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Month/Year of Review: February 2012
Generic Name: roflumilast
PDL Class: No current PDL class
Preferred COPD medications: formoterol, ipratropium, ipratropim/albuterol, salmeterol, tiotropium
Non-preferred: ICS/LABA combination products, and indacaterol (pending)

End date of literature search: November 2011
Brand Name (Manufacturer): Daliresp (Forest Pharmaceuticals)
Comparator Therapies: salmeterol, tiotropium, formoterol
Dossier received: Yes

EXECUTIVE SUMMARY:

FDA Approved Indications:
Roflumilast is indicated as a 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[1]

Background: Current standard of care for COPD patients is usually stepwise and generally guided by disease severity. Several guidelines advocate the use of long-acting bronchodilators beta-2 alpha adrenergic antagonists (LABA) or muscarinic antagonists (LAMA) for initial maintenance of symptom control. With more severe symptoms (i.e. patients with exacerbations) an inhaled corticosteroid (ICS) may be added.[2, 3, 4] Unfortunately, COPD is a progressive disease and often more medications are added with different mechanisms of action in order to control symptoms and improve patient quality of life. Eventually, most patients are on a combination of LABA, LAMA, and ICS as dual or triple therapy. Roflumilast is the first approved phosphodiesterase type-4 inhibitor. It is most closely related mechanistically to the phosphodiesterase inhibitor theophylline, but roflumilast has a more targeted site of action and narrow indication for use.[5] Roflumilast is approved to help reduce exacerbations. It is not intended to improve lung function.

Issues:
Key questions:

1. Is roflumilast more effective than currently preferred agents in the treatment of COPD to decrease exacerbations and mortality?
2. Is roflumilast better tolerated than current agents including formoterol, ipratropium, ipratropim/albuterol, salmeterol, or tiotropium?
3. Are there specific populations for which roflumilast is better tolerated or more effective?

Efficacy: Outcomes of interest when evaluating drugs for COPD include mortality, hospitalizations, pneumonia, exacerbations, quality of life and symptom control. The primary efficacy outcome reported in the roflumilast studies was improvement in pre-bronchodilator forced expiratory volume in one second (FEV_1). FEV_1 is an important measurement in diagnosing and staging COPD. It is also commonly used in COPD clinical trials because it is an objective, reproducible measurement of lung function. It is not, however, an ideal outcome measure for roflumilast as it doesn't provide any information about risk of exacerbation.

FDA approval of roflumilast relied on two good quality, randomized control trials (RCT), M2-124 and M2-125.[5] The trials had identical design and included only patients with severe or very severe COPD, with chronic bronchitis and a history of exacerbations. The primary study outcomes were change in pre-bronchodilator FEV_1 and rate of COPD exacerbations per patient per year. These trials demonstrated that roflumilast 500 mg once daily produced an improvement in pre-bronchodilator FEV_1 (roflumilast = 40ml vs. placebo = -9 ml, P < 0.0001). It was associated with fewer patients with severe exacerbations (roflumilast: 157 [10.2%] vs. placebo: 198 [12.7%], RR: 0.80 95% CI 0.66 –0.98), fewer patients with moderate exacerbations (roflumilast: 624 [40.6%] vs. placebo: 723 [46.5%], RR: 0.87 95% CI 0.80 – 0.95).[6] There was no difference in mortality.

There were four additional RCTs conducted in pairs: M2-111, M2-112 and M2-127, M2-128. These studies evaluated the efficacy and safety of roflumilast versus placebo in patients over 40 years old with moderate to severe COPD.[7, 8] All but M2-111, were published and of good quality.[6, 7, 8] M2-112[7] demonstrated that roflumilast 500 mg once daily produced an improvement in pre-bronchodilator FEV_1 (roflumilast: 9ml vs. placebo: -27ml, P< 0.002). There was no difference in rates of moderate to severe exacerbations or death from any cause.

Studies M2-127 and M2-128 evaluated lung function and exacerbations when roflumilast was used as add-on therapy.[8] Study M2-127 compared roflumilast plus salmeterol versus placebo plus salmeterol and study M2-128 compared roflumilast plus tiotropium versus placebo plus tiotropium. Both trials showed significant improvement in FEV_1 (both trials: p<0.001). The proportion of patients on roflumilast with moderate to severe exacerbations was fewer that those on placebo in both studies. M2-127 reported roflumilast: 51 (10.9%) vs. placebo: 83 (17.8%), RR: 0.62 95% CI: 0.45 – 0.85, P=0.0015 and M2-128 reported roflumilast: 42 (11.3%) vs. placebo: 58 (15.6%) RR: 0.72 95% CI: 0.50 – 1.05, P=0.0867. Death was not reported. These studies used different definitions of exacerbation and inclusion criteria than the prior studies.[5]

Safety: Rates of attrition were fairly high among studies but were comparable for treatment and placebo arms. Loss to follow-up was generally low and similar. But, the reason for withdrawal varied. More patients on roflumilast withdrew for adverse events whereas more patients on placebo withdrew for exacerbations. The most common adverse side effects were diarrhea, nausea and weight loss. Weight loss was moderate (5-10% of body weight) to severe (> 10% of body weight); and patients with more severe disease or those with lower baseline body weights experienced a higher occurrence of weight loss.[5, 6, 7, 8]

More serious adverse events documented through the trials were psychiatric in nature. Anxiety, insomnia and suicide ideation rates were increased in the roflumilast subjects compared with placebo. One patient committed suicide and two others attempted suicide in the roflumilast treatment arms during clinical trials. There were no attempts of suicide in the placebo groups, although one patient experienced suicide ideation.[5] These side effects could be an area of concern in populations with high rates of psychiatric co-morbidities, such as Medicaid patients. Roflumilast caused an increase in cancer in animal studies. In clinical trials, although cancer rates were higher in intervention subjects compared with placebo, the overall incidence was low and statistically insignificant.[5]

The data presented for adverse events was not always complete or easy to track. Weight loss was not followed consistently through all studies[7] and patient psychiatric adverse events were not always transparent. For example, the safety information available in FDA summary review documents was not in published studies.[5]

Conclusions: There is high level evidence roflumilast is superior to placebo in improving FEV_1 in patients with severe COPD, although the clinical significance of this is unclear. There is low to moderate level evidence that roflumilast modestly reduces the proportion of patients experiencing a moderate to severe exacerbation. There is insufficient evidence to determine comparative efficacy or safety with other medications indicated for the reduction of COPD exacerbations. Evidence for the approved indication is based on two placebo-controlled studies with very specific inclusion criteria (severe COPD, history of exacerbations, current bronchitis symptoms), limiting the applicability of the data for the population at large.[5, 6, 7, 8]

Overall, the studies were of short term duration and have not been shown to decrease mortality. Withdrawal due to adverse events was statistically higher for roflumilast with most due to diarrhea, nausea and weight loss. Unresolved safety concerns include suicide risk, which is not seen with other COPD medications.

Although roflumilast is the first in its class and in the future may be a valuable addition to COPD treatment, it has not been shown to be superior to other available treatments for COPD. Additional evidence and clinical experience will be helpful in the future to determine the appropriate place in therapy for roflumilast.

Recommendations:
Recommend maintaining roflumilast as non-preferred agent and include the following clinical criteria necessary for approval to ensure it is only used in the appropriate population:

- Patient has severe or very severe COPD with chronic bronchitis and frequent exacerbation.
- Patient has documented failure with an ICS or ICS combination product or tiotropium
- Patient is on a concurrent long acting controller medication (LABA or LAMA) as monotherapy or in combination with other therapies.

BACKGROUND/CURRENT LANDSCAPE

Medication management is based on severity of disease and degree of symptoms. There are clear shared recommendations through guidelines from the Global Initiative for COPD (GOLD) within the World Health Organization, the National Institute for Health and Clinical Excellence (NICE) in the United Kingdom and collaborating organizations the American College of Physicians, the American Thoracic Society, the American College of Chest Physicians, and the European Respiratory Society (CHEST). Patients with moderate stage COPD (FEV_1>50%) experiencing dyspnea symptoms are recommended a long-acting bronchodilator (LABA or LAMA). Patients with more severe disease (stage $\geq$ 3; repeated exacerbations) can add an ICS. NICE and GOLD guidelines recommend a short acting bronchodilator throughout all stages of disease (barring contraindications) to manage immediate symptoms. None of the existing COPD classes have been shown to modify long term decline in lung function[5] and reduction of therapy once symptoms are controlled is not always possible. Further deterioration of lung function frequently requires the progressive introduction of more medications. All guidelines treat progressing COPD disease in the same stepwise fashion: short-acting bronchodilator, long-acting bronchodilator, additional long-acting product(s)-LABA, LAMA, or ICS, and finally long-term O_2 therapy. No guideline favors an individual product; all products within a class are considered equivalent.[2, 3, 4]

CLINICAL PHARMACOLOGY [1, 9]

Roflumilast is most closely mechanistically related to theophylline, a non-specific phosphodiesterase inhibitor. Roflumilast differs from theophylline in that, it is a selective inhibitor of phosphodiesterase 4 (PDE 4). Phosphodiesterases, including PDE4, are enzymes that break down cyclic '3,'5-adenosine monophosphate (cyclic AMP). The specific mechanism of action of roflumilast in COPD is unknown. However, PDE4 works primarily in the lung tissue. By inhibiting PDE4, roflumilast and its active metabolite (roflumilast N-oxide) are believed to cause an accumulation of intracellular cyclic AMP in lung cells. Roflumilast also reduces the recruitment of inflammatory cells such as neutrophils, macrophages into the bronchi.

PHARMACOKINETICS[1, 9]

Table 4

Parameter	Result
Oral Bioavailability	80%
Protein Binding	99%
Elimination	70% urine
Half-Life	roflumilast 17 hours roflumilast N-oxide 30 hours
Metabolism	Extensively metabolized by phase I (CYP 1A2 & 3A4) and Phase II (conjugation) reactions. N-oxide is major metabolite*

*The N-oxide metabolite is active but is less potent than roflumilast

COMPARATIVE CLINICAL EFFICACY

Relevant Endpoints:

1) Mortality
2) Severe Exacerbation (resulting in hospitalization or death)
3) Moderate Exacerbation (requiring corticosteroid rescue)
4) Withdrawals due to adverse events

Primary Study Endpoint:

1) Mean change in pre-bronchodilator FEV_1
2) Moderate to Severe Exacerbations per patient per year

Evidence Table

Ref./ Study Design	Drug Regimens	Patient Population	N	Duration	Efficacy Results[b]	ARR / NNT	Safety Results (CI, p-values)	ARI / NNH	Quality Rating[d]; Comments
M2-124 & M125[6]									
Calverley et. al. PC, RCT, DB, PG	R: Roflumilast 500µg QD P: Placebo QD	Patients with severe to very severe COPD Mean Age:64 yrs Male: 75% White: 84% Current smokers: 41% Inclusion: COPD w/$FEV_1 \leq 50\%$,Smoking history $\geq$ 20 pack year, $\geq$ 40 yo, hx of bronchitis and exacerbation Exclusion: Asthma or other lung disease; cardiopulmonary abnormalities; abnormal labs; pregnant/ planned pregnancy /breast feeding /females of child-bearing age not using contraception; history of GI bleeds within last year; part of another clinical trial within 30 days; current part in within 3 months of the run-in period of a pulmonary rehab program; immunosuppressive meds within 4 weeks; Alpha-1-antitrypsin deficiency; HIV infection; active hepatitis; any cancer (other than basal cell) within 5 years; abnormal ECG results; alcohol or drug abuse; hypersensitivity to study med	R: 1537 P: 1554	Outcomes assessed at 52 weeks	Death any cause R: 42(2.7%) P: 42 (2.7%) RR: 1.01 95% CI 0.66 – 1.54 (NS) Severe Exacerbations R: 157 (10.2%) P: 198 (12.7%) RR: 0.80 95% CI 0.66 –0.98 Moderate Exacerbations R: 624 (40.6%) P: 723 (46.5%) RR: 0.87 95% CI 0.80 – 0.95 Mean change in pre-bronchodilator FEV1 (mL): R: 40 mL P: -9 ml Difference: 48 ml 95% CI: 35 – 62 P <0.0001	ARR: 0% NNT: NS ARR:2.5% NNT: 40 ARR: 5.9% NNT: 17 ARR: NA NNT: NA	Withdrawals due to Adverse events: R: 220 (14.3%) P: 161 (10.4%) RR: 1.38 95% CI 1.14 – 1.67	ARI: 3.95% NNH: 25	Good; Total attrition rates: R: 510 (33.2%) P: 482 (31.0%) Overall attrition rate: 32.4% Attrition is >20% but loss to follow-up was the same in both groups. There were differential rates in withdrawals due to adverse events and for COPD exacerbation. Adherence to treatment was similar in all groups with a mean compliance of 93% (R) and 95% (P). ICS and LAMA use prohibited; LABA and SAMA use allowed at stable doses. 4-week placebo run-in used to select patients with severe disease. Moderate exacerbation defined as a patient receiving any dose of oral or parenteral steroids to control symptoms. Severe exacerbation defined as any stay in hospital for symptoms or death.

M2-112[7]									Good
Calverley et. al. Phase III, RCT, DB, PC, PG	R: Roflumilast 500µg QD P: Placebo QD X52 weeks; mean:	Patients with severe to very severe COPD Mean Age: 65 yrs Male: 76% Current smokers: 37% Inclusion: COPD w/$FEV_1 \leq$ 50%,Smoking history $\geq$ 10 pack year, $\geq$ 40 yo Exclusion: Asthma hx or other relevant lung dx (lung CA, bronchiectasis) long term O2, or other clinically significant cardio-pulmonary co-morbidity	R: 760 P: 753	Outcomes reported for 52 weeks.	Death from any cause: R: 12 (1.6%) P: 20 (2.7%) RR: 0.59 95% CI 0.29 – 1.21 (NS) Overall moderate or severe exacerbations (rate/patient/yr): R: 0.857 P: 0.918 RR: 0.9 P=0.451 Change in Pre-bronchodilator FEV1 versus from baseline (mL): R: 9ml P: -27ml P< 0.002	ARR: 1.0% NNT: NS ARR: NA NNT: NA ARR: NA NNT: NA	Withdrawals due to Adverse events: R: 103 (14.6%) P: 56 (7.4%) RR: 1.82 95% CI (1.34 – 2.48)	ARI: 6.1% NNH: 16	Total attrition rates: R: 217 (29%) P: 163 (22%) Overall: 25% Attrition rate >20% but there was no reported loss to follow-up. Differential rate due to withdrawals for adverse events. Withdrawals due to exacerbations were similar. Adherence rates not reported by authors. LABA and LAMA use prohibited; ICS use allowed. 4-week placebo run-in used to select patient with severe disease. Change in pre-bronchodilator reported as secondary outcome. Moderate exacerbation defined as a patient receiving any dose of oral or parenteral steroids to control symptoms. Severe exacerbation defined as any stay in hospital for symptoms or death.

M2-127[8]									Good;
Fabbri et. al. RCT, DB, PG	R: Roflumilast 500μg QD + salmeterol P: Placebo QD + salmeterol X24 weeks	Patients with Moderate to Severe COPD Mean Age: 65 yrs Male: 66% Current smoker: 39% Inclusion: COPD w/$FEV_1 \leq$ 70%,Smoking history $\geq$ 10 pack year, $\geq$ 40 yo Exclusion: Asthma or other lung disease; lower respiratory tract infection in last 4 weeks; cardiopulmonary abnormalities; abnormal labs; pregnant/ planned pregnancy /breast feeding /females of child-bearing age not using contraception; part of another clinical trial within 30 days; current part in within 3 months of the run in period of a pulmonary rehab program; immunosuppressive meds within 4 weeks; Alpha-1-antitrypsin deficiency; HIV infection; active hepatitis; any cancer (other than basal cell) within 5 years; abnormal ECG results; alcohol or drug abuse; hypersensitivity to study med	R: 466 P: 467	Outcomes assessed Every 4 weeks up to week 12, and every 6 weeks thereafter until week 24.	Moderate or Severe Exacerbation: R: 51 (10.9%) P: 83 (17.8%) RR: 0.62 95% CI: 0.45 – 0.85 P=0.0015 Mean change in pre-bronchodilator FEV_1 relative to placebo: R: 39ml P: -10ml 95% CI: 27 – 71 P=<0.0001	ARR:6.8% NNT 15 ARR: NA NNT: NA	Withdrawals due to Adverse events: R: 77 (16.5%) P: 45 (9.6%) RR: 1.71 95% CI: 1.21 – 2.42 P=0.0019	ARI: 6.9% NNH: 15	Total attrition rates: R: 33 (7.1%) P: 20 (4.3%) Overall: 5.7% Rates of attrition were acceptable. Differential rates due to adverse events. COPD exacerbation withdrawals also varied (R: 16, P: 27). Adherence to treatment was similar in all groups with a mean compliance between 94% and 97%. 4-week placebo run-in period to select moderate to severe patients. Chronic bronchitis was not an inclusion criterion. ICS use prohibited. Shorter duration. Outcomes assessed at each visit; unclear when outcomes that were reported were assessed. Moderate exacerbation defined as a patient receiving any dose of oral or parenteral steroids to control symptoms. Severe exacerbation defined as any stay in hospital for symptoms or death.

M2-128[8]									Good;
Fabbri et. al. RCT, DB, PG	R: Roflumilast 500μg QD + tiotropium P: Placebo QD + tiotropium X24 weeks	Patients with Moderate to Severe COPD Mean Age: 64 yrs Male: 80% Current smoker: 40% Inclusion: COPD w/$FEV_1 \leq$ 50%,Smoking history $\geq$ 20 pack year, $\geq$ 40 yo, hx of bronchitis, pretreatment with tiotropium for $\geq$ 3months Exclusion: Asthma or other lung disease; lower respiratory tract infection in last 4 weeks; cardiopulmonary abnormalities; abnormal labs; pregnant/ planned pregnancy /breast feeding /females of child-bearing age not using contraception; part of another clinical trial within 30 days; curren part in within 3 months of the run in period of a pulmonary rehab program; immunosuppressive meds within 4 weeks; Alpha-1-antitrypsin deficiency; HIV infection; active hepatitis; any cancer (other than basal cell) within 5 years; abnormal ECG results; alcohol or drug abuse; hypersensitivity to study med	R: 371 P: 372	Outcomes assessed Every 4 weeks up t week 12, and every 6weeks thereafter until week 24.	Moderate or Severe Exacerbation: R: 42 (11.3%) P: 58 (15.6%) RR: 0.72 95% CI: 0.50 – 1.05 (NS) P=0.0867 Mean change in prebronchodilator FEV_1 relative to placebo: R: 65ml P: -16 ml 95% CI: 51 – 110 P=<0.0001	ARR: 4.3% NNT: NS ARR: NA NNT: NA	Withdrawals due to Adverse events: R: 33 (8.9%) P: 20 (5.4%) P=0.0864	ARI: 3.5% NNH: 29	Total attrition rates: R: 62 (16.7%) P: 39 (10.5%) Overall: 13.6% Rates of attrition were acceptable. No difference in loss to follow-up. Differential rates due to adverse events. COPD exacerbation withdrawals also varied (R: 4, P 8). Adherence to treatment was similar in all groups with a mean compliance between 94% and 97%. ICS use prohibited. Moderate exacerbation defined as a patient receiving any dose of oral or parenteral steroids to control symptoms. Severe exacerbation defined as any stay in hospital for symptoms or death.

[a]**Study design abbreviations:** DB = double-blind, RCT = randomized trial, PC = placebo-controlled, PG = parallel -group.
[b]**Results abbreviations**: RRR = relative risk reduction, RR =relative risk, OR= Odds Ratio, HR = Hazard Ratio, ARR = absolute risk reduction, ARI=absolute risk increase
NNT = number needed to treat, NNH = number needed to harm, CI = confidence interval, NS = Not Significant, NA = Not Applicable
Other abbreviations: COPD = chronic obstructive pulmonary disease, R = roflumilast, P=placebo

CLINICAL EFFICACY

FDA approval was based upon six phase III efficacy trials submitted by Forest Pharmaceuticals. All studies showed some degree of improvement in lung function compared with placebo, measured by forced expiratory volume in one second (FEV_1). Measurement of FEV_1 is important in the diagnosis and staging of COPD. Demonstrating change in FEV_1 is also frequently used in clinical trials as a primary outcome as it is an objective and reproducible measurement that correlates to

lung function. Improving lung function in COPD, however, is usually transitory, and promising gains seen at the beginning of treatment frequently disappear with long-term therapy.[10] It is also difficult to translate change in FEV_1 to improvement in other outcomes relevant to COPD management: mortality, hospitalizations, and symptoms (especially exacerbations).[2]

Population inclusion/exclusion criteria, study outcomes, and design evolved with the roflumilast clinical program. Quality of life outcomes (i.e. St George Respiratory Questionnaire score) used in prior safety and efficacy trials were not emphasized. Change in FEV_1 and rate of exacerbation versus placebo were the endpoints examined for the six pivotal trials. Secondary outcomes varied per trial. [5, 6, 7, 8]

All six trials showed a significant improvement compared with placebo in change in FEV_1. [5, 6, 7, 8] Roflumilast is not a bronchodilator or indicated for symptom maintenance; it is approved to decrease risk of exacerbation. The FEV_1 measurement does not provide any clinical efficacy information for roflumilast. Only one pair of studies (M2-124 & M2-125) showed statistical improvement in rate of exacerbations per patient per year with roflumilast versus placebo.[6]

The trials M2-124 and M2-125 were fundamental to FDA approval. For these trials, inclusion criteria were more specific and patients without a history of exacerbation and chronic bronchitis were excluded. Both trials demonstrated a significant decrease in moderate or severe exacerbations per patient per year (M2-124: 1.08 vs. 1.27, P = 0.0278; M2-125: 1.21 vs. 1.49, P = 0.0035). Moderate exacerbation was defined as a patient receiving any dose of oral or parenteral steroids to control symptoms; severe was defined as any stay in hospital for symptoms or death.[6]

None of the four supporting trials were significant compared with placebo in exacerbation reduction. One of these trials (M2-111) was not published and is unavailable for further evaluation.[5] Two of the trials, M2-127 and M2-128, were designed to examine what extent the concurrent use of a long-acting bronchodilator added to roflumilast. In M2-127, patients received either roflumilast plus salmeterol, or placebo plus salmeterol. In M2-128, patients received roflumilast plus tiotropium, or placebo plus tiotropium. These studies used a different definition of exacerbation and inclusion criteria as the prior studies.[5] In both trials, mild, moderate and severe exacerbations rates were included together and roflumilast was not significantly different than the placebo arms.[8] However, in the FDA statistical study when mild exacerbations were omitted, the rate for the roflumilast group in trial 127 was significantly improved (37% reduction, RR 0.63, P=0.032), although this was not true for M2-128. In the pooled analysis, there was no difference in exacerbation rates.[5]

In general, sensitivity analysis showed the finding for primary endpoints to be robust with regard to missing data and dropouts. In the five published trials, the internal validity was good. Blinding and allocation concealment were not consistently explicit, but inclusion/exclusion criteria and randomization were uniformly transparent. Baseline populations were evenly matched. All trials had a high attrition rate, and it is not clear if any sensitivity analysis were done to account for this. However, rates were similar between groups, and the COPD population recruited was those with the most severe disease. [5, 6, 7, 8]

The main limitation of these studies was in testing efficacy against a placebo control. Additionally, patients were allowed use of a concurrent long-acting COPD medication in all six trials, making it difficult to establish the efficacy of roflumilast as a monotherapy agent or to compare its effectiveness against other standard therapy. Another limitation is the use of FEV_1 as a primary outcome. Examination of more relevant outcomes (mortality, hospitalizations) would require studies of longer duration.

There have been no head-to-head trials of roflumilast and comparator therapy. Until roflumilast is actively compared with other COPD medications used to decrease exacerbations (ICS), no judgment can be made on its place in therapy.

DRUG SAFETY

Serious (REMS, Black Box Warnings, Contraindications):

Roflumilast is not a bronchodilator and should not be used to treat acute bronchospasm. Roflumilast is contraindicated in patients with moderate to severe liver impairment (Child-Pugh score B or C). Recommend precaution in patients with mild liver impairment, a history of depression or a history of suicide ideation.[1] Mortality rates were low, and rates were similar between placebo and roflumilast groups.[6, 7, 8]

Weight Loss

Weight loss was a common side effect reported throughout the roflumilast clinical program. This side effect was seen in studies for indications other than COPD which may suggest this effect is not disease specific.[1] In the M2-124 and M2-125 trials, 62.4% subjects in the roflumilast group versus 37.7% placebo patients lost some weight from their baseline.[5] In these studies' pooled data, 20% and 7% of roflumilast subjects experienced moderate (5-10%of total body weight) and severe (>10% body weight) respectively, compared with 7% and 2% of placebo subjects.[1] Patients with more severe disease lost more weight than those with less severe COPD.[5]

Psychiatric Adverse Events

Psychiatric adverse events were more common in the roflumilast treatment groups than in the placebo groups during the clinical program. The most common events were insomnia (3.0% roflumilast vs. 1.1% placebo), anxiety (1.4% vs. 0.8%), and depression (1.4% vs. 0.8%).[5] In subjects enrolled in the clinical program and receiving treatment, there were three suicide adverse events. One patient committed suicide and two attempted suicide in the roflumilast groups. There was one report of suicide ideation but no attempts in the placebo population.[1] Two other suicides were reported in patients who had discontinued roflumilast at least 21 days prior. None of the three completed suicides had a history of depression; the two attempted suicides, however, did.[5]

For FDA approval, Forest Laboratories performed analyses to calculate the possible suicide-related adverse events (PSRAE) risk. In this analysis, the two suicides which occurred after discontinuation of roflumilast were excluded due to lack of evidence of causation. Forest pooled all the patients included in any controlled parallel group study including indications beyond COPD. From 36 studies, the pool comprised of 21,263 patients; 11,848 received roflumilast. No new cases of suicide-related adverse effects were found beyond the three cases in the roflumilast group and one in the placebo groups reported above. The risk rate per 1000 patient years for a PSRAE when taking roflumilast was 0.793 versus 0.284 for placebo.[5]

Cancer risk

Animal studies with hamsters and mice saw a statistically significant increase roflumilast treated animals developing nasal epithelium carcinomas. The carcinogenicity appeared dose-related and was attributed primarily to the active metabolite roflumilast N-oxide.[1] In clinical trials, the rate of development of tumors of any kind was comparable between roflumilast and placebo treated patients (1.6% vs.1.5%). However, rates of new diagnoses of several specific cancers were higher in roflumilast groups compared with those on placebo: lung cancer 0.5% vs. 0.3%, prostate cancer 0.2% vs. 0.09%, and colorectal cancer 0.15% vs. 0.04%. Some of these cancers may have been present but undiagnosed prior to initiation of treatment. A conclusive association between human use of roflumilast and cancer cannot be proven.[5]

Adverse Effects

The most common side effects experienced by patients receiving roflumilast were diarrhea, nausea and weight loss.

Table 1 summarizes the adverse reactions from eight COPD controlled trials. Events recorded were reported by ≥ 2% of patients in the roflumilast population and were greater than the event recorded in the placebo population.[1]

Table 1: Adverse reactions reported by ≥ 2% of patients treated with roflumilast 500 mcg daily and greater than placebo treatment event rate[1]

Adverse Reactions	Roflumilast N=4438 (%)	Placebo N=4192 (%)
Diarrhea	420 (9.5)	113 (2.7)
Weight decreased	331 (7.5)	89 (2.1)
Nausea	209 (4.7)	60 (1.4)
Headache	195 (4.4)	87 (2.1)
Back pain	142 (3.2)	92 (2.2)
Influenza	124 (2.8)	112 (2.7)
Insomnia	105 (2.4)	41 (1.0)
Dizziness	92 (2.1)	45 (1.1)
Decreased appetite	91 (2.1)	15 (0.4)

Tolerability (Drop-out rates, management strategies):[6, 7, 8]

Attrition rates were similar in the placebo and intervention populations in all published studies.

Pregnancy/Lactation rating:[1, 9]

Roflumilast is rated Pregnancy Category C. Roflumilast was not found to be teratogenic during animal studies. Dosing hasn't been studied in pregnant women and it should only be given if the potential benefit outweighs the risk to the mother and fetus. Roflumilast was shown to be secreted into milk when studied in rats. Its use should be avoided by nursing mothers.

Unanswered safety questions:

The safety of taking roflumilast long term is unknown. There is some concern with use in populations prone to depression and in populations under-weight; both conditions are seen in patients with COPD. In addition, the possible increase in cancer risk warrants more investigation. Prospective surveillance for adverse events related to roflumilast is ongoing and may help better understand the risk-benefit profile especially for patients with history of psychiatric disorder.[1]

Dose Index (efficacy/toxic):[1, 9]

Patients should take the recommended dose of one 500 mcg tablet per day without regard to food.

No reports of overdose have been reported with roflumilast. During dose-ranging trials, the following symptoms were observed at an increased rate after a single oral dose of 2500 mcg and a single dose of 5000 mcg: headache, gastrointestinal disorders, dizziness, palpitations, lightheadedness, clamminess and arterial hypotension.

In case of overdose, patients should seek immediate medical help. Appropriate supportive medical care should be provided. Since roflumilast is highly protein bound, hemodialysis is not likely to be an efficient method of drug removal. It is not known whether roflumilast is dialyzable by peritoneal dialysis.

Monitoring:[1]

Patients with history of depression or suicidal thoughts should be monitored closely when receiving roflumilast.

Patient weight should be monitored regularly while on roflumilast.

Look-alike / Sound-alike (LA/SA) Error Risk Potential:

LA/SA names are assessed during the PDL selection of drugs. Based on clinical judgment and an evaluation of LA/SA information from four data sources, the following drug names may cause LASA confusion:

Table 2

NME Drug Name	Lexi-Comp	USP Online	MicroMedex	ISMP	Clinical Judgment
LA/SA for roflumilast (generic)	None	None	None	None	None
LA/SA for Daliresp (brand)	None	None	None	None	None

DOSE & AVAILABILITY[1, 9]

Table 3

STRENGTH	FORM	ROUTE	FREQUENCY	RENAL ADJ	HEPATIC ADJ	Pediatric Dose	Elderly Dose	OTHER DOSING CONSIDERATIONS
Roflumilast 500 mcg	Tablet	Oral	Once daily	No dosage adjustment necessary	Use with caution in mild hepatic impairment Avoid use in moderate or severe hepatic impairment	N/A	No dosage adjustment necessary	-Very narrow indication; not a maintenance medication to improve symptoms or lung function -Use with caution in patients with low baseline weight -Use with caution in patients with history of depression - May be given with or without food

ALLERGIES/INTERACTIONS[1, 9]

Drug-Drug:
Roflumilast is a substrate for CYP 1A2 and 3A4. CYP 450 inducers such as rifampin, phenobarbital, phenytoin, and carbamazepine resulted in reduction in exposure and decrease in therapeutic effectiveness of roflumilast (79% reduction in AUC for roflumilast). Increased plasma concentrations of roflumilast can occur with concomitant administration of CYP inhibitors such as fluvoxamine, enoxacin, cimetidine, erythromycin ketoconazole, itraconazole, lopinavir/ritonavir, ritonavir, indinavir/ritonavir and conivaptan. The co-administration of roflumilast with oral contraceptives containing gestodene and ethinyl estradiol may increase roflumilast systemic exposure and may result in increased side effects.

Food-Drug:
No food-drug interactions have been reported. Bioavailability is not affected by food, but delays T_{max} by 1 hour and reduces C_{max} by 40 %.

Allergy/Cross Reactive Substances:
Not established

CONCLUSIONS AND RECOMMENDATIONS

There is high level evidence roflumilast is superior to placebo in improving FEV_1 in patients with moderate to severe COPD, although the clinical significance of this is uncertain. There is low to moderate level evidence that roflumilast modestly reduces the proportion of patients experiencing a moderate to severe exacerbations. There is insufficient evidence to determine comparative efficacy or safety with other medications indicated for the reduction of COPD exacerbations. Evidence for the approved indication is based on two placebo-controlled studies with very specific inclusion criteria (severe COPD, history of exacerbations, current bronchitis symptoms), limiting the applicability of the data for the population at large.[5, 6, 7, 8]

Serious safety concerns remain concerning roflumilast that are not seen with other COPD medications. Some weight loss from baseline was seen in the majority of patients in the M2-124 and M2-125 trials. Patients with more severe disease tended to have greater loss than those less ill. This could be a potentially serious adverse event in patients who are underweight or near underweight; weight should be monitored throughout treatment with roflumilast.

A more serious side effect which was uncovered during clinical trials was development of suicidal ideation. In clinical trials, one patient taking roflumilast committed suicide while two others who discontinued roflumilast three weeks prior also committed suicide. Another two patients in a roflumilast group attempted suicide but did not succeed. In all trials, one placebo patient exhibited signs of suicidal ideation. Rates of psychiatric adverse events (insomnia, anxiety or depression) were higher in roflumilast than in the placebo groups. Although total incidence of suicide ideation and psychiatric events were very low overall, further safety evaluation is needed.

Roflumilast is the first in its class and in the future may be a valuable addition to COPD treatment, but it has not been shown to be superior to other available treatments for COPD. Additional evidence and clinical experience will be helpful in the future to determine the appropriate place in therapy for roflumilast.
It is recommended roflumilast be a non-preferred agent in the COPD PDL class and use clinical prior authorization criteria to limit use to severe or very severe COPD patients.

APPENDIX:
Suggested PA Criteria

Roflumilast

Goal(s):

- Decrease the number of COPD exacerbations in patients with severe COPD and chronic bronchitis and a history of prior exacerbations.

Length of Authorization: 1 year

Covered Alternatives: Listed at; http://www.oregon.gov/DHS/healthplan/tools_prov/pdl.shtml

Approval Criteria		
1. What is the diagnosis?	Record ICD-9 code	
2. Is the diagnosis an OHP covered diagnosis?	**Yes:** Go to #3.	**No:** Pass to RPh, Deny for OHP Coverage.
3. Does the patient have documented severe or very severe (Stage III or Stage IV) COPD?	**Yes:** Go to #4	**No:** Deny (medical inappropriateness)
4. Does the patient have a history of chronic bronchitis AND Prior COPD exacerbations?	**Yes:** Go to #5	**No:** Deny (medical inappropriateness)
5. Is the patient currently on a long-acting bronchodilator?	**Yes:** Go to #6	**No:** Deny. Recommend trial of preferred long-acting bronchodilators
6. Has the patient failed an inhaled corticosteroid (ICS) or tiotropium (LAMA)?	**Yes:** Approve up to 1 year	**No:** Deny. Recommend trial of preferred long-acting ICS or LAMA

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