Therapeutic Class Overview
Phosphodiesterase (PDE) 4 Inhibitors

Therapeutic Class

- **Overview/Summary:** Daliresp® (roflumilast) is a first in class oral phosphodiesterase (PDE) 4 inhibitor that is Food and Drug Administration (FDA)-approved to reduce the risk of chronic obstructive pulmonary disease (COPD) exacerbations in patients with severe COPD associated with chronic bronchitis and a history of exacerbations. Roflumilast and its active metabolite selectively inhibit PDE4, a major cyclic-3',5'-adenosine monophosphate (cyclic AMP)-metabolizing enzyme in lung tissue, resulting in the accumulation of intracellular cyclic AMP. The specific mechanisms by which roflumilast exerts its therapeutic action in COPD is not well defined; however, it is believed to be related to the effects of increased intracellular cyclic AMP in lung cells.[1] It is important to note that roflumilast is not a bronchodilator and is not indicated for the relief of acute bronchospasm.

Table 1. Current Medications Available in Therapeutic Class[1]

Generic (Trade Name)	Food and Drug Administration Approved Indications	Dosage Form/Strength	Generic Availability
Roflumilast (Daliresp®)	To reduce the risk of chronic obstructive pulmonary disease (COPD) exacerbations in patients with severe COPD associated with chronic bronchitis and a history of exacerbations	Tablet: 500 µg	-

Evidence-based Medicine

- Several, placebo-controlled trials of patients with moderate to severe chronic obstructive pulmonary disease (COPD) found that treatment with roflumilast significantly reduced exacerbations and improved lung function (pre- and post-bronchodilator levels) when added to first line COPD maintenance therapy; however, results were not consistent for reducing COPD exacerbations.[2-6]
    - After six months, patients receiving roflumilast (250 or 500 µg/day), as add-on therapy to daily short acting anticholinergics, achieved significant improvements in post-bronchodilator forced expiratory volume in one second (FEV_1) compared to baseline (P<0.05 for both doses) and placebo (P<0.03 for both doses). Significant improvements in baseline Saint George's Respiratory Questionnaire were also achieved with roflumilast (P<0.001 and P<0.0001).[2]
    - After one year, patients receiving roflumilast (500 µg/day), as add-on therapy to daily short acting anticholinergics and inhaled corticosteroids, achieved significant improvements in post-bronchodilator FEV_1 compared to placebo (P<0.001). No difference in the rate of moderate or severe COPD exacerbations was observed between the two treatments (0.86 vs 0.92 per patient per year; P value not reported).[3]
        - Post-hoc analyses revealed that COPD exacerbations were overall more frequent in Global Initiative for Chronic Obstructive Lung Disease Stage IV COPD patients, and within this group; exacerbations were significantly less among those receiving roflumilast (P=0.024 vs placebo).[3]
    - Pooled analysis of two, one year trials revealed that patients receiving roflumilast achieved "superior" improvements in post-bronchodilator levels and experienced a significantly lower rate of moderate to severe COPD exacerbations compared to placebo (P=0.026).[4]
    - Two additional one year trials found that patients who received roflumilast, as add-on therapy to daily short acting anticholinergics and long-acting β-agonists, achieved significant improvements in pre-bronchodilator FEV_1 (P<0.0001) and had a significantly lower rate of moderate or severe COPD exacerbations (relative risk, 0.83; 95% confidence interval, 0.75 to 0.95; P=0.0003) compared to placebo.[5]
    - Results from two six month trials revealed that patients who received roflumilast, in combination with a long acting bronchodilator (salmeterol or tiotropium), achieved significant improvements from baseline pre-bronchodilator FEV_1 levels compared to placebo (P<0.0001 for both). The rate per patient per year of mild, moderate or severe COPD exacerbations did not differ between the two treatments (P=0.1408 and P=0.3573). In these two trials, patients

were allowed to receive inhaled corticosteroids, short acting anticholinergics, other long acting bronchodilators, theophylline and other respiratory drugs as background therapy.[6]

Key Points within the Medication Class

- According to Current Clinical Guidelines:
  - Inhaled bronchodilators are preferred for the management of chronic obstructive pulmonary disease (COPD). [7,8]
  - Choice of agent should be based on availability and individual response in terms of symptom relief and side effects. [7,8]
  - Roflumilast has been shown to improve FEV_1 in patients treated with salmeterol or tiotropium. In patients with COPD stage III or COPD stage IV and a history of chronic bronchitis and exacerbations, roflumilast reduces exacerbations. No recommendation has made in regard to its place in the management of patients with COPD.[7]
- Other Key Facts:
  - Roflumilast is the first, orally administered, phosphodiesterase 4 inhibitor Food and Drug Administration (FDA) approved for the treatment of COPD, and is approved for use in a specific subset of COPD patients.[1]
  - In April 2010, an FDA Advisory Committee voted 10 to five against the use of roflumilast, stating that the agent was associated with too many adverse effects to offset what the FDA had referred to as a "modest" increase in lung function. In addition, use of roflumilast has been associated with psychiatric adverse events (including insomnia, anxiety, depression, suicidal ideation and behavior and completed suicide) and weight loss.[9]

References

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Therapeutic Class Review
Phosphodiesterase (PDE) 4 Inhibitors

Overview/Summary

Daliresp® (roflumilast) is an oral phosphodiesterase (PDE) 4 inhibitor Food and Drug Administration (FDA)-approved to reduce the risk of chronic obstructive pulmonary disease (COPD) exacerbations in patients with severe COPD associated with chronic bronchitis and a history of exacerbations. The agent is not to be used as a bronchodilator and is not indicated for the relief of acute bronchospasm. Roflumilast and its active metabolite selectively inhibit PDE4, a major cyclic-3',5'-adenosine monophosphate (cyclic AMP)-metabolizing enzyme in lung tissue, resulting in the accumulation of intracellular cyclic AMP. The specific mechanisms by which roflumilast exerts its therapeutic action in COPD patients is not well defined; however, it is believed to be related to the effects of increased intracellular cyclic AMP in lung cells.[1]

According to the Global Initiative for Chronic Obstructive Lung Disease and the National Institute for Health and Clinical Excellence guidelines, inhaled bronchodilators are preferred for the management of COPD. The guidelines state that regular use of long acting β_2-agonists (LABAs) or short or long acting anticholinergics improves health status and long acting anticholinergics reduce the rate of COPD exacerbations and improve the effectiveness of pulmonary rehabilitation.[2,3] Long acting bronchodilators are more effective and convenient than short acting bronchodilators; however, short acting bronchodilators should be considered initial empiric therapy.[3] The choice of agent should be based on availability and individual response in terms of symptom relief and side effects. Combining bronchodilators with different mechanisms of action and duration may increase the degree of bronchodilation with equivalent or lesser side effects. Current guidelines do not establish the place of roflumilast in the management algorithm of COPD.[2,3]

In April 2010, the FDA Pulmonary-Allergy Drugs Advisory Committee voted 10 to five against the use of roflumilast. At that time, it was concluded that the safety and efficacy data for the agent did not appear to be strong enough to warrant approval. The overall opinion of the Committee was that roflumilast was associated with too many adverse effects to offset what the FDA had referred to as a "modest" increase in lung function. The Committee also stated that they could not adequately compare the relative efficacy of roflumilast to other approved COPD medications as only placebo-controlled trials had been conducted.[4]

According to the FDA, the safety and efficacy of roflumilast was demonstrated in two Phase III clinical trials that included more than 1,500 COPD patients 40 years of age or older. Enrolled patients had moderate to severe COPD, a history of COPD associated with chronic bronchitis and had experienced an exacerbation of the disease during the 12 months prior to beginning treatment with roflumilast.[5] Overall, results from these and other published trials demonstrate that treatment with roflumilast significantly reduces exacerbations and improves lung function when added to first line COPD maintenance therapy.[6-12]

Table 1. Medications Included Within Class Review

Generic Name (Trade name)	Medication Class	Generic Availability
Roflumilast (Daliresp®)	Phosphodiesterase 4 inhibitor	-

Table 2. Food and Drug Administration Approved Indications[1]

Generic Name	To Reduce the Risk of Chronic Obstructive Pulmonary Disease (COPD) Exacerbations in Patients with Severe COPD Associated with Chronic Bronchitis and a History of Exacerbations
Roflumilast	✔

Pharmacokinetics

Table 3. Pharmacokinetics[1,15]

Generic Name	Bioavailability (%)	Renal Excretion (%)	Active Metabolites	Serum Half-Life (hours)
Roflumilast	80	70	Roflumilast N-oxide	17

Clinical Trials

In a trial conducted by Rabe et al, 1,411 patients with moderate to severe chronic obstructive pulmonary disease (COPD) were randomized to treatment with roflumilast 250 or 500 µg/day or placebo for six months. Concurrent COPD medications allowed were short acting β-agonists, as rescue therapy, and short acting anticholinergics at a constant daily dose. After six months, patients treated with roflumilast achieved significant improvements in post-bronchodilator forced expiratory volume in one second (FEV_1) levels compared to baseline (P<0.05 for both doses) and patients treated with placebo (P<0.03 for both doses). Improvements from baseline Saint George's Respiratory Questionnaire (SGRQ) scores were also significant for both doses of roflumilast (P<0.001 and P<0.0001), but not when compared to placebo (P=0.053 and P=0.077). As for the secondary endpoints evaluated, treatment with roflumilast was associated with significant reductions in acute COPD exacerbations compared to treatment with placebo (P=0.0029); the greatest effect being a 34% reduction with the 500 µg dose compared to placebo.[7]

In another placebo-controlled trial conducted by Calverley et al, patients with moderate to severe COPD were randomized to roflumilast 500 µg or placebo for one year. In this trial, concurrent COPD medications allowed were short acting β-agonists, as rescue therapy, short acting anticholinergics and inhaled corticosteroids (≤2,000 µg beclomethasone or equivalent). Again, patients treated with roflumilast achieved significant improvements in post-bronchodilator FEV_1 levels compared to placebo-treated patients (P<0.001). In this trial; however, the rate of moderate or severe COPD exacerbations, a co-primary endpoint, was not significantly different between roflumilast- and placebo-treated patients (0.86 vs 0.92 per patient per year; P value not reported). A post-hoc analysis of the data revealed that COPD exacerbations were overall more frequent in Global Initiative for Chronic Obstructive Lung Disease Stage IV COPD patients. However, within this group, exacerbations were significantly less frequent among those treated with roflumilast compared to those treated with placebo (P=0.024). Changes in SGRQ scores were again evaluated as a secondary endpoint but were found to not differ between treatment groups (P=0.086).[8] Results from Calverley et al were pooled with an identical, one year, placebo-controlled trial conducted by Rennard et al. In this pooled analysis, improvements in pre- (secondary endpoint) and post-bronchodilator levels (primary endpoint) were again significantly greater among roflumilast-treated patients compared to placebo-treated patients. Moreover, treatment with roflumilast was associated with a significantly lower rate of moderate to severe exacerbations (primary endpoint) compared to treatment with placebo (P=0.026).[9]

Two additional, identical one year, placebo-controlled trials conducted by Calverley et al were the first to evaluate the effects of roflumilast on pre-bronchodilator FEV_1 values as a co-primary endpoint, along with the rate of moderate or severe acute exacerbations. In addition, this is the first trial to allow concurrent use of long acting β-agonists, in addition to short acting β-agonists, as rescue therapy, and short acting anticholinergics. At the end of one year, pooled analysis revealed that patients treated with roflumilast achieved significant improvements in pre-bronchodilator FEV_1 levels (P<0.0001) and had a significantly lower rate of moderate or severe acute exacerbations (relative risk, 0.83; 95% confidence interval [CI], 0.75 to 0.95; P=0.0003) compared to patients treated with placebo. Of the secondary outcomes evaluated, only the pooled Transition Dyspnea Index (TDI) focal scores were significantly improved in roflumilast-treated patients compared to placebo treated patients (P=0.0009). Mortality rates (P values not reported) and time to mortality did not differ between treatment groups (206.1 vs 211.7 days; hazard ratio, 1.1; 95% CI, 0.7 to 1.8; P=0.5452).[10]

Two identical, placebo-controlled, six month trials assessed the efficacy of roflumilast in combination with a long acting bronchodilator (salmeterol or tiotropium) in moderate to severe COPD patients. Additional concurrent CODP medications allowed included short acting β-agonists, as rescue therapy, inhaled

corticosteroids, short acting anticholinergics, other long acting bronchodilators, theophylline and other respiratory drugs. For the sole primary endpoint, significant improvements from baseline in pre-bronchodilator FEV_1 levels were achieved in patients treated with roflumilast compared to patients treated with placebo (P<0.0001 for both trials). For secondary patient-reported outcomes evaluated (change in TDI score, Shortness of Breath Questionnaire score and use of rescue medication), the beneficial effects of roflumilast were more pronounced in patients receiving combination therapy with tiotropium. In this trial, the rate per patient per year of mild, moderate or severe COPD exacerbations did not differ between treatment groups (P=0.1408 and P=0.3573).[12]

A meta-analysis of 26 randomized controlled trials had evaluated the roles of long acting β_2-agonist, long acting anticholinergics, inhaled corticosteroids, and roflumilast therapy, both alone and in combination, on the rate of COPD exacerbations.[13] The primary endpoint was reported in terms of an absolute treatment effect, reflecting the mean exacerbations experienced per patient per year. A regimen composed of roflumilast, long acting β_2-agonist, long acting anticholinergics and an inhaled corticosteroids was associated with the greatest reduction in the number of exacerbations (absolute treatment effect, 0.53; 95% CI, 0.43 to 0.64). In comparison, the treatment effect of roflumilast monotherapy was 1.01 (95% CI, 1.17 to 1.23). A combination of long acting anticholinergics, long acting β_2-agonist and inhaled corticosteroids therapies was associated with a treatment of effect of 0.63 (95% CI, 0.54 to 0.73). In addition, a Cochrane systematic review reported a significant improvement in pulmonary function with roflumilast therapy, regardless of COPD severity.[14]

Table 4. Clinical Trials

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Rabe et al[7] Roflumilast 500 µg QD vs roflumilast 250 µg QD vs placebo All patients went through a 4 week, SB, run-in period with placebo and salbutamol as rescue medication. Concomitant respiratory medications allowed throughout the trial were salbutamol, as rescue medication, and short acting anticholinergics at a constant daily dose. Oral corticosteroids for exacerbation treatment were allowed. All other respiratory medications (e.g., ICSs) were withdrawn 4 weeks before randomization.	DB, MC, PC, PG, RCT Patients ≥40 years of age with a history of COPD >12 months, current or ex-smoker (>1 year of smoking cessation) with a smoking history >10 pack/years, post-bronchodilator FEV_1 30 to 80% of predicted value, post-bronchodilator FEV_1/FVC <70%, reversibility of FEV_1 <12% and/or <200 mL after 400 µg inhaled salbutamol and stable clinical disease status with no change in COPD treatment during the 4 weeks before the run-in period	N=1,411 6 months	Primary: Change from baseline in post-bronchodilator FEV_1 and SGRQ total score Secondary: Change from baseline in pre-bronchodilator FEV_1 and post-bronchodilator FVC, FEV_6 and $FEF_{25\ to\ 75}$; number of COPD exacerbations; adverse events	Primary: Placebo-treated patients had a significant decline in FEV_1 at week 24 compared to baseline (*P*=0.0041). Improvement in FEV_1 in roflumilast-treated patients was noted within the first four weeks of treatment. Roflumilast-treated patients had significantly increased FEV_1 from baseline at all visits (*P*<0.05 for all) and was significant compared to placebo-treated patients for both roflumilast doses (*P*<0.03 for both doses). There were no differences between current and ex-smokers in roflumilast-treated patients (data not shown). A post-hoc analysis revealed that FEV_1 increased significantly in roflumilast 250 and 500 µg-treated patients compared to placebo in moderate COPD (*P*=0.0001 and *P*<0.0001). Significant increases compared to placebo-treated patients was only revealed in roflumilast 500 µg-treated patients with severe COPD (*P*=0.0010). The changes from baseline in SGRQ total score were -3.4 (SD, 0.6; *P*<0.001), -3.5 (SD, 0.6; *P*<0.0001) and -1.8 units (SD, 0.8; *P*=0.0271) for roflumilast 250 µg-, roflumilast 500 µg- and placebo-treated patients. The improvement in SGRQ total score compared to placebo-treated patients was not significant for roflumilast-treated patients (250 µg; *P*=0.053 and 500 µg; *P*=0.077). Secondary: An improvement from baseline in prebronchodilator FEV_1 was achieved in roflumilast-treated patients compared to baseline (250 µg; *P*=0.0454 and 500 µg; *P*<0.0001) and placebo-treated patients (250 µg; *P*=0.0006 and 500 µg; *P*<0.0001). A dose dependent response was observed; however, the difference between roflumilast-treated patients was not significant. Postbronchodilator FVC, FEV_6 and $FEF_{25\ to\ 75}$ improved significantly in

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				roflumilast-treated patients compared to placebo-treated patients at 24 weeks (*P*<0.05 for all). The percentage of patients who had any exacerbation was lower in roflumilast 500 µg-treated patients compared to roflumilast 250 µg- and placebo-treated patients (*P*=0.0114). Treatment with roflumilast (250 µg, 1.03 and 500 µg, 0.75) also reduced the overall mean number of exacerbations per patient when compared to placebo-treated patients (1.13; *P*=0.0029). Comparison of the exacerbation rates revealed that the rate was 34% lower in roflumilast 500 µg-treated patients than in placebo-treated patients. This difference in the overall mean exacerbation rate was primarily due to the difference in mild exacerbations (500 µg vs placebo, 42% difference; *P*=0.004). The mean number of moderate and severe exacerbations per patient was low and closely similar between therapies. The most common adverse events reported were moderate or severe exacerbations of COPD and nasopharyngitis. The frequency of headache was low (4%) and comparable between therapies. Diarrhea occurred more frequently in roflumilast-treated patients and was more common within the first four weeks of treatment. Discontinuation due to adverse events were higher in roflumilast 500 µg-treated patients (15%) compared to roflumilast 200 µg- (10%) or placebo-treated patients (8%).
Calverley et al[8] Roflumilast 500 µg QD vs placebo All patients went through a 4 week, SB, run-in period with placebo and salbutamol as rescue medication.	DB, MC, PC, PG PRO, RCT Patients ≥40 years of age with COPD, current or ex-smoker (≥1 year of no tobacco) with a smoking history >10 pack/years, post-bronchodilator	N=1,513 1 year	Primary: Change from baseline in post-bronchodilator FEV_1, number of moderate or severe exacerbations per patient per year Secondary: Change from	Primary: After one year, the improvement in roflumilast-treated patients in post-bronchodilator FEV_1 from baseline compared to placebo-treated patients was 39 mL (SE, 12; *P*=0.001). Patients with GOLD Stage IV COPD revealed a smaller improvement in post-bronchodilator FEV_1 (16 mL [SE, 25]) compared to GOLD Stage III COPD patients (42 mL [SE, 13]). The rate of moderate or severe exacerbations was not different in roflumilast- (0.86 per patient per year) or placebo-treated patients (0.92 per patient per year; *P* value not reported). Exacerbations were more frequent in GOLD Stage IV COPD patients overall, with 36% fewer in

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Concomitant respiratory medications allowed throughout the trial were ICSs (≤2,000 µg beclomethasone or equivalent) and short acting anticholinergics at a constant daily dose if they were used before trial entry, and inhaled salbutamol as rescue medication. All other COPD medications were withdrawn 4 weeks before randomization.	FEV_1 <50% of predicted value, post-bronchodilator FEV_1/FVC <70%, reversibility of FEV_1 <15% and/or <200 mL after 200 µg inhaled salbutamol and stable clinical disease status with no change in COPD treatment during the 4 weeks before the run-in period		baseline in SGRQ total score; pre-bronchodilator FEV_1 and post-bronchodilator FVC, FEV_6 and $FEF_{25\ to\ 75}$; number of moderate or severe COPD exacerbations requiring oral corticosteroid treatment per patients per year; safety	roflumilast-treated patients compared to placebo-treated patients (1.01 vs 1.59 per patient per year; *P*=0.024). Secondary: A decrease in SGRQ total scores occurred with both treatments by week 12 (first measured time point) and was maintained throughout the trial. At one year, the change in total score was -1.7 and -2.0 units in roflumilast- and placebo-treated patients (*P*<0.05 for both), with no difference between the two treatments (*P*=0.651). Roflumilast-treated patients had similar improvements compared to placebo-treated patients in other lung function measurements that were observed for change in post-bronchodilator FEV_1. In all patients, the rate of exacerbations requiring oral corticosteroids as outpatients (but no hospitalization) was significantly lower in roflumilast-treated patients compared to placebo-treated patients (*P*=0.029). Eighteen percent fewer episodes were reported in roflumilast-treated patients. The hospitalization rate due to COPD exacerbations was low with both treatments, with no difference between them (*P*=0.697). Smoking status or concomitant use of ICSs did not influence the effect of roflumilast therapy on lung function, exacerbation rate or quality of life in the population as a whole. In GOLD Stage IV patients, moderate or severe exacerbations were 58 and 22% lower in roflumilast-treated patients without (*P*=0.014) and with (*P*=0.377) concomitant ICSs. The most commonly reported adverse event was exacerbation of COPD. The incidence of adverse events judged to be treatment-related was 17.8 vs 5.6% for roflumilast and placebo therapy. Most of the roflumilast adverse events affected the gastrointestinal tract and the nervous system, with diarrhea, nausea and headache being the most common. Treatment-related adverse events explained the greater number of roflumilast-treated patients withdrawing from the trial (diarrhea, 2.8 vs 0.0%; nausea, 1.6 vs 0.3% and headache, 0.7 vs 0.1%). More patients died during the trial while receiving placebo than roflumilast (20 vs 12

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				patients, respectively). The most frequent causes of death were respiratory disorders (1.1 vs 0.5%, respectively), infections (0.9 vs 0.5%, respectively) and cardiac disorders (1.1 vs 0.1%, respectively).
Rennard et al[9] Roflumilast 500 µg QD vs placebo All patients went through a 4 week, SB, run-in period with placebo and salbutamol as rescue medication. Concomitant respiratory medications allowed throughout the trial were ICSs (≤2,000 µg beclomethasone or equivalent) and short acting anticholinergics at a constant daily dose if they were used before trial entry, and inhaled salbutamol as rescue medication. All other COPD medications were withdrawn 4 weeks before randomization.	2 DB, MC, PC, PG, PRO, RCTs (includes Calverley et al[8]) Patients ≥40 years of age with COPD, current or ex-smoker (≥1 year of no tobacco) with a smoking history >10 pack/years, post-bronchodilator FEV_1 <50% of predicted value, post-bronchodilator FEV_1/FVC <70%, reversibility of FEV_1 <15% and/or <200 mL after 200 µg inhaled salbutamol and stable clinical disease status with no change in COPD treatment during the 4 weeks before the run-in period	N=2,690 1 year	Primary: Change from baseline in post-bronchodilator FEV_1, number of moderate or severe exacerbations per patient per year Secondary: Change from baseline in SGRQ total score; pre-bronchodilator FEV_1 and post-bronchodilator FVC, FEV_6 and $FEF_{25\ to\ 75}$; safety	Primary: Roflumilast-treated patients achieved significant improvements in pre-bronchodilator FEV_1 compared to placebo treated patients. In the pooled analysis, improvement was evident at week four and was maintained throughout the year. After one year, the change in pre-bronchodilator FEV_1 from baseline in roflumilast-treated patients was 51 mL compared to placebo-treated patients (SE, 7; *P*<0.0001). Treatment with roflumilast consistently showed a significant improvement compared to treatment with placebo in pre-bronchodilator FEV_1 in all subgroups. The rate of moderate to severe exacerbations in the pooled analysis was 14.3% lower in roflumilast-treated patients compared to placebo-treated patients (0.52 vs 0.61 exacerbations per year; *P*=0.026). The median time to first moderate or severe exacerbation was comparable between the two treatment groups (120 vs 126 days, respectively; *P*=0.236). There were several subgroups in which the exacerbation rate appeared lower in roflumilast-treated patients, including patients with chronic bronchitis with or without emphysema (26.2% reduction vs placebo; *P*=0.001). Patients receiving concurrent ICSs experienced an 18.8% reduction compared to placebo (*P*=0.014), while patients not receiving ICSs exhibited no clinical benefit compared to placebo. A significant reduction in favor of roflumilast was observed in patients receiving short acting anticholinergic treatments (18.3%; *P*=0.012). Other subgroups, such as current vs former smokers or those based on spirometrically defined COPD severity, revealed no or little difference between the two treatments in exacerbation rates. Secondary: The change in post-bronchodilator FEV_1 levels in roflumilast-treated patients compared to placebo-treated patients was 53 mL (SE, 8; *P*<0.0001). Treatment with roflumilast consistently showed a significant improvement compared to treatment with placebo in post-bronchodilator

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				FEV_1 in all subgroups. In the pooled analysis, roflumilast- and placebo-treated patients did not differ in terms of change from baseline SGRQ total scores. In a subgroup analysis, a significant improvement was observed for patients with chronic bronchitis (*P*=0.0265), and was evident in patients with chronic bronchitis who were receiving ICSs (*P*=0.0397). It is noted that, adverse events were similar to those reported for roflumilast in previous trials. Roflumilast, compared to placebo, was not associated with an increase in adverse events in the subgroups that experienced a greater reduction in exacerbations with roflumilast. Concurrent ICSs did not affect the adverse event profile of roflumilast.
Calverley et al[10] Roflumilast 500 µg QD vs placebo All patients went through a 4 week, SB, run-in period with placebo, and recorded their use of short acting bronchodilators and production of cough and sputum. Concomitant respiratory medications allowed throughout the trial were short acting β_2-agonists, as rescue medication, and long acting β_2-	2 DB, MC, PC, RCTs Patients ≥40 years of age with COPD, current or ex-smoker with a smoking history ≥20 pack/years, chronic cough and sputum production, post-bronchodilator FEV_1 <50% of predicted value and ≥1 recorded COPD exacerbation requiring oral corticosteroids or treatment in hospital, or both, in the previous	N=3,096 (Trial 1, n=1,571; Trial 2, n=1,525) 1 year	Primary: Change from baseline in pre-bronchodilator FEV_1, rate of exacerbations Secondary: Change from baseline in post-bronchodilator FEV_1, time to death from any cause, natural log-transformed C-reactive protein concentration, TDI focal score, safety	Primary: In the pooled analysis, pre-bronchodilator FEV_1 increased significantly from baseline in roflumilast-treated patients compared to placebo-treated patients (*P*<0.0001). In the pooled analysis, the estimated rate of exacerbations per patient per year that were moderate or severe was 17% lower in roflumilast-treated patients compared to placebo-treated patients (RR, 0.83; 95% CI, 0.75 to 0.92; *P*=0.0003). The difference in rates between therapies was independent of concomitant long acting β_2-agonist use (*P*=0.5382). In the pooled analysis, the total number of exacerbations (excluding severe events) requiring treatment with oral corticosteroids or antibiotics, or both, was lower in roflumilast-treated patients (16% reduction; RR, 0.84; 95% CI, 0.76 to 0.92; *P*=0.0003). The times to first and second episodes of exacerbations that were moderate to severe were significantly prolonged in roflumilast-treated patients (HR, 0.89; 95% CI, 0.80 to 0.98; *P*=0.0185). Secondary: In the pooled analysis, post-bronchodilator FEV_1 increased significantly from baseline in roflumilast-treated patients compared to placebo-treated patients (*P*<0.0001). The mortality rates per year did not differ in roflumilast- and placebo-

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
agonist or short acting anticholinergics at stable doses. Other respiratory medications (ICSs and long acting anticholinergics) were not allowed during the trial.	year			treated patients in Trial 1 (two vs two percent) and 2 (three vs three percent). In the pooled analysis, time to mortality also did not differ between treatments (206.1 vs 211.7; HR, 1.1; 95% CI, 0.7 to 1.8; *P*=0.5452). Baseline concentrations of C-reactive protein varied widely and did not change significantly during the trial or with roflumilast treatment (pooled analysis; *P*=0.8670). A small improvement was noted in TDI focal score from baseline in roflumilast-treated patients compared to placebo-treated patients (pooled analysis; *P*=0.0009). Adverse events in the pooled analysis were reported by 67 vs 62% of roflumilast- and placebo- treated patients, with serious adverse events being reported by 19 vs 22%, respectively. Discontinuations associated with adverse events were more common in the pooled roflumilast-treated patients compared to the pooled placebo-treated patients (14 vs 11%). The most common adverse events leading to discontinuation, with the exception of COPD, were diarrhea, nausea and headache. More roflumilast-treated patients had weight loss (mean weight change, 2.09 [SD, 3.98] vs 0.08 [SD, 3.48] kg).
Bateman et al[11] Roflumilast 500 µg QD vs placebo All patients went through a 4 week, SB, run-in period with placebo, and recorded their use of short acting bronchodilators and	2 DB, MC, PC, RCTs Patients ≥40 years of age with COPD, current or ex-smoker with a smoking history of ≥20 pack/years, chronic cough and sputum production, post-bronchodilator	N=3,091 1 year	Primary: Change from baseline in pre-bronchodilator FEV_1, rate of moderate-severe exacerbations Secondary: Change from baseline in post-bronchodilator FEV_1, time to	Primary: Pre-bronchodilator FEV_1 significantly improved in patients receiving roflumilast therapy compared to patients receiving placebo and did not vary with or without concomitant use of long acting β_2-agonists, short-acting antimuscarinic agents, or previous ICS use (*P* value not reported). The estimated rate of exacerbations per patient per year that were moderate or severe was 17% lower in roflumilast-treated patients compared to placebo-treated patients (RR, 0.83; 95% CI, 0.75 to 0.92; *P*=0.0003) and regardless of the concomitant use of long acting β_2-agonists (RR, 0.79; 95% CI, 0.69 to 0.91; *P*=0.0011). The relative reduction in moderate or severe exacerbation rates in patients treated with long acting β_2-agonists was 20.7% (absolute

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
production of cough and sputum. Concomitant respiratory medications allowed throughout the trial were short acting β_2-agonists, as rescue medication, and long acting β_2-agonist or short acting anticholinergics at stable doses. Other respiratory medications (ICSs and long acting anticholinergics) were not allowed during the trial.	FEV_1 <50% of predicted value and ≥1 recorded COPD exacerbation requiring oral corticosteroids or treatment in hospital, or both, in the previous year		death from any cause, natural log-transformed C-reactive protein concentration, TDI focal score, safety	reduction was 0.322 exacerbations per patient per year). The calculated NNT to prevent one moderate-severe exacerbation per year was 3.2. Both, patients with concomitant long acting β_2-agonist (RR, 0.79; 95% CI, 0.69 to 0.91; *P*=0.0011) and without concomitant long acting β_2-agonist therapy (RR, 0.85; 95% CI, 0.74 to 0.99; *P*=0.0387) were associated with statistically significant reductions in the rate of moderate-severe COPD exacerbations per year. The time to onset of the first, second, and third moderate-severe COPD exacerbation was significantly delayed across all patients and in the subgroup using long acting β_2-agonists (*P*=0.0348, *P*=0.0179 and *P*=0.0075, respectively). However, in patients not receiving concomitant long acting β_2-agonists, only the time to onset of the second exacerbation was significantly reduced (*P*=0.049). In both frequent (RR, 0.78; 95% CI, 0.66 to 0.91; *P*=0.0017) and infrequent exacerbators (RR, 0.84; 95% CI, 0.73 to 0.95; *P*=0.0062), roflumilast was associated with statistically significant reductions in the mean rate of moderate-severe exacerbations. Time to onset of second (*P*=0.011) and third exacerbation (*P*=0.007) was significantly delayed with roflumilast in patients who had a baseline history of frequent exacerbations. Patients who did not have a history of frequent exacerbations at baseline experienced a delay in the time to onset of second COPD exacerbation (*P*=0.024). The mean rate of exacerbations was significantly reduced with roflumilast vs placebo, regardless of short-acting antimuscarinic agent use or prior treatment with ICS (*P* value not reported). Secondary: The TDI focal score was significantly reduced in patients receiving roflumilast compared to placebo-treated patients in both patients who received concomitant long acting β_2-agonist therapy and those who did not (*P*=0.0066 and P=0.0477, respectively).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				The TDI focal score was significantly reduced in patients receiving roflumilast compared to placebo-treated patients in those patients who had reported frequent exacerbations at baseline (*P*=0.0008). Patients without a baseline history of frequent COPD exacerbations didn't experience a statistically significant improvement in TDI focal scores with roflumilast therapy (*P*=0.095). Post-bronchodilator FEV_1 significantly improved in patients receiving roflumilast therapy compared to patients receiving placebo and did not vary with or without concomitant use of long acting β_2-agonists, short-acting antimuscarinic agents, or previous ICS use (*P* value not reported). The most commonly reported adverse events associated with roflumilast therapy were diarrhea (7.7 to 9.1%) and weight loss (~10%), which occurred at a similar rate in patients with or without concomitant long acting β_2-agonist therapy.
Fabbri et al[12] Roflumilast 500 µg QD plus salmeterol (Trial 1) or tiotropium (Trial 2) vs placebo plus salmeterol (Trial 1) or tiotropium (Trial 2) All patients went through a 4 week, SB, run-in period with placebo, and recorded their use of short acting bronchodilators and production of cough and	2 DB, MC, PC, RCTs Patients >40 years of age with COPD, current or ex-smoker (≥1 year of smoking cessation) with a smoking history ≥10 pack/years, post-bronchodilator FEV_1 40 to 70% of predicted value, post-bronchodilator FEV_1/FVC <70%, reversibility of	N=1,679 (Trial 1, n=935; Trial 2, n=744) 24 weeks	Primary: Change from baseline in mean pre-bronchodilator FEV_1 Secondary: Post-bronchodilator FEV_1 and FVC, TDI score, SOBQ, use of rescue medications, rate of COPD exacerbations, safety	Primary: The pre-bronchodilator FEV_1 increased significantly in roflumilast-treated patients compared to placebo-treated patients in both trials (Trial 1 and 2; *P*<0.0001). Secondary: The post-bronchodilator FEV_1 (Trial 1 and 2; *P*<0.0001) and FVC (Trial 1; *P*=0.0028 and Trial 2; *P*=0.0004) increased significantly in roflumilast-treated patients compared to placebo-treated patients in both trials. The beneficial effect of roflumilast therapy on the patient-reported outcomes (change in TDI score; *P*=0.0032 vs *P*=0.4654, change in SOBQ score; *P*=0.0051 vs *P*=0.5457 and change in use of rescue medication; *P*=0.0004 vs *P*=0.3689) was more pronounced in roflumilast plus tiotropium-treated patients than in roflumilast plus salmeterol-treated patients compared to placebo-treated patients. Roflumilast therapy had a variable effect on symptomatic outcomes including exacerbations in both trials. The mean rate per patient per year

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
sputum. Concomitant respiratory medications (ICSs, short acting anticholinergics, other long acting bronchodilators, theophylline or other respiratory drugs) were allowed after trial enrolment.	FEV_1 ≤15% and/or <200 mL after 400 µg inhaled albuterol and stable disease			of mild, moderate or severe exacerbations were not significantly different between roflumilast and placebo-treated patients (Trial 1: 1.9 vs 2.4; RR, 0.79; 95% CI, 0.58 to 1.08; *P*=0.1408 and Trial 2: 1.8 vs 2.2; RR, 0.84; 95% CI, 0.57 to 1.23; *P*=0.3573). More patients receiving combination therapy experienced an adverse event compared to placebo-treated patients. The most frequently reported adverse events in both trials were COPD related. Diarrhea, nausea and weight loss were the most common treatment-related adverse events, with no major difference between the two trials. Compared to placebo, roflumilast was associated with increased withdrawal from the trial (Trial 1; *P*=0.0019 and Trial 2; *P*=0.0864).
Mills EJ et al[13] Roflumilast, long acting β_2-agonist, long-acting antimuscarinic agent, and ICS monotherapy or in combination vs placebo	MA RCTs evaluating long acting β_2-agonists, long-acting antimuscarinic agents, ICS and roflumilast, in combination or as monotherapy, in patients with moderate-severe COPD	N=36,312 (26 studies) ≥24 weeks	Primary: Event rate of exacerbations Secondary: Not reported	Primary: The combination of roflumilast and long-acting antimuscarinic agent was associated with the largest absolute treatment effect of 0.75 (expressed as mean exacerbations experienced per patient per year) (95% CI, 0.53 to 1.02). The combination of ICS, long acting β_2-agonist and long-acting antimuscarinic agent was associated with an absolute treatment effect of 0.82 (95% CI, 0.57 to 1.15). The combination of ICS and long acting β_2-agonist was associated with an absolute treatment effect of 0.83 (95% CI, 0.73 to 0.93). The combination of roflumilast and long acting β_2-agonist was associated with an absolute treatment effect of 0.81 (95% CI, 0.58 to 1.10). The combination of long-acting antimuscarinic agent and long acting β_2-agonist was associated with an absolute treatment effect of 0.97 (95% CI, 0.67 to 1.34). Long acting β_2-agonist therapy was associated with an absolute treatment effect of 1.01 (95% CI, 0.90 to 1.11). Long-acting antimuscarinic agent therapy was associated with an

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				absolute treatment effect of 0.89 (95% CI, 0.80 to 0.98). ICS therapy was associated with an absolute treatment effect of 0.96 (95% CI, 0.85 to 1.08). Roflumilast therapy was associated with an absolute treatment effect of 1.03 (95% CI, 0.87 to 1.21). Secondary: Not reported
Chong J, et al[14] Phosphodiesterase 4 inhibitors (roflumilast, cilomilast†)	MA RCTs comparing orally administered phosphor-diesterase 4 inhibitors with placebo in adults >18 years of age, diagnosed with COPD, defined by GOLD, with FEV_1 <80% the predicted value and FEV_1/FVC of ≤0.70	N=9,211 (23 roflumilast studies) N=6,457 (14 cilomilast) ≤12 months	Primary: Improvement from baseline in lung function (FEV_1, FVC and PEF), rate of exacerbations, improvement in health related quality of life Secondary: Improvement in exercise tolerance	Primary: In general, phosphodiesterase 4 inhibitors were associated with a statistically significant improvement in FEV_1 from baseline compared to placebo (*P*<0.00001). There was an improvement in FEV_1 of 54.32 mL with roflumilast 500 µg and a 55.00 mL improvement with 250 µg compared to placebo (95% CI, 44.90 to 64.25 for 500 µg and 95% CI, 22.10 to 81.96 for 250 µg). The changes in FEV_1 were statistically significant regardless of GOLD stage I, II, III, or IV status. The largest affect on FEV_1 values was seen in patients randomized to receive roflumilast in combination with a bronchodilator (mean difference, 60.52 mL; 95% CI, 40.57 to 80.46). The next improvements were seen in trials where all other medications were stopped (mean difference, 43.77 mL; 95% CI, 36.63 to 50.91). Phosphodiesterase 4 inhibitor therapy was associated with a significant change from baseline in FVC (mean difference, 82.67 mL; 95% CI, 66.10 to 99.24; *P*<0.00001). Phosphodiesterase 4 inhibitor therapy was associated with a significant improvement in the health related quality of life SGRQ scores compared to placebo (mean difference, -1.04; 95% CI, -1.66 to -0.41; *P*=0.001). PDE4 inhibitor-treated patients were approximately 25% less likely to have an exacerbation compared to placebo treated patients (OR, 0.78; 95% CI, 0.72 to 0.85; *P*<0.0001).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				Secondary: Only cilomilast trials had significant improvements in symptoms and exercise tolerance. Data from roflumilast trials was not reported.

*Study grading according to Agency for Healthcare Research and Quality (AHRQ) (See Appendix I for definition of ratings). Studies falling outside of the grading criteria defined by AHRQ will be noted as "Not Applicable". This indicates that the grading criteria did not appropriately fit the design of the included study, but that it was included due to the potential value of the presented data.
†Not Food and Drug Administration approved, under investigation.
Study design abbreviations: CI=confidence interval, DB=double-blind, HR=hazard ratio, MA=meta-analysis, MC=multicenter, NNT=number needed to treat, OR=odds ratio, PC=placebo-controlled, PG=parallel group, PRO=prospective, RCT=randomized controlled trial, RR=relative risk, SB=single-blind, SD=standard deviation, SE=standard error, QD=once daily
Miscellaneous abbreviations: COPD=chronic obstructive pulmonary disease, FEV_1=forced expiratory volume in 1 second, FEV_6=forced expiratory volume in the first 6 seconds, $FEF_{25\ to\ 75}$=forced expiratory flow between 25 and 75% of the vital capacity, FVC=forced vital capacity, ICS=inhaled corticosteroid, GOLD=Global Initiative for Chronic Obstructive Lung Disease, PEF=peak expiratory flow rate, SGRQ=St. George's respiratory questionnaire, SOBQ=Shortness of Breath Questionnaire, TDI=transition dyspnea index

Special Populations

Table 5. Special Populations[1]

Generic Name	Population and Precaution				
	Elderly/ Children	Renal Dysfunction	Hepatic Dysfunction	Pregnancy Category	Excreted in Breast Milk
Roflumilast	No evidence of overall differences in safety or efficacy observed between elderly and younger adult patients Safety and efficacy in children have not been established.	No dosage adjustment required.	No dosage adjustment required.	C	Not reported

Adverse Drug Events

Table 6. Adverse Drug Events (%)[1]

Adverse Event	Reported Frequency	
	Roflumilast, 500 mg Once Daily n (%), N=4,438	Placebo n (%), N=4,192
Back pain	142 (3.2)	92 (2.2)
Decreased appetite	91 (2.1)	15 (0.4)
Diarrhea	420 (9.5)	113 (2.7)
Dizziness	92 (2.1)	45 (1.1)
Headache	195 (4.4)	87 (2.1)
Influenza	124 (2.8)	112 (2.7)
Insomnia	105 (2.4)	41 (1.0)
Nausea	209 (4.7)	60 (1.4)
Weight decreased	331 (7.5)	89 (2.1)

Other adverse reactions associated with roflumilast therapy, occurring at a frequency of one to two percent, include abdominal pain, dyspepsia, gastritis, vomiting, rhinitis, sinusitis, urinary tract infection, muscle spasms, tremor, anxiety and depression.[1]

Contraindications/Precautions

Roflumilast is contraindicated in patients with moderate to severe liver impairment.[1]

Use of roflumilast is associated with an increase in psychiatric adverse reactions. In clinical trials, the most commonly reported psychiatric adverse events included insomnia, anxiety and depression. Instances of suicidal ideation and behavior, including completed suicide, have also been observed in patients receiving roflumilast. Due to these risks, before initiating roflumilast in patients with a history of depression and/or suicidal thoughts or behavior, health care providers should weigh the risks and benefits of treatment in such patents.[1]

Weight loss was also commonly observed in clinical trials evaluating roflumilast; therefore, patients receiving the agent should have their weight monitored regularly. If unexplained or clinically significant weight loss occurs, weight loss should be evaluated, and discontinuation of therapy should be considered.[1]

Drug Interactions

Strong cytochrome P450 (CYP) enzyme inducers (e.g., carbamazepine, phenobarbital, phenytoin, rifampicin) decrease systemic exposure to roflumilast and may reduce its therapeutic effectiveness, and

concurrent use is not recommended. Concurrent administration of roflumilast with CYP3A4 inhibitors or dual inhibitors that inhibit both CYP3A4 and 1A2 (e.g., cimetidine, enoxacin, erythromycin, fluvoxamine, ketoconazole) simultaneously may increase roflumilast systemic exposure and may result in increased adverse reactions. In addition, the concurrent administration of roflumilast and oral contraceptives containing gestodene and ethinyl estradiol may increase roflumilast systemic exposure and may result in increased side effects. The risk of such concurrent use should be weighted carefully against benefit.[1]

Dosage and Administration

Table 7. Dosing and Administration[1]

Adult Dose	Pediatric Dose	Availability
Treatment to reduce the risk of chronic obstructive pulmonary disease exacerbations in patients with severe chronic obstructive pulmonary disease associated with chronic bronchitis and a history of exacerbations: Tablet: 500 µg/day	Safety and efficacy in children have not been established.	Tablet: 500 µg

Clinical Guidelines

Table 8. Clinical Guidelines

Clinical Guideline	Recommendations
Global Initiative for Chronic Obstructive Lung Disease: **Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Pulmonary Disease (Updated 2010)**[2]	Diagnosis • A clinical diagnosis of chronic obstructive pulmonary disease (COPD) should be considered in any patient who has dyspnea, chronic cough or sputum production and/or a history of exposure to risk factors for the disease. • A diagnosis of COPD should be confirmed by spirometry. • The presence of a post-bronchodilator forced expiratory volume in one second (FEV_1)/forced vital capacity (FVC) <0.70 confirms the presence of airflow limitation that is not fully reversible. • Assessment of COPD severity is based on the patient's level of symptoms, the severity of the spirometric abnormality and the presence of complications. • A detailed medical history should be obtained for all patients suspected of developing COPD. • Severity of COPD is based on the patient's level of symptoms, the severity of the spirometric abnormality and the presence of complications such as respiratory failure, right heart failure, weight loss and arterial hypoxemia. • Chest radiograph may be useful to rule out other diagnoses and to establish the presence of significant comorbidities such as cardiac failure. • Arterial blood gas tension measurements should be considered for all patients with FEV_1 <50% predicted or clinical signs suggestive of respiratory failure or right heart failure. • COPD is typically a progressive disease; therefore, lung function can be expected to worsen over time, even with the best available care. • Symptoms and objective measures of airflow limitation should be monitored to determine when to modify therapy. In addition, symptom monitoring is used to determine when to modify therapy and to identify any complications that may develop. • Comorbidities are common in COPD and should be actively identified. Comorbidities often complicate the management of COPD, and vice versa.

Clinical Guideline	Recommendations
	• Screening for α_1-antitrypsin deficiency may be valuable in patients of Caucasian decent who develop COPD at a young age (<45 years of age) or who have a strong family history of the disease. • In some patients with chronic asthma, a clear distinction from COPD is not possible using current imaging and physiological testing techniques and it is assumed that asthma and COPD coexist in these patients. In these instances, current management is similar to that of asthma. Other potential diagnoses (e.g., congestive heart failure, bronchiectasis, tuberculosis, obliterative bronchiolitis, and diffuse panbronchiolitis) are usually easier to distinguish from COPD. Treatment • The management of COPD should be individualized to address symptoms and improve the patient's quality of life. • None of the medications for COPD have been shown to modify the long term decline in lung function that is hallmark of this disease. Treatment should be focused on reducing symptoms and complications. • Choice of agent within each medication class depends on the availability of medication and the patient's response. • Bronchodilator medications are central to the symptomatic management of COPD. They are given on an as needed basis for relief of persistent or worsening symptoms or on a regular basis to prevent or reduce symptoms. • Inhaled therapy is preferred. • When treatment is given by the inhaled route, attention to effective drug delivery and training in inhaler technique is essential. COPD patients may have more problems in effective coordination with a metered dose inhaler compared to healthy patients; alternative breath-activated or spacer devices are available for most formulations. Dry powder inhalers may be more convenient and possibly provide improved drug deposition, although this has not been established in COPD. • Principle bronchodilators include β_2-agonists, anticholinergics and methylxanthines used as monotherapy or in combination. • Regular treatment with long-acting bronchodilators is more effective and convenient than short-acting bronchodilators. • The choice between β_2-agonists, anticholinergics, theophylline or combination therapy depends on availability and individual response in terms of symptom relief and side effects. • The order in which the bronchodilator medications are normally introduced into patient care (based on the level of disease severity and clinical symptoms) is: β-agonists, anticholinergics and methylxanthines. • Regular use of long acting β-agonists (LABAs) or short- or long-acting anticholinergics improves health status. • Long-acting anticholinergics reduce the rate of COPD exacerbations and improve the effectiveness of pulmonary rehabilitation. • Theophylline is effective in COPD, but due to its potential toxicity inhaled bronchodilators are preferred when available. All theophylline studies were performed with slow-release preparations. • Combining bronchodilators of different pharmacological classes may improve efficacy and decrease the risk of side effects compared to

Clinical Guideline	Recommendations
	increasing the dose of a single bronchodilator. • For single-dose, as needed use, there is no advantage in using levalbuterol over conventional nebulized bronchodilators. • The addition of regular treatment with inhaled corticosteroids (ICSs) to bronchodilator treatment is appropriate for symptomatic COPD patients with an FEV_1 <50% predicted and repeated exacerbations. • Regular treatment with ICSs has been shown to reduce the frequency of exacerbations and thus improve health status for symptomatic patients with an FEV_1 <50% of the predicted value and repeated exacerbations. • Treatment with ICSs increases the likelihood of pneumonia and does not reduce overall mortality. • An ICS combined with a LABA is more effective than the individual components in reducing exacerbations and improving lung function and health status. • Combination ICS/LABA therapy increases the likelihood of pneumonia. • Addition of an ICS/LABA to an anticholinergic appears to provide additional benefits. • There is insufficient evidence to recommend a therapeutic trial with systemic corticosteroids in patients with Stage II, Stage III or Stage IV COPD and poor response to an inhaled bronchodilator. • Chronic treatment with systemic corticosteroids should be avoided due to an unfavorable risk-benefit ratio. • In COPD patients influenza vaccines can reduce serious illness. • The pneumococcal polysaccharide vaccine is recommended for COPD patients ≥65 years old or for patients <65 years old with an FEV_1 <40% of the predicted value. • Long-term administration of oxygen (>15 hours/day) increases survival in patients with chronic respiratory failure. • Roflumilast has been shown to improve FEV_1 in patients treated with salmeterol or tiotropium. In patients with COPD stage III or COPD stage IV and a history of chronic bronchitis and exacerbations, roflumilast reduces exacerbations. There are no comparison studies when used with inhaled glucocorticosteroids. <u>Management of exacerbations</u> • The most common causes of an exacerbation are tracheobronchial tree infections and air pollution. • Inhaled β_2-agonists (particularly inhaled β_2-agonists with or without anticholinergics) and systemic corticosteroids are effective treatments for exacerbations of COPD. • Patients experiencing COPD exacerbations with clinical signs of airway infection may benefit from antibiotic treatment.
National Institute for Health and Clinical Excellence: **Chronic Obstructive Pulmonary Disease: Management of Chronic Obstructive Pulmonary Disease in Adults in Primary and Secondary Care (partial update)**	<u>Diagnosis</u> • Diagnosis should be considered in patients >35 years of age who have a risk factor for the development of COPD and who present with exertional breathlessness, chronic cough, regular sputum production, frequent winter bronchitis or wheeze. • The primary risk factor is smoking. • Spirometry is diagnostic of airflow obstruction. Airflow obstruction is defined as FEV_1 <80% predicted and FEV_1/FVC <70%.

Clinical Guideline	Recommendations
(2010)[3]	Treatment • Smoking cessation should be encouraged for all patients with COPD. • Short-acting bronchodilators, as necessary, should be the initial empiric treatment for the relief of breathlessness and exercise limitation. • Long-acting bronchodilators (β_2-agonists and/or anticholinergics) should be given to patients who remain symptomatic even with short-acting bronchodilators. • Once-daily long-acting muscarinic antagonists are preferred compared to four-times-daily short-acting muscarinic antagonists in patients with stable COPD who remain breathless or who have exacerbations despite the use of short-acting bronchodilators as required and in whom a decision has been made to begin regular maintenance bronchodilator therapy with a muscarinic antagonist. o FEV_1 $\geq$50% predicted: LABA or long-acting muscarinic antagonist. o FEV_1 <50% predicted: either LABA with an ICS in a combination inhaler or a long-acting muscarinic antagonist. • In patients with stable COPD and FEV_1 $\geq$50% who remain breathless or have exacerbations despite maintenance therapy with a LABA, consider adding an ICS in a combination inhaler or a long-acting muscarinic antagonist when ICSs are not tolerated or declined. • Consider a long-acting muscarinic antagonist in patients remaining breathless or having exacerbations despite therapy with LABA and ICS and vice versa. • Choice of drug should take in to consideration the patient's symptomatic response, preference, potential to reduce exacerbations, and side effects and costs. • In most cases, inhaled bronchodilator therapy is preferred. • Oral corticosteroids are not normally recommended and should be reserved for those patients with advanced COPD in whom therapy cannot be withdrawn following an exacerbation. • Theophylline should only be used after a trial of long-acting and short-acting bronchodilators or if the patient is unable to take inhaled therapy. Combination therapy with β_2-agonists and theophylline or anticholinergics and theophylline may be considered in patients remaining symptomatic on monotherapy. • Pulmonary rehabilitation should be made available to patients. • Noninvasive ventilation should be used for patients with persistent hypercapnic respiratory failure. Management of exacerbations • Patients with exacerbations should be evaluated for hospital admission. • Patients should receive a chest radiograph, have arterial blood gases monitored, have sputum cultured if it is purulent, and have blood cultures taken if pyrexial. • Oral corticosteroids should be used in all patients admitted to the hospital who do not have contraindications to therapy. The course of therapy should be no longer than 14 days. • Oxygen should be given to maintain oxygen saturation above 90%. • Patients should receive invasive and noninvasive ventilation as necessary.

Clinical Guideline	Recommendations
	• Respiratory physiotherapy may be used to help remove sputum. • Before discharge, patients should be evaluated by spirometry. • Patients should be properly educated on their inhaler technique and the necessity of usage and should schedule a follow up appointment with a health care professional.

Conclusions

Daliresp® (roflumilast) is a first in class, phosphodiesterase 4 inhibitor Food and Drug Administration (FDA)-approved as treatment to reduce the risk of chronic obstructive pulmonary disease (COPD) exacerbations in patients with severe COPD associated with chronic bronchitis and a history of exacerbations. The specific mechanism by which roflumilast exerts its therapeutic action is not well defined, but it is believed to be related to the effects of increased intracellular cyclic-3',5'-adenosine monophosphate levels in lung cells that results from the agent's inhibitory action.[1]

According to treatment guidelines, inhaled bronchodilators are preferred for the management of COPD and choice of agent should be based on availability and individual response in terms of symptom relief and side effects.[2,3] Currently, treatment guidelines acknowledge clinical trials showing improvement in FEV_1 and reduction in the frequency of exacerbations, but do not address its role in the management of COPD. However, based on the data from clinical trials, it appears that this agent will primarily be used as an add-on therapy in patients who are refractory to standard first line COPD maintenance therapy. Roflumilast has been evaluated in several placebo-controlled clinical trials and overall, results demonstrate that treatment with roflumilast significantly reduces exacerbations and improves lung function in patients with moderate to severe COPD.[6-12]

In April of 2010, the FDA Advisory Committee voted 10 to five against the use of roflumilast. At that time one of their concerns was that the agent was associated with too many adverse effects to offset what the FDA had referred to as a "modest" increase in lung function.[4] Clinical trial data suggests that roflumilast is associated with gastrointestinal and central nervous system adverse events, and in addition, use of this agent has been associated with psychiatric adverse events (including insomnia, anxiety, depression, suicidal ideation and behavior and completed suicide) and weight loss.[1,6-12]

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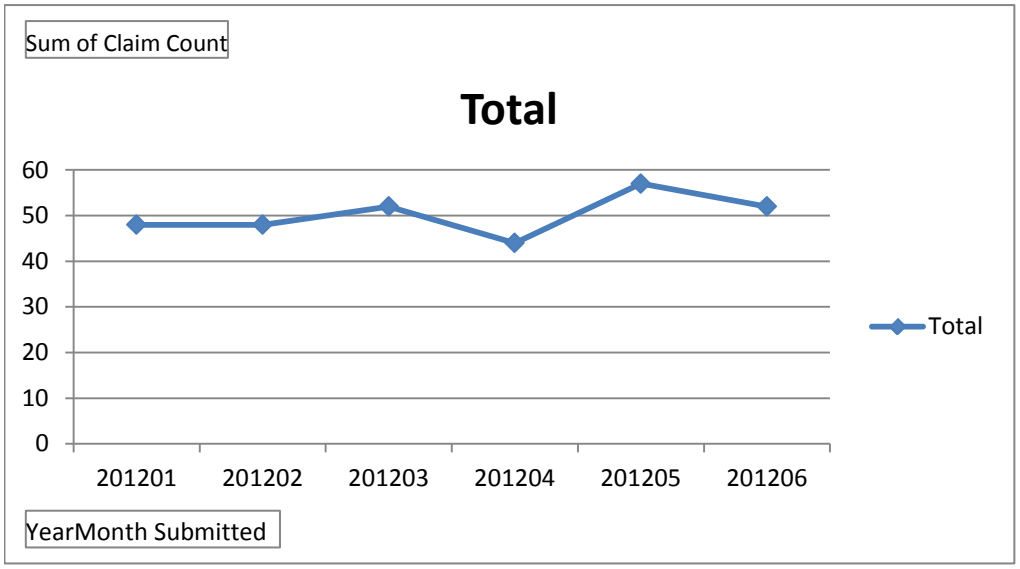
2012 Q1 and Q2 Daliresp Utilization

YearMonth Submitted	Drug Label Name	Claim Count	Sbm Qty Dispense	Sbm Days Supply	App Dispensing	App Total Amount
201201	DALIRESP TAB 500MCG	48	1,352	1,367	$ 199.92	$ 6,198.22
201202	DALIRESP TAB 500MCG	48	1,441	1,441	$ 209.44	$ 6,975.93
201203	DALIRESP TAB 500MCG	52	1,560	1,560	$ 199.92	$ 7,328.86
201204	DALIRESP TAB 500MCG	44	1,325	1,328	$ 166.60	$ 6,080.11
201205	DALIRESP TAB 500MCG	57	1,669	1,681	$ 228.48	$ 8,344.30
201206	DALIRESP TAB 500MCG	52	1,445	1,445	$ 233.24	$ 8,071.22



DIVISION OF HEALTH CARE FINANCING AND POLICY
NEVADA MEDICAID
DRUG USE REVIEW (DUR) BOARD
PROPOSED PRIOR AUTHORIZATION CRITERIA

Daliresp® (roflumilast) is a covered benefit of Nevada Medicaid for recipients who meet the criteria for coverage.

1. Coverage and Limitations:
Authorization will be given if the following criteria are met and documented:

a. The recipient has a diagnosis of severe Chronic Obstructive Pulmonary Disease (COPD) associated with chronic bronchitis.
AND
b. The recipient has a history of COPD exacerbations.
AND
c. The recipient has experienced an inadequate response, adverse event or has a contraindication to a long-acting anticholinergic agent.
AND
d. The recipient has experienced an inadequate response, adverse event or has a contraindication to a long-acting β agonist.
AND
e. The recipient has experienced an inadequate response, adverse event or has a contraindication to an inhaled corticosteroid.

2. PA Guidelines:
Prior Authorization approval will be for 1 year.

3. Quantity Limitations:
30 tablets per rolling 25 days