roflumilast (Daliresp®)

EOCCO POLICY

Policy Type: PA Pharmacy Coverage Policy: EOCCO105

Description

Roflumilast (Daliresp) is an oral phosphodiesterase 4 (PDE4) inhibitor that selectively inhibits a cyclic-AMP (cAMP) metabolism in the lung tissue.

Length of Authorization

- Initial: 12 months
- Renewal: 12 months

Quantity limits

Product Name	Indication	Dosage Form	Quantity Limit
generic roflumilast	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	250 mcg tablet	Initial month: 30 tablets/30 days*
		500 mcg tablet	30 tablets/30 days
roflumilast (Daliresp)		250 mcg tablet	Initial month: 30 tablets/30 days*
		500 mcg tablet	30 tablets/30 days

**Coverage of 250 mcg daily dose limited to one month for medication titration; quantity exceptions not allowed.*

Initial Evaluation

I. **Roflumilast (Daliresp**) may be considered medically necessary when the following criteria are met:
   A. Member is 18 years of age or older; **AND**
   B. Diagnosis of severe or very severe COPD (GOLD 3 or 4; FEV_1 < 50% predicted); **AND**
   C. Diagnosis of chronic bronchitis; **AND**
   D. Member has a history of at least one COPD exacerbation in the past year; **AND**
   E. Triple therapy with long-acting beta agonist (LABA), long-acting muscarinic antagonist (LAMA), and inhaled corticosteroid (ICS) has been ineffective, contraindicated, not tolerated or will be continued with roflumilast (Daliresp) [see appendix for examples]; **OR**
      1. Dual therapy with LABA and LAMA therapy has been ineffective, contraindicated, or not tolerated if eosinophil level is < 100 cells/uL; **AND**
   F. At least one long-acting bronchodilator therapy (LAMA and/or LABA) will be continued in combination with roflumilast (Daliresp); **AND**
   G. Request is for generic roflumilast (generic for Daliresp), unless member has a contraindication to generic product

II. Roflumilast (Daliresp) is considered not medically necessary when criteria above are not met and/or when used for:
   A. Roflumilast (Daliresp) daily dose of 250 mcg for longer than the one-month initiation period for tolerability. This has been deemed a subtherapeutic dose by the drug manufacturer and FDA.

III. Roflumilast (Daliresp) is considered investigational when used for all other conditions, including but not limited to:
   A. Pediatric COPD
   B. Asthma

Renewal Evaluation

I. Member has received a previous prior authorization approval for this agent through this health plan or has been established on therapy from a previous health plan; **AND**

II. Member is not continuing therapy based off being established on therapy through samples, manufacturer coupons, or otherwise. If they have, initial policy criteria must be met for the member to qualify for renewal evaluation through this health plan; **AND**

III. Provider attestation of one of the following:
   A. The member has exhibited stability or improvement in rate or severity of exacerbations or improvement in lung function; **OR**
   B. Continuation of therapy is medically necessary despite lack of benefit in exacerbations or lung function (documentation is required).

Supporting Evidence

I. Roflumilast (Daliresp) starting dose is 250 mcg per day to improve tolerability and reduce likelihood of discontinuation due to adverse effects; however, this dose is subtherapeutic. The 250 mcg tablets are administered once daily for four weeks; thereafter, 500 mcg daily is used for maintenance. A 250mcg daily maintenance or quantity exceptions to utilize two x 250 mcg tablets daily are not covered. The 500mcg tablet is administered once daily and has an extended half-life, eliminating the need for twice daily dosing. Additionally, the 500mcg tablet is more cost efficient.

II. Roflumilast (Daliresp) is indicated to reduce the risk of COPD exacerbations in patients with severe or very severe COPD associated with chronic bronchitis and have a history of exacerbations. It has only been evaluated in adults; safety and efficacy are unknown when used in pediatrics. COPD does not normally occur in children and rare cases may be due to genetic conditions; however, roflumilast (Daliresp) has unknown consequences in these settings.

III. Chronic bronchitis is defined as chronic productive cough for three months in each of two successive years in a patient whom other causes of chronic cough have been excluded.

IV. Effects of roflumilast (Daliresp) have been evaluated in nine phase 3 clinical trials and other supplemental studies. The majority of trials failed to show clinical improvement in lung function, exacerbation rate, survival, or quality of life in the general COPD population. Exploratory analyses of early clinical trials identified a subpopulation of patients that appeared to demonstrate a better response to roflumilast (Daliresp); those with severe COPD associated with chronic bronchitis that have a history of COPD exacerbations within the last year. Several clinical trials have demonstrated lack of clinical benefit of roflumilast (Daliresp) in an unselected patient population with COPD. Given the lack of benefit outside of the FDA-approved population coupled with specific safety concerns (e.g., psychiatric adverse effects including but not limited to suicide and suicidal ideation), coverage is limited to a narrow population.

V. The FDA-approval for roflumilast (Daliresp) is based on trials five and six of the clinical program that demonstrated a modest reduction in exacerbations vs. placebo and a statistically significant, but non-clinically significant, increase in FEV1. Patients were allowed to be on LABA or short-acting muscarinic antagonist (SAMA) therapy, and all patients had at least one recorded exacerbation requiring systemic corticosteroids or hospital admission within the previous year.

VI. A Cochrane Systematic Review of PDE4 inhibitors for COPD was conducted in 2020 to evaluate the extensive evidence for roflumilast (Daliresp) and other non FDA-approved therapies in this class. The conclusions of the review are as follows: PDE4 inhibitors in people with COPD may have additional but limited value and act independently of bronchodilators in patients with COPD. These therapies have a small benefit over placebo in reducing lung function or reducing likelihood of exacerbations. There is no known impact on quality of life or symptom control; however, there is cautious support for use and the identified place in therapy is as add-on therapy for patients with persistent symptoms or exacerbations despite optimal COPD management.

VII. The Global Initiative for Chronic Obstructive Lung Disease (GOLD) 2022 report stance: roflumilast (Daliresp) may reduce exacerbation rates in those with severe or very severe COPD with chronic bronchitis and a history of exacerbations – mirroring the FDA approved indication. It is noted that roflumilast (Daliresp) benefits may be greater in patients with a prior hospitalization for acute COPD exacerbation; however, it is unknown if the benefit is selective to those with prior exacerbation requiring hospitalization (subgroup analyses of trials signal a greater benefit in those with prior hospitalization). The GOLD report recommends the following therapy in patients with persistent exacerbations despite long-acting bronchodilator monotherapy:

- Escalate to LABA/LAMA or LABA/ICS unless eosinophil level is < 100 cells/uL.
- In those with exacerbation while on LABA/ICS: add a LAMA or switch to LABA/LAMA.
- In those with exacerbation on either triple therapy LABA/LAMA/ICS or in those with exacerbation on dual therapy with LABA/LAMA for which ICS was inappropriate:

roflumilast (Daliresp) may be added in the setting of severe or very severe disease, chronic bronchitis, and if patients have a history of exacerbation; particularly in those that have been hospitalized for an exacerbation in the previous year.

VIII. The Canadian Thoracic Society and European Respiratory Society/American Thoracic Society guidelines provide similar recommendations for use or roflumilast (Daliresp). Roflumilast (Daliresp) is not a bronchodilator therapy and should not be used for the relief of acute bronchospasm. It is not recommended to be used as monotherapy given lack of benefit in symptom control or quality of life, and the medication has unknown effects on exacerbation rate when used alone. It is recommended that dual or triple therapy be used prior to initiation of roflumilast (Daliresp) and that at least one bronchodilator (LABA and/or LAMA) be continued with roflumilast (Daliresp). It is also appropriate for roflumilast (Daliresp) to be added to triple therapy (LABA/LAMA/ICS). Some evidence suggests that roflumilast (Daliresp) may have additive effects with ICS; however, ICS may not be appropriate for all patients (e.g., not tolerated, low eosinophil level). When eosinophil levels are < 100 cells/uL, it is unlikely that ICS will be an effective therapy for patients with COPD and is not a required therapy under this condition. When eosinophil level is adequate and tolerated, ICS is guideline recommended therapy prior to treatment initiation with roflumilast (Daliresp).

Investigational or Not Medically Necessary Uses

I. Roflumilast (Daliresp) has not been FDA-approved, or sufficiently studied for safety and efficacy for the conditions or settings listed below and are considered experimental and investigational:
   A. Pediatric COPD
   B. Asthma

II. Roflumilast (Daliresp) daily dose of 250 mcg for longer than the one-month initiation period for tolerability is considered not medically necessary. This has been deemed a subtherapeutic dose by the drug manufacturer and FDA.

Appendix

I. GOLD Classification of Airflow Limitation Severity in COPD
   A. GOLD 1: Mild COPD, FEV1 is ≥ 80% predicted
   B. GOLD 2: Moderate COPD, FEV1 is ≥ 50% predicted but < 80% predicted
   C. GOLD 3: Severe COPD, FEV1 is ≥ 30% predicted but <50 predicted
   D. GOLD 4: Very Severe COPD, FEV1 is < 30% predicted

II. Long-acting beta agonists (LABA):
   A. Formoterol (Foradil Aeorolizer)

B. Salmeterol (Serevent Diskus)
C. Olodaterol (Striverdi Respimat)
D. Formoterol (Performist)
E. Arformoterol (Brovana)
F. May also be a part of combination inhalers: budesonide/formoterol (Symbicort), fluticasone/umeclidinium/vilanterol (Trelegy Ellipta), budesonide/glycopyrrolate/formoterol (Breztri Aerosphere), fluticasone/salmeterol (Advair, AirDuo, generic), fluticasone/vilanterol (Breo Ellipta), etc.

III. Long-acting muscarinic antagonists (LAMA):
A. Umeclidinium (Incruse Ellipta)
B. Glycopyrrolate (Seebri Neohaler, Lonhala), aclidiium (Tudorza Pressair), tiotropium (Spiriva)
C. May also be a part of combination inhalers: umeclidinium/vilanterol (Anoro), tiotropium/olodaterol (Stiolto), glycopyrrolate/formoterol (Vevespi), and glycopyrronium/indacaterol (Ultibron), etc.

IV. Inhaled corticosteroids (ICS)
A. Mometasone (Asmanex)
B. Beclomethasone (Qvar)
C. Budesonide (Pulmicort)
D. Fluticasone (Flovent, Armonair)
E. May also be part of combination inhalers, see above, etc.

Related Policies

Currently there are no related policies.

References

1. Global Initiative for Chronic Obstructive Lung Disease (GOLD) 2022 Report. Global strategy for prevention, diagnosis and management of chronic obstructive disease. National Institutes of Health, National Heart, Lung, and Blood Institute; Available at http://www.goldcopd.com/. Accessed July 7, 2022.
2. Daliresp [Package Insert]. Wilmington, DE. AstraZeneca Pharmaceuticals LP. Revised March, 2022.
3. Shen LF, Lv XD, Chen WY, Yang Q, Fang ZX, Lu WF. Effect of roflumilast on chronic obstructive pulmonary disease: a systematic review and meta-analysis. Ir J Med Sci. 2018;187(3):731-738.
4. Naseem S, Hassan M, Akhtar SN, Syed F, Khan NU, Usman M. Effectiveness of roflumilast in treating chronic obstructive pulmonary disease: a systematic review and meta-analysis. Cureus. 2022;14(3):e22843.
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6. Wedzicha JA, Calverley PMA, Albert RK, et al. Prevention of copd exacerbations: a european respiratory society/american thoracic society guideline. European Respiratory Journal. 2017;50(3).

7. Bourbeau J, Bhutani M, Hernandez P, et al. Canadian Thoracic Society Clinical Practice Guideline on pharmacotherapy in patients with COPD – 2019 update of evidence. Canadian Journal of Respiratory, Critical Care, and Sleep Medicine. 2019;3(4):210-232.

Policy Implementation/Update

Action and Summary of Changes	Date
Added requirement to try and fail generic roflumilast prior to using branded Daliresp	10/2022
Allowance of 250 mcg dose limited to one month titration period; Removal of requirement of recent hospitalization; Reworded to include very severe COPD patients for coverage allowance; Update to allow bypassing of ICS when eosinophil level is < 100 cells/uL; Updated to require continuation of a long-acting bronchodilator; Removal of requirement to continue ICS; Addition of adult age requirement. Policy updated to current format with inclusion of supplementary sections: E/I, NMN, Appendix, Related Policies. Added detailed supporting evidence.	08/2022
Criteria transitioned to policy format, with the following changes: further clarification around severe COPD definition, dose limit that it does not exceed 500 mcg per day if request is for a dose increase, supporting evidences were updated, and GOLD 2020 Report was updated.	11/2019
Criteria created	04/2018