 15% (p=0.0387).

A similar, supportive, 24-week study was conducted in 743 patients with moderate to severe COPD with chronic productive cough who had been receiving tiotropium for ≥ 3 months. Patients were randomised to roflumilast 500 micrograms or placebo once daily in addition to tiotropium treatment. Short-acting β₂-agonists as needed were permitted, however inhaled corticosteroids, short-acting anticholinergics, other long-acting bronchodilators, theophylline or other respiratory drugs were not allowed during the study period. The primary endpoint of mean change in pre-bronchodilator FEV₁ from baseline was significantly greater in the roflumilast than the placebo group (65ml versus -16ml respectively; difference 80ml (95% CI: 51 to 110)). There was no significant difference between roflumilast and placebo for the secondary outcome of the rate of exacerbations.

Other data were also assessed but remain commercially confidential.*

Summary of evidence on comparative safety

During the two one-year studies described above, adverse events were reported by 67% of roflumilast and 62% of placebo treated patients, with serious adverse events reported by 19% and 22% of patients respectively. Treatment discontinuation due to adverse events occurred in 14% of roflumilast and 11% of placebo treated patients. In the first 12 weeks of treatment, the probability of withdrawal due to adverse events was higher in the roflumilast than placebo group (8% versus 3% respectively), primarily due to diarrhoea, nausea and headache. However after 12 weeks, the probability of withdrawal due to adverse events was 9% in both groups.

The commonest adverse event was COPD which was reported in 9 to 11% of roflumilast and 11 to 15% of placebo treated patients. Other adverse events of note included diarrhoea (reported in 8 to 9% of roflumilast and 3% of placebo treated patients) and weight loss (reported in 8 to 12% of roflumilast and 3% of placebo treated patients). The mean change in weight was a reduction of 2.09kg (standard deviation [SD] 3.98) after one year of roflumilast and an increase of 0.08kg (SD 3.48) with placebo. Weight change in the roflumilast group occurred during the first 6 months and was greater in patients reporting diarrhoea, nausea, vomiting or headache.

Atrial fibrillation was an infrequent complication reported by 17 (1%) roflumilast and 7 (<1%) placebo patients.

Summary of clinical effectiveness issues

Roflumilast is the first selective PDE4 inhibitor and therefore offers another therapeutic class as well as an oral, once daily option for add-on therapy in patients with severe COPD. The efficacy studies described above demonstrate modest improvements in lung function which although statistically significant were smaller than the level generally considered clinically significant (120ml). However the aim of COPD treatment is to reduce exacerbation rates and slow the decline in health status and not to improve lung function per se. The rate of COPD exacerbations was significantly reduced with roflumilast compared to placebo in the two one-year studies but not in the 24 week study. However, this was a secondary outcome in the 24 week study and reported results also included mild exacerbations. The definitions used to categorise the severity of exacerbations were different in the one year and 24 week studies. In the two one-year studies, the reduction in exacerbation rate only reached statistical significance for moderate and not severe exacerbations.

Although a subgroup of the study population in the two one year studies represented the licensed population, concomitant medication used during the study period does not reflect clinical practice. The National Institute for Health and Clinical Excellence (NICE) clinical guideline on the management of COPD, recommends the use of LABA and/or anticholinergics and the addition of inhaled corticosteroids for patients with an FEV₁ <50% predicted, who are having two or more exacerbations that require treatment with antibiotics or oral corticosteroids in a 12-month period. In the two one-year studies, 42% of patients had been receiving inhaled corticosteroids prior to randomisation but were not permitted to continue during the study period. Approximately half of the patients received concomitant LABA during the study period. This restricts the generalisability of the study results to clinical practice. Furthermore, the study

results do not provide any indication as to which combinations of therapies may be most appropriate, and in particular, the use of roflumilast as an alternative or in addition to inhaled corticosteroids. These issues make the place of roflumilast in routine clinical practice difficult to determine.

There are no comparative data and the manufacturer has not performed an indirect comparison.

Summary of comparative health economic evidence

The manufacturer presented a cost-utility analysis comparing roflumilast plus LABA with LABA alone for the maintenance treatment of severe COPD in patients with a history of frequent exacerbations. The LABA used in the analysis was salmeterol. A 30-year time horizon was used which seems appropriate given the chronic nature of the condition. Shorter time horizons were explored in the sensitivity analysis. Results for the LABA subgroup from the pooled analysis of the two one-year pivotal studies were used in the economic analysis. Clinical data in the model related to exacerbation rates and improvements in lung function as measured by mean change in post-bronchodilator FEV₁.

The utility values for the severe and very severe COPD health states were taken from the LABA subgroup of the pooled analysis where patients completed EQ-5D within the trial at each study visit. Disutility values for exacerbations were taken from a literature study where the general public valued COPD health states using the time trade off method. Resource use associated with maintenance treatment of patients with severe and very severe COPD was based on a cost effectiveness study from the literature. Resource use to treat exacerbations was based on a combination of assumption (validated by Scottish experts) and NICE/Global Initiative for Chronic Lung Disease clinical guidelines.

The base case results indicated a cost per quality adjusted life year (QALY) of £13,212 (incremental cost of £3,398 and QALY gain of 0.257). The cost per exacerbation avoided was also calculated and this was estimated to be £1,327.

The following weaknesses were noted:

- A key weakness of the economic analysis was the choice of comparator. SMC clinical experts indicated that current treatment for patients with severe COPD and a history of frequent exacerbations is to use LABA/ inhaled corticosteroid combination therapy, often combined with a long-acting anticholinergic agent. Therefore clinical experts suggested that the extra health benefits of roflumilast in addition to LABA/inhaled corticosteroid combination therapy, or in place of inhaled corticosteroids should have been demonstrated.
- There were some weaknesses with the clinical data. In particular, the assumed benefit of roflumilast in reducing severe exacerbations was not appropriate as the difference between the treatments was not statistically significant either in the whole trial population or in the LABA subgroup. However, the studies were not powered to detect a statistically significant difference between treatment arms in severe exacerbations.
- The one-way sensitivity analyses showed the results were most sensitive to changes in the relative risk of exacerbations. The relative risk reduction used in the base case was 0.8. Using the upper 95% CI (0.914) resulted in a cost per QALY of around £27k.
- Additional scenario analyses were requested from the manufacturer to test the exacerbation rate used in the model. When the costs and utility decrement associated with severe exacerbations were set to zero, the ICER increased to £75k per QALY. Assuming the costs

and utility decrement for a severe exacerbation were the same as a moderate exacerbation increased the ICER to £66k per QALY. Finally, assuming the relative risk reduction of severe exacerbations from the trial (0.863) applied to all exacerbations increased the ICER to £18k per QALY.

Due to the inappropriate comparator and the weaknesses with the clinical data used in the economics in relation to the exacerbation rate, the economic case has not been demonstrated.

Summary of patient and public involvement

A Patient Interest Group Submission was not made.

Additional information: guidelines and protocols

The National Institute for Health and Clinical Excellence (NICE) published clinical guideline 12: management of COPD in adults in primary and secondary care in February 2004. This guideline recommends initial treatment with a short-acting bronchodilator when required. In patients who remain symptomatic a long-acting bronchodilator (long-acting beta₂-adrenergic agonists or tiotropium) or a short-acting anticholinergic is recommended. Long-acting bronchodilators should also be used in patients who have two or more exacerbations per year. The choice of drug(s) should take into account the patient's response to a trial of the drug, the drug's side effects, patient preference and cost. In addition, inhaled corticosteroids should be prescribed for patients with an FEV₁ <50% predicted, who are having two or more exacerbations that require treatment with antibiotics or oral corticosteroids in a 12-month period. The aim of treatment is to reduce exacerbation rates and slow the decline in health status and not to improve lung function per se. The NICE COPD guidance is currently under review with expected publication in June 2010.

Additional information: comparators

The company submission suggests that roflumilast will be added to existing treatments and will not replace any current treatments.

Cost of relevant comparators

Drug	Dose Regimen	Cost Per Year (£)
Roflumilast	500 micrograms orally once daily	458

Doses are for general comparison and do not imply therapeutic equivalence. Cost taken from manufacturer's submission is provisional and awaiting agreement with the Department of Health.

Additional information: budget impact

The manufacturer estimated the net budget impact would be £770k in year 1 rising to £4.73m in year 5. 1,678 patients were estimated to be treated in year 1, assuming a market share of 6.6%, and 10,312 patients in year 5, assuming a market share of 38%.

References

The undernoted references were supplied with the submission.

Calverley PMA, Rabe KF, Goehring U-M, et al. Roflumilast in symptomatic chronic obstructive pulmonary disease: two randomised clinical trials. *Lancet* 2009; 347; 695-694.

Fabbri LM, Calverley PMA, Izquierdo-Alonso JL, et al. Roflumilast in moderate-to-severe chronic obstructive pulmonary disease treated with longacting bronchodilators: two randomised clinical trials. *Lancet* 2009; 374: 695-703

This assessment is based on data submitted by the applicant company up to and including 16 July 2010.

Drug prices are those available at the time the papers were issued to SMC for consideration. These have been confirmed from the eVadis drug database. SMC is aware that for some hospital-only products national or local contracts may be in place for comparator products that can significantly reduce the acquisition cost to Health Boards. These contract prices are commercial in confidence and cannot be put in the public domain, including via the SMC Detailed Advice Document. Area Drug and Therapeutics Committees and NHS Boards are therefore asked to consider contract pricing when reviewing advice on medicines accepted by SMC.

**Agreement between the Association of the British Pharmaceutical Industry (ABPI) and the SMC on guidelines for the release of company data into the public domain during a health technology appraisal: <http://www.scottishmedicines.org.uk/>*

Advice context:

No part of this advice may be used without the whole of the advice being quoted in full.

This advice represents the view of the Scottish Medicines Consortium and was arrived at after careful consideration and evaluation of the available evidence. It is provided to inform the considerations of Area Drug & Therapeutics Committees and NHS Boards in Scotland in determining medicines for local use or local formulary inclusion. This advice does not override the individual responsibility of health professionals to make decisions in the exercise of their clinical judgement in the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.