Therapeutic Class Overview
Phosphodiesterase-4 inhibitor for COPD

INTRODUCTION

- Chronic obstructive pulmonary disease (COPD) is characterized by airflow limitation that is persistent and usually progressive. There are several pathologic mechanisms underlying the airflow limitation, including airway inflammation and fibrosis, luminal plugs, increased airway resistance, parenchymal destruction, loss of alveolar attachments, and decrease of elastic recoil. Exacerbations and comorbidities contribute to the severity of COPD (*Global Initiative for Chronic Obstructive Lung Disease [GOLD] 2018).*
- COPD affects more than 5% of the adult population and is the third leading cause of death in the United States. In addition, COPD is the twelfth leading cause of morbidity in the United States (*Qaseem et al 2011*).
- Cigarette smoking is a primary risk factor for COPD. Approximately 85 to 90% of COPD cases are caused by smoking. Other risk factors include heredity, air pollution exposure, second-hand smoke, occupational dust and chemicals, and a history of childhood respiratory infections (*American Lung Association [ALA] 2019*).
- Pharmacologic therapy for COPD can reduce symptoms, reduce the frequency and severity of exacerbations, and improve patients' health status and exercise tolerance. There is no conclusive evidence that COPD medications modify the long-term decline in lung function characteristic of COPD (*GOLD 2018*).
- Daliresp (roflumilast) is an oral selective phosphodiesterase (PDE)-4 inhibitor that is Food and Drug Administration (FDA)-approved to reduce the risk of COPD exacerbations in patients with severe COPD associated with chronic bronchitis and a history of exacerbations. Daliresp is not a bronchodilator and is not indicated for the relief of acute bronchospasm.
- The GOLD guidelines state that roflumilast is an alternative (not first-choice) addition to the treatment regimen of selected patients who are not adequately controlled by their current therapy (*GOLD 2018*).
- Roflumilast is the only FDA-approved medication in the PDE-4 inhibitor category with a respiratory indication, and thus the only medication included in this review.
- Medispan class: Anti-asthmatic and Bronchodilator agents, Selective PDE-4 Inhibitors

Table 1. Medications Included Within Class Review

Drug	Generic Availability
Daliresp (roflumilast)	-*

* Generic roflumilast has been FDA approved but is not yet commercially available
(*Drugs@FDA 2019, Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations 2019*)

INDICATIONS

- Roflumilast is indicated as a treatment to reduce the risk of COPD exacerbations in patients with severe COPD associated with chronic bronchitis and a history of exacerbations.
  - Limitations of use:
    - Roflumilast is not a bronchodilator and is not indicated for the relief of acute bronchospasm.
    - Roflumilast 250 mcg is a starting dose used only for the first 4 weeks of treatment and is not the effective (therapeutic) dose.

(*Daliresp prescribing information 2018*)

- Information on indications, mechanism of action, pharmacokinetics, dosing, and safety has been obtained from the prescribing information for the individual products, except where noted otherwise.

CLINICAL EFFICACY SUMMARY

- Roflumilast has been evaluated in a number of placebo-controlled clinical trials. In some trials, concomitant treatment with a long-acting bronchodilator was permitted or required (in agreement with the GOLD guidelines) (*Bateman et al 2011, Calverley et al 2009, Fabbri et al 2009*). In other studies, concurrent therapy with only short-acting bronchodilators

with or without inhaled corticosteroids (ICS) was permitted (*Calverley et al 2007, Lee et al 2011, O'Donnell et al 2012, Rabe et al 2005, Rennard et al 2011*). Roflumilast has not been directly compared to other active agents for the treatment of COPD.

- In a trial conducted by *Rabe et al*, 1411 patients with moderate to severe COPD were randomized to treatment with roflumilast 250 or 500 mcg/day or placebo for 6 months. Concurrent COPD medications allowed were short-acting β-agonists (SABAs) as rescue therapy and short-acting anticholinergics at a constant daily dose. After 6 months, patients treated with roflumilast achieved significant improvements in post-bronchodilator forced expiratory volume in 1 second (FEV_1) compared to baseline ($p < 0.05$ for both doses) and compared to 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, roflumilast was associated with significant reductions in acute COPD exacerbations compared to treatment with placebo ($p = 0.0029$); the greatest effect was a 34% reduction with the 500 mcg dose compared to placebo (*Rabe et al 2005*).
- In another placebo-controlled trial conducted by *Calverley et al*, patients with moderate to severe COPD were randomized to roflumilast 500 mcg daily or placebo for 1 year. In this trial, concurrent COPD medications allowed were SABA as rescue therapy, short-acting anticholinergics, and ICS (≤ 2000 mcg beclomethasone or equivalent). Again, patients treated with roflumilast achieved significant improvements in post-bronchodilator FEV_1 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 more frequent in GOLD Stage IV COPD patients. 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 ($p = 0.086$) (*Calverley et al 2007*).
- *Rennard et al* pooled the results from *Calverley et al* with an identical, 1-year, placebo-controlled trial, both of which were inconclusive regarding the effect of roflumilast on exacerbations. Improvements in pre- and post-bronchodilator FEV_1, the primary and secondary endpoint, were again significantly greater among roflumilast-treated patients compared to placebo-treated patients. In the pooled analysis, treatment with roflumilast was associated with a 14.3% lower rate (0.52 vs 0.61 per year) of moderate to severe exacerbations (co-primary endpoint) compared to treatment with placebo ($p = 0.026$) (*Rennard et al 2011*).
- Two additional, identical, 1-year, placebo-controlled trials conducted by *Calverley et al* evaluated 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. These trials allowed concurrent use of long-acting β-agonists (LABAs), in addition to SABAs as rescue therapy and short-acting anticholinergics. At the end of 1 year, pooled analysis revealed that patients treated with roflumilast achieved significant improvements in pre-bronchodilator FEV_1 ($p < 0.0001$) and had a significantly lower rate of moderate or severe acute exacerbations (relative risk [RR], 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; $p = 0.5452$) (*Calverley et al 2009*).
- A similar 12-week study compared roflumilast 500 mcg daily to placebo in 411 Asian patients with COPD. Patients were allowed salbutamol as rescue medication and short-acting anticholinergics at a constant daily dosage; however, other medications including LABAs and long-acting anticholinergics were not allowed. Similar to other trials, the primary outcome, change in post-bronchodilator FEV_1, was significantly improved in the roflumilast group (+52 mL, 95% CI, 13 to 91) compared to the placebo group (-27 mL, 95% CI, -66 to 12). No improvement in the secondary outcome of COPD exacerbations was noted in the roflumilast group compared to the placebo group; however, the study was not powered to detect these differences (*Lee et al 2011*).
- A 24-week study, also in Asian patients, compared roflumilast 500 mcg daily to placebo in 626 patients with COPD. Patients were permitted to continue taking fixed combinations of ICS/LABA, or short- or long-acting muscarinic antagonists (LAMA) at a stable dose, as well as rescue medication (product and dose not specified). Results demonstrated an improvement in the primary endpoint, change in FEV_1, with an increase in the roflumilast group (0.049 L; 95% CI, 0.032 to 0.066) and a decrease in the placebo group (-0.022 L; 95% CI, -0.039 to -0.005). The difference of 0.071 L was statistically significant ($p < 0.0001$). Other lung function endpoints were also significantly improved with

roflumilast. However, no improvement in several secondary endpoints, including the exacerbation rate, use of rescue medication, or TDI score, was observed (*Zheng et al 2014*).

- *Bateman et al* reported results of 2 double-blind, multicenter, randomized controlled trials (RCTs) comparing roflumilast to placebo in patients with COPD. Concomitant respiratory medications permitted during the trial were SABAs as rescue medication, LABAs, and short-acting anticholinergics at stable doses. Results demonstrated that roflumilast led to improvements in pre-bronchodilator and post-bronchodilator FEV_1, as well as the rate of exacerbations per year. The reduction in exacerbations was similar in patients with and without concomitant LABA use (*Bateman et al 2011*).
- A study conducted by *O'Donnell et al* evaluated the effects of roflumilast on airway physiology during rest and exercise in 250 patients with COPD in a 12-week, placebo-controlled trial. Patients were allowed salbutamol as rescue medication, ipratropium at a constant daily dosage, and ICS at a constant daily dosage; other medications were not permitted. Results demonstrated no significant treatment difference in the primary endpoint, exercise endurance time. For secondary endpoints, small changes in airway function were observed, including those for pre- and post-bronchodilator FEV_1 and FEV_1/forced vital capacity (FVC). Additionally, small improvements in selected physiologic endpoints were noted during exercise, including ventilation at peak exercise and arterial oxygen saturation. The clinical significance of these physiologic changes requires further study (*O'Donnell et al 2012*).
- *Fabbri et al* reported results of 2 double-blind, multicenter, placebo-controlled trials. In Trial 1 (n = 935), roflumilast 500 mcg daily was given concomitantly with salmeterol, and in Trial 2 (n = 744), it was given concomitantly with tiotropium. Both trials demonstrated improvements in pre-bronchodilator and post-bronchodilator FEV_1, and post-bronchodilator FVC with roflumilast. However, the rate of mild, moderate, or severe COPD exacerbations was not significantly reduced with roflumilast in either trial (*Fabbri et al 2009*).
- *Martinez et al* reported results of a double-blind, multicenter, placebo-controlled trial (N = 1945) that enrolled COPD patients with severe airflow limitation (FEV_1/FVC < 0.7 and post-bronchodilator $FEV_1 \leq 50\%$ predicted) and a history of ≥ 2 exacerbations in the previous year. Patients must have been taking a combination ICS/LABA for ≥ 12 months with a stable dose for ≥ 3 months. Concomitant tiotropium was allowed but not required. Patients were randomized to receive roflumilast 500 mcg daily or placebo for 52 weeks. The primary endpoint, the rate of moderate-to-severe COPD exacerbations per patient per year, was 0.805 with roflumilast and 0.927 with placebo (RR, 0.868; 95% CI, 0.753 to 1.002; p = 0.0529) according to the Poisson regression analysis. Results were similar using a different type of statistical analysis, negative binomial regression, and with this method results were statistically significant (p = 0.0424). Roflumilast reduced the incidence of severe exacerbations (RR, 0.757; p = 0.0175) and exacerbations necessitating hospital admission (RR, 0.761; p = 0.0209). Roflumilast treatment also improved FEV_1 and FVC, with differences from placebo of 56 mL and 92 mL, respectively (p < 0.0001 for both comparisons). Although results on the primary endpoint were of borderline statistical significance, this study demonstrates some benefit with roflumilast in this high-risk group of patients who were concomitantly treated with ICS/LABA (*Martinez et al 2015*).
- A meta-analysis reported pooled data from 4 placebo-controlled RCTs (total N = 5595) to evaluate the effects of roflumilast on dyspnea in patients with moderate to very severe COPD. The meta-analysis demonstrated that at week 52, roflumilast significantly improved the mean TDI focal score, with a difference of 0.327 units (95% CI, 0.166 to 0.488; p < 0.0001). This mean change was less than the minimum clinically important difference of 1 unit. However, the authors report that the percentage of TDI responders (≥ 1 unit) was greater in patients treated with roflumilast (39%) than in patients treated with placebo (33.9%) (p < 0.01) (*Rennard et al 2014*).
- A meta-analysis of 26 RCTs evaluated the roles of LABA, long-acting anticholinergics, ICS, and roflumilast therapy, both alone and in combination, on the rate of COPD exacerbations. The primary endpoint was reported in terms of an absolute treatment effect, expressed as mean exacerbations experienced per patient per year. A regimen composed of roflumilast, LABA, long-acting anticholinergics, and an ICS 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, 0.89 to 1.14). A combination of long-acting anticholinergic, LABA and ICS therapies was associated with a treatment effect of 0.63 (95% CI, 0.54 to 0.73) (*Mills et al 2011*). A smaller meta-analysis of 8 clinical trials found that roflumilast reduced the overall rate of exacerbations compared to placebo (-0.41 events/patient-year; 95% CI, -0.72 to -0.11) (*Oba and Lone 2013*).
- A Cochrane systematic review reported a significant improvement in pulmonary function with roflumilast therapy. The review of PDE-4 inhibitors for COPD found small improvements in quality of life and COPD-related symptoms, but not exercise tolerance. An evaluation of 23 trials (N = 19,948) showed that treatment with PDE-4 inhibitors was associated with a reduced likelihood of COPD exacerbation (odds ratio [OR] 0.78; 95% CI, 0.73 to 0.83). Roflumilast was associated with diarrhea, weight loss, increased insomnia, and depressive mood symptoms (*Chong et al 2017*).

- In the 52-week, multicenter, randomized, double-blind, placebo-controlled RE^{2}SPOND trial, patients with severe to very severe COPD, chronic bronchitis, 2 or more exacerbations in the previous year, and on standard ICS/LABA with or without LAMA therapy were randomized to receive roflumilast (n = 1178) or placebo (n = 1176). The primary endpoint, reduction in moderate and/or severe exacerbations, was not found to be statistically significant (95% CI, 0.81 to 1.04; p = 0.163). Roflumilast was, however, shown to improve FEV_1 from baseline (p < 0.0001) as similarly demonstrated by previous studies. Post hoc analysis demonstrated a statistically significant reduction of moderate to severe exacerbations in the subset of patients with a history of higher exacerbation burden (> 3 exacerbations per year) and hospitalization, suggesting roflumilast may have a place in therapy for this demographic (*Martinez et al 2016*).
- The beneficial effects of roflumilast have been reported to be greater in patients with a prior history of hospitalization for an acute exacerbation (*GOLD 2018, Rabe et al 2017*).
- There has been no study directly comparing roflumilast with an ICS (*GOLD 2018*).

CLINICAL GUIDELINES

- Treatment guidelines for COPD include:
  - Global Initiative for Chronic Obstructive Lung Disease (GOLD): Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Pulmonary Disease (*GOLD 2018*)
  - Diagnosis and Management of Stable Chronic Obstructive Pulmonary Disease: A Clinical Practice Guideline Update from the American College of Physicians (ACP), American College of Chest Physicians (ACCP), American Thoracic Society (ATS), and European Respiratory Society (ERS) (*Qaseem et al 2011*)
  - Institute for Clinical Systems Improvement (ICSI): Diagnosis and Management of Chronic Obstructive Pulmonary Disease (COPD) (*Anderson et al 2016*)
  - American College of Chest Physicians (ACCP) and Canadian Thoracic Society (CTS): Prevention of Acute Exacerbations of COPD (*Criner et al 2015*)
- In the GOLD guidelines, treatment strategies are based on a combination of a patient's symptoms and impairment as determined by the COPD Assessment Test (CAT) or Modified British Medical Research Council (mMRC) Questionnaire, spirometry results, and exacerbation history. The guidelines note that in patients with chronic bronchitis, severe to very severe COPD, and a history of exacerbations, roflumilast may be added to therapy to improve lung function and reduce moderate and severe exacerbations. Roflumilast may also improve lung function and reduce exacerbations in patients not well-controlled on fixed-dose LABA/ICS combinations. First-choice recommendations in the GOLD guidelines are as follows:
  - **Group A** (0 to 1 exacerbations not leading to hospital admission, CAT < 10/mMRC 0 to 1): short or long-acting bronchodilator as needed
  - **Group B** (0 to 1 exacerbations not leading to hospital admission, CAT ≥ 10/mMRC ≥ 2): long-acting bronchodilator (LABA or LAMA); may progress to LAMA + LABA if symptoms persist
  - **Group C** (≥ 2 exacerbations or ≥ 1 leading to hospital admission, CAT < 10/mMRC 0 to 1): LAMA; may progress to LAMA + LABA (preferred) or LABA + ICS for persistent exacerbations
  - **Group D** (≥ 2 exacerbations or ≥ 1 leading to hospital admission, CAT ≥ 10/mMRC ≥ 2): LAMA + LABA; may progress to LAMA + LABA + ICS for persistent exacerbations; if exacerbations persist, may add roflumilast for patients with an FEV_1 < 50% predicted and chronic bronchitis, or a macrolide for former smokers (*GOLD 2018*)
- The ACP/ACCP/ATS/ERS guidelines do not include information or recommendations about roflumilast. Key recommendations in this guideline include:
  - For symptomatic patients with COPD and FEV_1 < 60% predicted, it is recommended that clinicians prescribe monotherapy using either long-acting inhaled anticholinergics or LABAs (strong recommendation, moderate-quality evidence). For this group of patients, it is suggested that clinicians may administer combination inhaled therapies (long-acting inhaled anticholinergics, LABAs, or ICS) (weak recommendation, moderate-quality evidence) (*Qaseem et al 2011*).
- The ICSI guidelines recommend against roflumilast in patients with confirmed, stable COPD in primary care without consultation with a pulmonologist. The guidelines note that roflumilast leads to a modest improvement in airflow and a reduction in exacerbations, and patients most likely to benefit are those with a history of frequent exacerbations, chronic bronchitis, cough, and sputum production (*Anderson et al 2016*).
- The ACCP/CTS guidelines suggest the use of roflumilast to prevent acute exacerbations of COPD in patients with moderate to severe COPD with chronic bronchitis and a history of at least 1 exacerbation in the previous year (*Criner et al 2015*).

SAFETY SUMMARY

- Roflumilast is contraindicated in moderate to severe liver impairment (Child-Pugh B or C).
- Warnings and precautions include the following:
  - Roflumilast is not a bronchodilator and should not be used for the relief of acute bronchospasm.
  - Psychiatric events including suicidality: Treatment is associated with an increase in psychiatric adverse reactions, including insomnia, anxiety, and depression. Instances of suicidal ideation and behavior, including completed suicide, have been observed in clinical trials with roflumilast in patients with and without a history of depression.
    - Prescribers should carefully weigh risks and benefits of treatment with roflumilast before using in patients with a history of depression and/or suicidal thoughts or behavior. Patients, caregivers, and families should be advised of the need to be alert for psychiatric adverse events.
    - An analysis of FDA Adverse Event Reporting System (FAERS) reports conducted by the Institute for Safe Medication Practices (ISMP) and published in April 2017 identified a confirming signal for suicidal and self-injurious behaviors (*ISMP 2017*).
  - Weight decrease: Weight loss may occur with roflumilast use.
    - Patients should have their weight monitored regularly. If unexplained or clinically significant weight loss occurs, weight loss should be evaluated and discontinuation of roflumilast should be considered.
- Drug Interactions include the following:
  - Strong cytochrome P (CYP) 450 enzyme inducers (eg, carbamazepine, phenobarbital, phenytoin, rifampicin) decrease systemic exposure to roflumilast and may reduce its therapeutic effectiveness; concurrent use is not recommended.
  - Concurrent administration of roflumilast with CYP3A4 inhibitors or dual inhibitors that inhibit CYP3A4 and 1A2 simultaneously (eg, cimetidine, enoxacin [not available in the U.S.], erythromycin, fluvoxamine, ketoconazole) may increase roflumilast systemic exposure and may result in increased adverse reactions. The risk of concurrent use should be weighed carefully against benefit.
  - The concurrent administration of roflumilast and oral contraceptives containing gestodene (not available in U.S.) and ethinyl estradiol may increase roflumilast systemic exposure and may result in increased adverse effects. The risk of such concurrent use should be weighed carefully against benefit.
- Common adverse events (incidence ≥ 2%) include diarrhea, weight loss, headache, nausea, back pain, insomnia, influenza, dizziness, and decreased appetite.

DOSING AND ADMINISTRATION

Table 2. Dosing and Administration

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
Daliresp (roflumilast)	Tablets	Oral	Once daily	May be taken with or without food.

See the current prescribing information for full details

CONCLUSION

- Roflumilast is a once-daily, orally administered PDE-4 inhibitor indicated as a treatment to reduce the risk of COPD exacerbations in patients with severe COPD associated with chronic bronchitis and a history of exacerbations. The agent is not a bronchodilator and is not indicated for the relief of acute bronchospasm.
- Some (but not all) RCTs have demonstrated the ability of roflumilast to reduce exacerbations in patients at high risk of exacerbations (*Bateman et al 2011, Calverley et al 2009, Martinez et al 2015*). Roflumilast does not replace bronchodilators, but it is used adjunctively in appropriate patients.
- The beneficial effects of roflumilast have been reported to be greater in patients with a prior history of hospitalization for an acute exacerbation (*GOLD 2018, Rabe et al 2017*).
- Roflumilast is generally well tolerated, with the most frequent adverse events being diarrhea, nausea, and headache. Roflumilast has also been associated with psychiatric events including suicidality. Roflumilast should be used with caution in patients with depression. Potential drug interactions and weight loss are also considerations.

- The GOLD treatment guideline positions PDE-4 inhibitors as additional therapeutic agents for patients with COPD exacerbations despite long-acting bronchodilator therapy, particularly if they have experienced at least 1 hospitalization for an exacerbation in the previous year. It is acknowledged that PDE-4 inhibitors have more adverse events than inhaled medications for COPD including nausea, reduced appetite, weight loss, abdominal pain, diarrhea, sleep disturbance, and headache; however, adverse events seem to occur early and diminish over time (*GOLD 2018*). The ICSI guideline states that the exact place in treatment for roflumilast is not defined (*Anderson et al 2016*). A guideline from ACCP/CTS suggests the use of roflumilast to prevent acute exacerbations of COPD in patients with moderate to severe COPD with chronic bronchitis and a history of at least 1 exacerbation in the previous year (*Criner et al 2015*).
- Although not a first-line agent, roflumilast is unique because it is the only medication in the PDE-4 inhibitor class indicated for management of COPD. It is included in clinical guidelines and has a role in the treatment of appropriately selected patients with COPD.

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