

**Brand Name:** <sup>1, 2,3,4,5</sup>

Daliresp™

**Generic Name:** <sup>1, 2,3,4,5</sup>

roflumilast

**Manufacturer:** <sup>3, 4, 5</sup>

Forest Pharmaceuticals, Inc.

**Drug Class:** <sup>1, 2,4,5,7</sup>

Second-Generation Phosphodiesterase-4 (PDE 4) inhibitor

**Labeled Uses:** <sup>1, 2,3,4,5</sup>

prophylaxis against chronic obstructive pulmonary disease (COPD) exacerbations in patients with severe COPD associated with chronic bronchitis and a history of exacerbations

**Mechanism of Action:** <sup>2, 3,4,5,7</sup>

Roflumilast and its active N-oxide metabolite selectively and competitively inhibit phosphodiesterase-4 (PDE4). PDE4 is a major cyclic-3' 5'-adenosine monophosphate [cyclic AMP]-metabolizing enzyme in lung tissue and is mainly expressed in inflammatory cells. Inhibition of PDE4 leads to intracellular accumulation of cyclic AMP (cAMP) and downregulation of inflammatory cell activity. The anti-inflammatory effects that follow may include suppression of cytokine release, inhibition of lung infiltration by neutrophils and other leukocytes, and attenuation of pulmonary remodeling and mucociliary malfunction.

**Pharmacokinetics:** <sup>1, 2,3,4,5</sup>

**Absorption:**

T <sub>max</sub> *	~1 hour (Ranges from 0.5-2 hours, delayed by food) ~8 hours for the N-oxide metabolite (Ranges from 4-13 hours)
V <sub>d</sub>	2.9 L/kg
t <sub>½</sub>	17 hours 30 hours for the N-oxide metabolite
Clearance	9.6 L/h
Protein binding	99% 97% for the N-oxide metabolite
Bioavailability	~80%

\*Food delays roflumilast T<sub>max</sub> by 1 hour and reduces its C<sub>max</sub> ~40%, but does not affect total PDE4 inhibition; C<sub>max</sub> and T<sub>max</sub> of roflumilast N-oxide (active metabolite) are unaffected by food.

### **Metabolism:**

Roflumilast is extensively metabolized via Phase I (cytochrome P450) and Phase II (conjugation) reactions. A major step in roflumilast metabolism is the N-oxidation of roflumilast to roflumilast N-oxide by CYP3A4 and CYP1A2. This N-oxide metabolite is the only major metabolite observed in the plasma of humans. Together, roflumilast and roflumilast N-oxide account for the majority (87.5%) of total dose administered in plasma. The activity of this metabolite is only slightly less than the parent compound and both contribute to pharmacologic effects.

### **Elimination:**

Conjugated metabolites such as roflumilast N-oxide glucuronide and 4-amino-3,5-dichloropyridine N-oxide are detected in urine. Roflumilast is not detectable, while roflumilast N-oxide is only a trace metabolite (< 1%).

### **Efficacy:**<sup>6, 7, 8</sup>

**Caverley PMA, et. Al. Roflumilast in symptomatic chronic obstructive pulmonary disease: two randomised clinical trials. Lancet. 2009; 374:685-94.**

- **Study Design:** This study described two placebo-controlled, multicenter, double-blind, randomized clinical trials.
- **Description of Study:**
  - **Objective:** to investigate whether roflumilast would reduce the frequency of exacerbations requiring corticosteroids in patients with COPD
  - **Methods:** Patients with COPD older than 40 years, with severe airflow limitation, bronchitic symptoms, and a history of exacerbations were randomly assigned to treatment for 52 weeks. They were stratified according to smoking status and treatment with long-acting  $\beta_2$  agonists. 1537 total patients received roflumilast 500  $\mu\text{g}$  per day (766 for trial M2-124 and 773 for trial M2-125) and 1554 total patients received placebo (759 for trial M2-124 and 798 for trial M2-125). Patients could use short-acting  $\beta_2$  agonists as needed and could continue treatment with long-acting  $\beta_2$  agonists or short-acting anticholinergic drugs.
  - **Endpoints:** Primary endpoints were change in pre-bronchodilator forced expiratory volume in 1 second ( $\text{FEV}_1$ ) and the rate of COPD exacerbations. Key secondary outcomes included post-bronchodilator  $\text{FEV}_1$ , time to death from any cause, natural log-transformed C-reactive protein concentration and TDI focal score (during treatment).
  - **Outcome Results:** In a pooled analysis, pre-bronchodilator  $\text{FEV}_1$  increased by 48 ml with roflumilast compared with placebo ( $p < 0.0001$ ). The rate of exacerbations that were moderate or severe per patient per year was 1.14 with roflumilast and 1.37 with placebo (reduction 17% [95% CI 8-25],  $p < 0.0003$ ). A range of predicted adverse events occurred with roflumilast (insomnia, nausea, headache, and diarrhea) and were most evident in the first 4-12 weeks of treatment.

- **Limitations:** This study recruited patients that were likely to adhere to treatment, therefore, caution is needed if findings are to be generalized to the general clinical population. Conflicts of interest included involvement of the drug company with the study. Some results were shown to be statistically significant; however, clinical significance is yet to be determined.
- **Conclusion:** Roflumilast appears to improve lung function and may reduce the frequency of exacerbations in patients with bronchitic symptoms and airflow limitation. Further studies are needed to test the effectiveness of inhaled corticosteroids alone or in combination with roflumilast.

**Fabbri LM, et. Al. Roflumilast in moderate-to-severe chronic obstructive pulmonary disease treated with long-acting bronchodilators: two randomized clinical trials. Lancet. 2009; 374:695-703.**

- **Study Design:** This study described two double-blind, multicenter, multinational, placebo-controlled, parallel group, randomized clinical trials.
- **Description of Study:**
  - **Objective:** to assess whether roflumilast provides benefit to patients with COPD who are regularly treated with long-acting inhaled bronchodilators
  - **Methods:** After a 4-week run-in, patients older than 40 years with moderate-to-severe COPD were randomly assigned to oral roflumilast 500 µg or placebo once daily for 24 weeks, in addition to salmeterol (M2-127 study) or tiotropium (M2-128 study). In the salmeterol plus roflumilast trial, 466 patients were assigned to and treated with roflumilast and 467 with placebo; in the tiotropium plus roflumilast trial, 371 patients were assigned to and treated with roflumilast and 372 with placebo.
  - **Endpoints:** The primary endpoint for both trials was change in mean pre-bronchodilator forced expiratory volume in 1 second (FEV<sub>1</sub>) from baseline to each post-randomization visit. Secondary endpoints included post-bronchodilator FEV<sub>1</sub> and forced vital capacity (FVC), rate of COPD exacerbations, and use of rescue medications. At each visit, safety assessments included inquiries about the occurrence of adverse events.
  - **Outcome Results:** Compared with placebo, roflumilast consistently improved mean pre-bronchodilator FEV<sub>1</sub> by 49 ml (p<0.0001) in patients treated with salmeterol, and 80 ml (p<0.0001) in those treated with tiotropium. Results for the change in the mean pre-bronchodilator FEV<sub>1</sub> (ml) from baseline was a difference of 49, p<0.0001 for the salmeterol trial and a difference of 80, p<0.0001 for the tiotropium trial. Change in post-bronchodilator FEV<sub>1</sub> (ml) was significant for each roflumilast group compared to placebo. Roflumilast had a variable effect on symptomatic outcomes such as respiratory symptoms, use of rescue medications, and exacerbations in both trials. In general, the beneficial effect of roflumilast on some patient-reported outcomes was more pronounced in the tiotropium plus roflumilast trial than in the salmeterol plus roflumilast trial.

- **Adverse Events:** Diarrhea, nausea, and weight loss were the most common treatment-related adverse events.
- **Limitations:** Conflicts of interest included involvement of the drug company with the study. Inclusion criteria, including smoking history and absence of inhaled glucocorticosteroids, may limit extrapolation to patient populations. Patients recruited to the tiotropium plus roflumilast trial were more symptomatic at baseline which might increase the chance of detecting an effect of roflumilast on patient-reported outcomes such as dyspnea and use of as-needed medications. Some results were shown to be statistically significant; however, clinical significance is yet to be determined.
- **Conclusion:** Roflumilast may improve lung function in patients with moderate-to-severe COPD who are already being treated with long-acting bronchodilators (such as salmeterol or tiotropium), and could become an important, concomitant treatment for these patients. However, these beneficial effects are also associated with some adverse effects of roflumilast, and clinical significance is still unknown. Additional studies are needed to investigate the mechanism of improvement in lung function provided by roflumilast in patients given long-acting bronchodilators. Whether roflumilast would maintain this additive effect in patients concomitantly treated with long-acting bronchodilators and glucocorticosteroids remains to be established. Further studies are needed to investigate whether roflumilast has an additive effect on exacerbations when combined with long-acting bronchodilators or used in combination of inhaled bronchodilators and glucocorticosteroids.

**Calverley PMA, et. Al. Effect of 1-Year Treatment with Roflumilast in Severe Chronic Obstructive Pulmonary Disease. Am J Respir Crit Care Med. Vol 176; 2007:154-61.**

- **Study Design:** This study described a double-blind, multicenter, multinational, placebo-controlled, parallel group, randomized clinical trial.
- **Description of Study:**
  - **Objective:** to determine whether roflumilast improved lung function and decreased exacerbation frequency over 1 year in patients with stable COPD
  - **Methods:** 1,513 patients with a mean post-bronchodilator FEV<sub>1</sub> 41% predicted were recruited into the study. 760 received oral 500 µg roflumilast and 753 received placebo once daily. The study had a 4-week run-in period before patients were randomized to treatment for 52 weeks.
  - **Endpoints:** The primary efficacy variables were the change from baseline in post-bronchodilator FEV<sub>1</sub> and the number of moderate or severe exacerbations per patient per year. Other efficacy variables included change from baseline in pre-bronchodilator FEV<sub>1</sub> and number of moderate or severe COPD exacerbations requiring systemic corticosteroid treatment per patient per year.
  - **Outcome Results:** Post-bronchodilator FEV<sub>1</sub> increased by 39ml with roflumilast compared with placebo by 52 weeks (p=0.001). The mean exacerbation rate was low and comparable in both treatment groups (0.86 vs. 0.92 exacerbations per patient per year for roflumilast and placebo respectively). The most common

adverse events related to roflumilast treatment were diarrhea, nausea, and headache, which usually subsided during continued treatment.

- **Limitations:** One year of treatment may be insufficient to assess the rate of decline in FEV<sub>1</sub> accurately, and larger, longer studies with roflumilast are required to determine if this is the case. Patients selected were poorly reversible to bronchodilator drugs, so the magnitude of the lung function change reported may be a conservative estimate of the benefit in a less-restricted population. Conflicts of interest included involvement of the drug company with the study. Some results were shown to be statistically significant; however, clinical significance is yet to be determined.
- **Conclusion:** Roflumilast produces a modest but statistically significant improvement in post-bronchodilator lung function in stable patients with stages III and IV COPD. Combining roflumilast with long-acting bronchodilators may provide an acceptable alternative to systemic or inhaled therapy with corticosteroids in patients with more severe COPD. How treatment benefits with roflumilast can be integrated into current therapeutic regimens remains to be established. Further trials are needed in patients with severe COPD who exacerbate frequently.

**Contraindications:** <sup>1, 2,3,4,5</sup>

**Moderate to severe hepatic disease (Child-Pugh B or C)**

- Clinical studies show increases in drug exposure and increases in the AUC and C<sub>max</sub> of roflumilast and its active metabolite roflumilast N-oxide.

**Precautions:** <sup>1, 2,3,4,5</sup>

**Breast-Feeding**

- Roflumilast should not be used by women who are breast-feeding.
- The drug and/or its metabolites are excreted into the milk of lactating rats and the manufacturer states that such excretion into human breast milk is probable.
- There are no human studies that have investigated effects of roflumilast on breast-fed infants.

**Pregnancy**

- Roflumilast is classified as an FDA pregnancy category C medication.
- No adequate and well controlled studies have been conducted in pregnant women. Animal studies have also demonstrated reproductive toxicity at doses greater than the human recommended dose.
- The manufacturer recommends that roflumilast not be used during labor and obstetric delivery because disrupted labor and delivery process has been noted in animal studies.

**Cancer**

- Avoid or discontinue use in patients with cancer, excluding basal cell carcinoma.
- Carcinogenicity has been noted in animal studies. Treatment resulted in dose-related, statistically significant increases in the incidence of undifferentiated

carcinomas of nasal epithelium in animal studies at doses approximately 11 times the maximum recommended high dose.

#### **Heart Failure**

- Avoid use in patients with congestive heart failure (NYHA III/IV).
- Use in this patient population was not studied in clinical trials.

#### **Infection/Immunosuppression**

- Avoid or discontinue use in patients with a severe acute infection, severe immunosuppression, or those receiving immunosuppressive therapy (excludes short-term systemic corticosteroid use for COPD exacerbation).

#### **Hypersensitivity**

- Avoid use in patients with allergies to roflumilast or any component of the formulation.

#### **Suicidal Ideation**

- Suicidal ideation and attempts may also occur more frequently in roflumilast treated patients.
- Avoid use in patients with a history of depression with suicidal behaviors.

#### **Other Warnings/Precautions**

- Roflumilast is not a bronchodilator and should not be used for the relief of acute bronchospasm or for use as monotherapy of COPD. Use only as adjunctive therapy to bronchodilator therapy.

#### **Adverse Effects:** <sup>1,2,3,4,</sup>

##### **>4%**

##### *Endocrine/Metabolic:*

Weight Loss 7-20%

##### *Gastrointestinal:*

Diarrhea 9.5-12%

Nausea 4.7-5%

##### *Neurologic:*

Headache 4.4-5%

##### **0-4%**

##### *Cardiovascular*

Supraventricular Arrhythmia 1%

##### *Gastrointestinal:*

Abdominal Pain 1-4%

Decreased Appetite 2.1-3%

Dyspepsia 1-2%

Gastritis 1-2%

Vomiting 1-2%

##### *Musculoskeletal:*

Back Pain 3-3.2%

Muscle Spasms 1-2%

Muscle Cramps 1-2%

*Neurologic:*

Dizziness 2.1-3%

Insomnia 2-3%

Tremor 1-2%

*Psychiatric:*

Anxiety 1-2%

Depression 1-2%

*Renal:*

Urinary Tract Infection 1-2%

*Respiratory:*

Influenza 2.8%

Rhinitis 1-2%

Sinusitis 1-2%

*Other:*

Fatigue 1%

Hypersensitivity <1%

**Drug Interactions:** <sup>1, 2,3,4,5</sup>

**Strong CYP3A4 Inducers: phenobarbital, carbamazepine, phenytoin, rifampin**

- Severity – Major – Not Recommended
- Significant reduction in systemic exposure to roflumilast is expected with these medications. Avoid combining strong CYP3A4 inducers with roflumilast.

**Strong CYP3A4 Inhibitors: erythromycin, ketoconazole, fluvoxamine**

- Severity – Moderate - Use with Caution
- Increased systemic exposure to roflumilast has been demonstrated in pharmacokinetic studies and increased adverse reactions may result from combining these medications with roflumilast.

**Inhibitors of CYP3A4 and CYP1A2: enoxacin and cimetidine**

- Severity – Moderate - Use with Caution
- Increased systemic exposure to roflumilast has been demonstrated in pharmacokinetic studies and increased adverse reactions may result from combining these medications with roflumilast.

**Oral Contraceptives containing gestodene and ethinyl estradiol**

- Severity - Moderate
- Combination of these medications with roflumilast has resulted in increased drug exposure to roflumilast in pharmacokinetic studies and may result in increased side effects.

**Conivaptan**

- Risk D - Consider Therapy Modification
- Taking this medication with roflumilast may increase the serum concentrations of roflumilast. Upon completion or discontinuation of conivaptan, allow at least 7 days before initiating therapy with drugs that are CYP3A4 substrates.

**Deferasirox**

- Taking this medication with roflumilast may decrease the serum concentrations of roflumilast.

**Immunosuppressants**

- Avoid combination with these medications because roflumilast may enhance the immunosuppressive effect of these medications.

**Dosing/Administration:** <sup>1, 2,3,4,5</sup>**Adult Dosing**

- Take 500 mcg by mouth once daily without regard to meals.

**Dosing in Neonates, Infants, Children, and Adolescents**

- This medication is not recommended for use in patients <18 years of age.
- The safety and efficacy of roflumilast has not been established in this population

**Hepatic Impairment Dosing**

- Caution is recommended when using this medication in patients with mild hepatic impairment (Child-Pugh class A), but specific recommendations for roflumilast dosage adjustment are not available.
- Use is not recommended in patients with moderate to severe hepatic failure (Child-Pugh class B or C).

**Patients with Renal Impairment Dosing**

- No dosage adjustment is necessary for patients with renal impairment.

**Conclusion:** Roflumilast is a possible adjunct therapy for patients with chronic obstructive pulmonary disease (COPD). It may improve lung function and reduce the frequency of exacerbations in patients with bronchitic symptoms and airflow limitation. Statistical significance was seen with these outcomes, but clinical significance may be limited. Roflumilast appears to be safe to use with other COPD medications, however many potential interactions exist with CYP3A4 inducers and CYP1A2 and CYP3A4 inhibitors. The side effects of the drug appear to be minimal, with gastrointestinal effects (weight loss and diarrhea) being the most common. Further studies are needed to test the effectiveness of inhaled corticosteroids alone or in combination with roflumilast. More studies are also needed in patients with severe COPD who exacerbate frequently. How treatment benefits with roflumilast can be integrated into current therapeutic regimens remains to be established. However, roflumilast may benefit patients with COPD that are currently not controlled on other medications.



## **References:**

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