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APPLICATION NUMBER:

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SUMMARY REVIEW

SUMMARY REVIEW OF REGULATORY ACTION

Date:	February 25, 2011
From:	Badrul A. Chowdhury, MD, PhD Director, Division of Pulmonary, Allergy, and Rheumatology Products, CDER, FDA
Subject:	Division Director Summary Review
NDA Number:	22-522
Applicant Name:	Forest Pharmaceuticals, Inc.
Date of Submission:	August 30, 2010 (original submission was on July 15, 2009)
PDUFA Goal Date:	February 28, 2011
Proprietary Name:	Daliresp
Established Name:	Roflumilast
Dosage form:	Film-coated tablets
Strength:	500 mcg
Proposed Indications:	Chronic Obstructive Pulmonary Disease
Action:	Approval

1. Introduction

Forest Pharmaceuticals originally submitted this 505(b)(1) application on July 15, 2009, for use of roflumilast tablets 500 mcg for once daily treatment to reduce exacerbations of chronic obstructive pulmonary disease (COPD) associated with chronic bronchitis in patients at risk of exacerbation. A Complete Response action was taken on the original application citing three deficiencies: a) incomplete assessment of suicidality in the overall safety database, (b) (4) , and c) lack of complete in vitro evaluation of the potential of roflumilast as a substrate of P-gp. During the original review, the major issue was the risk benefit assessment balancing the strength of efficacy demonstrated in the clinical program against the risk of neuropsychiatric adverse events including suicides seen in the controlled clinical studies. Forest Pharmaceuticals submitted this complete response on August 30, 2010, satisfactorily addressing these deficiencies. This summary review will provide an overview of the application, both the original NDA submission and the complete response resubmission, with a focus on the clinical efficacy and safety studies.

2. Background

There are several drug classes available for the relief of airflow obstruction in patients with COPD. These include beta-2 adrenergic agonists, anticholinergic agents, combination products containing beta-2 adrenergic agonists and anticholinergic agents, combination products containing long-acting beta-2 adrenergic agonists and corticosteroids, and methylxanthines, such as theophylline.

Roflumilast is a new molecular entity that belongs to a class called phosphodiesterase type-4 (PDE-4) inhibitor. Roflumilast is functionally related to theophylline, which is a non-specific PDE inhibitor that has broad specificity to different types of PDEs. Although no PDE-4 inhibitor is approved for marketing in the United States, several have been studied for COPD, and one, cilomilast, was submitted to the FDA for marketing approval for use in COPD patients. The cilomilast application was discussed at a Pulmonary-Allergy Drugs Advisory Committee (PADAC) meeting on September 5, 2003, and not approved because of lack of substantial efficacy (discussed further in this review in section 7 c, under the sub-heading of efficacy findings and conclusions).

Nycomed submitted the roflumilast NDA to the FDA. Effective December 4, 2009, the ownership of the NDA was transferred to Forest Pharmaceuticals. The original indication as submitted by Nycomed was for "maintenance treatment of COPD associated with chronic bronchitis in patients with risk of exacerbation." After the change of ownership, Forest Pharmaceuticals revised the indication to "maintenance treatment to reduce exacerbation of COPD associated with chronic bronchitis in patients at risk of exacerbation." The revision is subtle, but is narrower and specific to maintenance treatment to reduce exacerbation. At the same time Forest also pointed out safety concerns with psychiatric adverse reactions and elevated this safety finding to a warning in the proposed product label. Subsequent to the PADAC discussion for roflumilast held on April 7, 2010 (discussed further in this review in section 9), Forest Pharmaceuticals further revised the indication and removed the "maintenance" wording.

3. Chemistry, Manufacturing, and Controls

The proposed commercial drug product, roflumilast tablets, contains 500 mcg roflumilast and standard compendial excipients. The drug product will be packaged in HDPE bottles containing 30 tablets or 90 tablets. The active pharmaceutical ingredient will be manufactured at (b) (4) – Nycomed GmbH, Germany, (b) (4) The drug product will be manufactured, packaged, released, and stability tested at Nycomed GmbH, Germany. The drug product will also be packaged at (b) (4). All manufacturing and testing facilities associated with this application have acceptable inspection status. The various DMFs associated with the manufacture of the product are adequate. An expiry of 2 years is proposed and supported by submitted data.

(b) (4)

(b) (4)

The proposal to market the formulation studied in pivotal studies is acceptable.

4. Nonclinical Pharmacology and Toxicology

Forest Pharmaceuticals conducted a complete and adequate toxicology program that included general toxicology studies in rodent and non-rodent species, embryofetal development studies, and carcinogenicity studies. In the general toxicology studies, the target organs of toxicity were the cardiovascular system, gastrointestinal system, reproductive system, and the nose. The proposed human dose has adequate safety margins for the animal toxicity findings. The embryofetal studies showed decreased number of live births and reduced pup viability. These findings support pregnancy category C classification for roflumilast. The carcinogenicity study showed increased incidence of nasal tumors in a 2-year hamster study. The carcinogenicity of roflumilast appears to be attributed to a metabolite, ADCP N-oxide that is further converted to a reactive intermediate, ADCP N-oxide epoxide in the nasal tissues. Both steps are catalyzed by cytochrome enzyme P450 CYP 2G1 in rodents. Human nasal tissues appear to lack active enzymes to convert ADCP to ADCP N-oxide, but ADCP N-oxide is found in human plasma and urine. Relevance of the tumor finding to humans is unknown since the tissues and enzymes involved in the production of ADCP N-oxide and its down-stream metabolite are unknown in humans. Nasal tumors with roflumilast do not appear to be a class effect of PDE-4 inhibitors. Of the nine PDE-4 inhibitors for which the Division has nonclinical toxicology data, four have submitted 2-year animal carcinogenicity date, and only one, piclamilast, which also forms the ADCP metabolites, has demonstrated nasal toxicities in rats and mice and nasal tumors in rats.

5. Clinical Pharmacology and Biopharmaceutics

Forest Pharmaceuticals submitted a complete and adequate clinical pharmacology program for roflumilast. Roflumilast oral bioavailability is approximately 80% and there is no food effect. Roflumilast is extensively metabolized via cytochrome P450 pathway and by conjugation reactions. Roflumilast N-oxide is the major metabolite observed in human plasma. The plasma AUC of roflumilast N-oxide, on average, is about 10-fold greater than that of roflumilast. *In vitro* metabolism studies using human liver microsomes and *in vivo* drug-drug interaction studies indicated that roflumilast is mainly metabolized by CYP3A4 and CYP1A2 and did not inhibit or induce the activity of the major CYP P450 enzymes. An *in vitro* study showed that roflumilast did not inhibit P-gp transport.

During the original NDA review, the clinical pharmacology discipline initially recommended four post-marketing studies, one as a PMR and three as PMCs. The PMR study was for quantification data for ADCP N-oxide. The PMC studies were to assess

the effect of CYP 2A7, 2F1 and 2C18 on production of ADCP N-oxide; re-evaluation of QT effect of roflumilast; and evaluation of roflumilast as a substrate for P-gp. The two post-marketing studies for further assessment of ADCP N-oxide were thought to be not necessary because it is already known that humans produce this carcinogenic metabolite. Furthermore, human data are available from a safety database of approximately 25,000 patients. It was thought that the post-marketing thorough QT study at this late clinical development stage would not be useful because the Applicant had already conducted a thorough QT study, albeit with a deficiency that the positive control did not perform as expected. Nevertheless the study was negative. Furthermore, controlled clinical studies involving approximately 25,000 patients, many with COPD, who are elderly with concomitant cardiac disease, did not show any cardiac findings or QT findings on ECGs. It was thought that the PMC study asking for evaluation of roflumilast as a substrate for P-gp would be of value because roflumilast will be dosed at the highest tolerated dose. The controlled clinical study excluded many concomitant drugs that may affect P-gp. Elucidating P-gp effect of roflumilast will provide information that will have safety labeling implications. With the above reasoning, during the original NDA review, the clinical pharmacology discipline revised its position and finally recommended one PMC, which is to evaluate roflumilast as a substrate for P-gp. This was conveyed to Forest Pharmaceuticals as a deficiency in the Complete Response to the original NDA.

With this complete response resubmission, Forest Pharmaceuticals submitted results of in vitro assessments of roflumilast and roflumilast N-oxide as potential substrates for P-gp. The determinations of P-gp substrate potential were conducted in cultured cell monolayers at four different concentrations of roflumilast or roflumilast N-oxide: 0.1, 0.5, 2, and 4 μM with appropriate controls. The results demonstrated that neither roflumilast nor roflumilast N-oxide are P-gp substrates. This study adequately addresses the safety concerns related to P-gp raised in the original NDA review.

6. Clinical Microbiology

Not applicable.

7. Clinical and Statistical – Efficacy

a. Overview of the clinical program

Some characteristics of the relevant clinical studies that form the basis of the review and regulatory decision for this application are shown in Table 1. The design and conduct of these studies are briefly described below, followed by efficacy findings and conclusions. Safety findings are discussed in the following section.

Table 1. Relevant COPD clinical studies with roflumilast

ID Year*	Study type	Study duration	Patient Age, yr	Treatment groups#	N (ITT)	Primary efficacy variables	Countries
Dose selection studies							
101 2001	Parallel arm	26 week	≥ 40	Rof 250 mcg Rof 500 mcg Placebo	176 169 172	FEV1 + SGRQ	Europe, South Africa

ID Year*	Study type	Study duration	Patient Age, yr	Treatment groups#	N (ITT)	Primary efficacy variables	Countries
107 2003	Parallel arm	24 week	≥ 40	Rof 250 mcg Rof 500 mcg Placebo	576 555 280	FEV1 + SGRQ	Europe, Canada, Australia, South Africa
Pivotal studies							
111 2005	Parallel arm	52 week	≥ 40	Rof 500 mcg Placebo	567 606	FEV1 + Exacerbation	US, Canada, S Africa, Europe
112 2004	Parallel arm	52 week	≥ 40	Rof 500 mcg Placebo	760 753	FEV1 + Exacerbation	Canada, Europe, S Africa
124 2008	Parallel arm	52 week	≥ 40	Rof 500 mcg Placebo	765 758	FEV1 + Exacerbation	US, Europe, Australia, NZ
125 2008	Parallel arm	52 week	≥ 40	Rof 500 mcg Placebo	772 796	FEV1 + Exacerbation	US, Canada, Europe, India, S Africa
127 2007	Parallel arm	24 week	≥ 40	Rof 500 mcg + salmeterol Placebo +salmeterol	566 467	FEV1	Canada, Europe, S Africa
128 2008	Parallel arm	24 week	≥ 40	Rof 500 mcg +tiotropium Placebo +tiotropium	371 372	FEV1	Europe
*Year study subject enrollment ended # Rof = Roflumilast capsules							

b. Design and conduct of the studies

The clinical development program for roflumilast was extensive and evolved over time. Dose ranging exploration was limited to studies 101 and 107. Latter studies apparently carried forward the highest tolerated dose. The once-daily dosing regimen was based on results of pharmacokinetic studies that showed 17-hour and 30-hour half-life for roflumilast and its active metabolite. Although Forest Pharmaceuticals has identified studies 124 and 125 as pivotal, all studies shown in Table 1 are relevant and any of the three pairs (101 and 107, 111 and 112, or 124 and 125) with successful outcome could have been adequate to support an NDA. The primary endpoint, patient eligibility criteria, and concomitant medication used during clinical development evolved over time with Forest Pharmaceuticals ultimately identifying a narrow COPD population in studies 124 and 125 where efficacy was demonstrated. Studies 127 and 128 were conducted to assess efficacy of roflumilast added to either a long-acting bronchodilator (LABA) or a long-acting anti-cholinergic (LAMA). The overall program is acceptable.

Studies 101 and 107:

Studies 101 and 107 were randomized, double blind, parallel group, in design, conducted in patients with full range of COPD severity. Patients were required to be 40 years of age and older, have a clinical diagnosis of COPD, FEV1 30 to 75% predicted (study 101) or 30 to 80% predicted (study 107), FEV1/FVC ≤70%, and be a current or previous smoker with a smoking history of ≥10 pack years. Patients were not required to have a history of

COPD exacerbations. Concomitant use of systemic or inhaled corticosteroids and LABAs were not permitted. Stable doses of short-acting anticholinergic were permitted. The studies each had a 2- or 4-week run-in period, followed by a 24- or 26-week double blind treatment period. There were three treatment arms as shown in Table 1. The co-primary efficacy variables were pre-bronchodilator FEV1 and SGRQ in study 101 and post-bronchodilator FEV1 and SGRQ in study 107. Safety assessment included adverse event recording, vital signs, physical examination, clinical laboratory and hematology measures, and ECGs.

Studies 111 and 112:

Studies 111 and 112 were randomized, double blind, parallel group, in design, conducted in patients with severe COPD. Patients were required to be 40 years of age and older, have a clinical diagnosis of COPD, FEV1/FVC ≤70%, FEV1 ≤50% predicted, and be a current or previous smoker with a smoking history of ≥10 pack years. Patients were not required to have a history of COPD exacerbations. Concomitant use of LABAs and LAMAs were not permitted. Stable doses of inhaled corticosteroids were permitted. The studies each had a 4-week run-in period, followed by a 52-week double blind treatment period. There were two treatment arms as shown in Table 1. The co-primary efficacy endpoints were mean change from baseline to the end of treatment in pre- or post-bronchodilator FEV1 (studies 111 and 112 respectively), and the number of moderate or severe COPD exacerbations. In study 111 COPD exacerbation was defined as an event requiring oral or parenteral corticosteroid (moderate exacerbation) or an event resulting in hospitalization or death (severe exacerbation). Exacerbations within 10 days of each other were merged and counted as one exacerbation. In study 112 COPD exacerbation was defined similarly, but also included events requiring antibiotic (moderate exacerbation), and death was added later in the protocol. Exacerbations within 1 day of each other were merged and counted as one exacerbation. Safety assessment included adverse event recording, vital signs, physical examination including body weight measurement, clinical laboratory and hematology measures, ECGs, and 24 hour Holter monitoring at selected sites in study 111.

Studies 124 and 125:

Studies 124 and 125 were randomized, double blind, parallel group, in design, conducted in patients with severe COPD associated with chronic bronchitis (cough and sputum production). Patients were required to be 40 years of age and older, have a clinical diagnosis of COPD associated with chronic bronchitis and a history of COPD exacerbation in the recent past, FEV1/FVC <70%, FEV1 ≤50% predicted, and be a current or previous smoker with a smoking history of ≥20 pack years. Concomitant use of inhaled corticosteroids and LAMAs were not permitted. Stable doses of short acting anti-cholinergics, short acting beta-agonists, and LABAs were permitted (LABA were used by about 50% patients). The studies each had a 4-week run-in period, followed by 52-week double blind treatment period. There were two treatment arms as shown in Table 1. The co-primary efficacy endpoints were mean change in pre-bronchodilator FEV1 from baseline to each post-randomization visit, and rate of moderate or severe

COPD exacerbations. COPD exacerbation was defined as in study 111 described above. Safety assessment included adverse event recording, vital signs, physical examination including body weight measurement, clinical laboratory and hematology measures, ECGs, and 24 hour Holter monitoring at selected US sites.

Studies 127 and 128:

Studies 127 and 128 were randomized, double blind, parallel group, in design, conducted in patients with moderate-to-severe COPD. Patients were required to be 40 years of age and older, have a clinical diagnosis of COPD (study 127) or COPD associated with chronic bronchitis (study 128), FEV1/FVC ≤70%, FEV1 ≤40% predicted, and be a current or previous smoker with a smoking history of ≥10 pack years. Concomitant use of inhaled corticosteroids was not permitted. Patients were on stable doses of LABA or LAMA according to the study protocol. The studies each had a 4-week run-in period, followed by a 24-week double blind treatment period. There were two treatment arms as shown in Table 1. The primary efficacy endpoint was the mean change in pre-bronchodilator FEV1 from baseline to each post-randomization visit during the treatment period. The studies also assessed mild, moderate, or severe COPD exacerbations as a key secondary endpoint. A COPD exacerbation was defined as increase in rescue bronchodilator use for 2 consecutive days (mild), event requiring oral or parenteral corticosteroid (moderate exacerbation), event resulting in hospitalization or death (severe exacerbation). Safety assessment included adverse event recording, vital signs, physical examination, clinical laboratory and hematology measures, and ECGs.

c. Efficacy findings and conclusions

The clinical program shows that roflumilast at a dose of 500 mcg once daily reduces the risk of COPD exacerbations in patients with severe COPD associated with chronic bronchitis and a history of exacerbations.

There are three components of efficacy that were assessed and relevant to this application. These are COPD exacerbation, airflow or FEV1, and SGRQ. In subsequent sections these three efficacy components are briefly described, followed by a summary. The summary also compares this program to a previous PDE-4 inhibitor called cilomilast, which was not approved.

COPD exacerbation

The definition of a COPD exacerbation used in various studies was similar with some minor differences noted above where the design and conduct of the studies are described. There is no generally accepted definition of COPD exacerbations, but it usually includes some combination of symptoms and a change of treatment. The roflumilast program defined an exacerbation in terms of change of treatment. This definition, though not ideal

(because underlying symptoms that led to intervention was not measured), is reasonable and generally follows the definitions used in the literature.[1]

The 52-week studies 111, 112, 124, and 125 were specifically designed to assess the effect of roflumilast on the rate of COPD exacerbations. Studies 111 and 112 did not show statistically significant separation between roflumilast and placebo arms (Table 2). The Applicant conducted further analysis of the data and identified patients who seemed to benefit. Studies 124 and 125 were conducted with modified selection criteria informed by analysis of data from studies 111 and 112. Patients in studies 124 and 125 were COPD patients who had chronic bronchitis (cough and sputum production) with a recent history of COPD exacerbation. In this narrow COPD population there was statistically significant difference between roflumilast and placebo (Table 2). Both moderate and severe COPD exacerbations showed benefit, although most of the events were moderate. Time to first moderate or severe exacerbation also favored roflumilast. Time to first COPD exacerbation was about 65 days longer in patients who received roflumilast compared to placebo. On an exploratory analysis, it appeared that the beneficial effect on COPD exacerbation was attenuated after 8 months. However, such analysis is complicated to interpret because of patient dropouts. Studies 127 and 128 included a broad range of COPD patients and measured COPD exacerbation as a secondary endpoint. One of the two studies showed statistically significant difference between roflumilast and placebo (Table 2).

The proposed indication of reducing the risk of COPD exacerbations is supported by the submitted clinical studies. Two earlier studies (Studies 111 and 112) conducted in broadly defined severe COPD patients failed to show efficacy, while two latter studies (Studies 124 and 125) with a targeted more narrow patients with severe COPD (those with chronic bronchitis and a history of exacerbations) did show efficacy (Table 2). The product label will reflect the narrow patient population where efficacy was demonstrated.

Table 2. Analysis of moderate or severe exacerbations (ITT population, pre-planned primary analysis)

	Poisson Exacerbation Rate					P-value
	Rof 500 mcg	Placebo	Absolute Reduction	Percent Reduction	Rate Ratio	
Study 111	0.6	0.7	0.1	13	0.87	0.129
Study 112	0.5	0.5	0.0	15	0.85	0.085
Study 124	1.1	1.3	0.2	15	0.85	0.028
Study 125	1.2	1.5	0.3	18	0.82	0.004
Study 127	0.3	0.5	0.2	37	0.63	0.032
Study 128	0.3	0.3	0.0	23	0.77	0.196

Absolute reduction measured as difference between placebo and roflumilast treated patients.

Percent reduction is defined as 100 (1-Rate Ratio)

[1] Cazzola M, MacNee W, Martinez FJ, et al. ATS/ERS Task Force Report: Outcomes for COPD pharmacological trials, from lung function to biomarkers. Eur Resp J 2008; 31: 416-468.

Airflow or FEV1

All studies included FEV1 as a measure of efficacy. Patients on roflumilast had a statistically significant benefit compared to placebo across studies with effect sizes ranging from 39 to 80 ml, with an average of approximately 50 mL. This effect size is generally small compared to drugs such as beta-agonists and anti-cholinergics whose primary mode of action is bronchodilation.

Table 3. Change in pre-bronchodilator FEV1 from baseline to end of treatment (ITT population)

	Pre-bronchodilator FEV1 (mL)			P-value
	Rof 500 mcg	Placebo	Difference	
Study 101	64	17	47	0.0776
Study 107	77	-1	78	<0.001
Study 111	30	-12	42	<0.001
Study 112	49	-8	58	<0.001
Study 124	46	8	39	<0.001
Study 125	33	-25	58	<0.001
Study 127	39	-10	49	<0.001
Study 128	65	-16	80	<0.001

SGRQ

SGRQ was measured in early studies and did not show a statistically significant difference between roflumilast treatment and placebo (Table 3). Later key studies did not use SGRQ as an efficacy endpoint.

Table 4. Change from baseline of SGRQ, total score

	SGRQ			P-value
	Rof 500 mcg	Placebo	Difference	
Study 101	-4.7	-4.5	-0.3	0.425
Study 107	-3.5	-1.8	-1.7	0.053
Study 111	-1.8	-0.3	-1.5	0.016
Study 112	-3.7	-3.2	-0.5	0.268

Summary

The clinical program evolved over time (Table 1), with later studies informed by data from early studies. Early studies 101 and 107 targeted a broad spectrum of COPD patients and aimed to demonstrate broad maintenance treatment benefit by assessing FEV1 and SGRQ. These studies failed to show substantial efficacy, particularly for SGRQ (Table 4). The later studies 111 and 112 targeted more severe COPD patients and aimed to demonstrate broad maintenance treatment benefit by assessing FEV1 and COPD exacerbation. These studies failed to show substantial efficacy for COPD exacerbation (Table 2). Subsequent studies 124 and 125 narrowed the patient population further by including COPD patients with chronic bronchitis and recent history of COPD

exacerbation. In this narrowly defined COPD population, benefit was demonstrated for reduction in COPD exacerbations. This benefit on COPD exacerbation was supported by FEV1, which is a well accepted efficacy variable in COPD studies. Roflumilast is not claimed or expected to be a bronchodilator, therefore, failure to demonstrate a large numerical improvement typical for bronchodilator is not surprising. The consistent small numerical benefit for FEV1 across studies (Table 3) is supportive of the COPD exacerbation benefit.

The roflumilast clinical program has shown benefit on two aspects of COPD, exacerbation and FEV1. The Applicant is not seeking a broad maintenance treatment of COPD claim, but a restricted claim of COPD exacerbation in a narrow COPD population (chronic bronchitis with history of COPD exacerbation). The submitted data are adequate to support this limited claim in a narrow COPD population that can be clinically identified.

The conclusion reached in this review is same as the conclusion reached in the CDTL review. There was a difference of opinion during the review of the original NDA with the primary clinical review and the CDTL review, which is no longer relevant.

For the sake of maintaining regulatory decision consistency, it is worth noting the difference between the roflumilast clinical program and the cilomilast clinical program. Cilomilast developed by GSK was submitted to the FDA for approval for use in COPD patients. GSK was seeking a maintenance treatment of lung function (FEV1) indication, and submitted results from 4 pivotal studies 24 weeks in duration with co-primary efficacy variables of change from baseline in trough FEV1 and SGRQ. The FEV1 improvement over 24 weeks was demonstrated, but was numerically modest as it was for roflumilast. Benefit in SGRQ was not demonstrated. The cilomilast application was discussed at a PADAC meeting on September 5, 2003. The majority opinion was that efficacy was not demonstrated because the benefit for FEV1 was not demonstrated over a long time period (such as 3 years) for a maintenance treatment of lung function (FEV1) claim, or benefit on two aspects of COPD was not demonstrated. In contrast to the cilomilast clinical program, the roflumilast clinical program has shown benefit in reducing the risk of COPD exacerbations, which is further supported by a modest improvement in FEV1. Additionally, Forest Pharmaceuticals is not seeking a broad maintenance treatment of COPD claim for roflumilast, but a restricted claim of COPD exacerbation in a narrow COPD population (chronic bronchitis with history of COPD exacerbation) that can be clinically identified. The Applicant for roflumilast reached this specific narrow COPD population through purposeful sequential studies.

8. Safety

a. Safety database

The safety assessment of roflumilast is based on the COPD studies shown in Table 1, and additional studies conducted for other indications, the largest program being that for asthma. The safety database is large and includes information from approximately

12,000 patients with COPD with approximately half of the patients receiving roflumilast, and additional 12,000 patients from other clinical programs.

b. Safety findings and conclusion

The safety data do not raise safety concerns in the COPD patients that would preclude approval. The safety findings of note with roflumilast are psychiatric adverse events including suicide, weight loss, gastrointestinal adverse events, and cancer. One particular issue form the original NDA review was incomplete assessment of psychiatric adverse events including suicide. Forest Pharmaceuticals has adequately addressed this issue in this complete response resubmission.

In the COPD safety population of approximately 12,000 patients there were 177 deaths. The large number of deaths is not surprising given the patient population who are elderly with COPD and other concomitant diseases. There was no imbalance in mortality between the groups and there is no signal seen from analysis of the mortality data. Serious adverse events (SAEs) were also common, which is expected for this type of study and the patient population. Analysis of SAEs did not raise a safety signal. Common adverse events included COPD exacerbation, weight loss, diarrhea, nausea, headache, insomnia, and dizziness. Weight loss, diarrhea, and nausea were more common in roflumilast treated patients compared to placebo (discussed further below). Clinical laboratory tests and ECGS did not raise any specific safety concerns.

There are four specific safety issues that are relevant to this application review. These are psychiatric adverse events including suicide, gastrointestinal adverse reactions, weight loss, and cancer. These four safety issues are briefly described below, followed by a summary.

Psychiatric adverse events including suicide

Psychiatric adverse events were more common in the roflumilast group compared to the placebo in the COPD clinical program. Common adverse events in this category were insomnia (3.0% roflumilast 500 mcg vs 1.1% placebo), anxiety (1.4% roflumilast 500 mcg vs 0.8% placebo), and depression (1.4% roflumilast 500 vs 0.8% placebo). Psychiatric adverse events were also more common in the roflumilast group compared to the placebo group in other roflumilast programs.

There were 3 completed suicides and 2 suicide attempts reported in the roflumilast COPD safety data base (n = 12,054 patients) in roflumilast treated patients compared to none in patients treated with placebo. There was one suicide ideation in a placebo treated patients. Of the three completed suicides none of the patients had a prior history of depression. Two cases of suicides were reported in patients who discontinued roflumilast approximately 20-21 days prior to the suicide event, which makes causal association somewhat distant. With regard to the suicide attempts, both patients had prior psychiatric histories (depression in one patient and previous suicide attempt in the other). Both patients were receiving roflumilast at the time of the suicide attempt. The Applicant had utilized the Columbia Classification Algorithm of Suicide Assessment (C-CASA) to

assess for additional potential suicide-related cases in the COPD safety database and presented the finding for the PADAC meeting. But the C-CASA was not discussed with the Agency and has not been submitted to the original NDA for FDA review. The extent and nature of the C-CASA analyses was not clear at the time of the original NDA review. The Applicant submitted a REMS (MedGuide) to inform patients and health care providers about the risks of psychiatric adverse events including suicide with use of roflumilast. The REMS was submitted on April 14, 2010, during review of the original NDA.

The Agency identified incomplete assessment of suicidality in the overall safety database as a deficiency in the Complete Response action of the original NDA. Forest Pharmaceuticals was asked to fully evaluate all roflumilast safety data to better understand the strength of the suicidality signal and assess the impact of any signal on the risk benefit assessment of roflumilast in the treatment of COPD.

In this complete response resubmission, Forest Laboratories submitted analysis of the COPD safety pool and overall pool using the Columbia Classification Algorithm of Suicide Assessment (C-CASA). The COPD safety pool comprised of 12,654 patients (6,972 receiving roflumilast) enrolled in 16 controlled parallel group studies. The overall pool comprised of 21,623 patients (11,848 receiving roflumilast) enrolled in 36 controlled parallel group studies across indications including COPD, arthritis, diabetes mellitus, and allergic rhinitis. The C-CASA analysis was performed according to procedure previously descried (Posner et al., Am J Psychiatry 2007; 164:1035-1043) and acceptable to the Agency. In this assessment, the number of possible suicide-related adverse events (PSRAEs) was 3 in roflumilast group (2 suicide attempts and 1 completed suicide) and 1 in control group (suicide ideation) in the COPD safety pool as well as in the overall pool. The suicides that occurred 3 weeks after discontinuation of roflumilast were excluded based on C-CASA criteria. The new analysis, including both the COPD safety pool and overall pool, did not identify any new PSRAEs that were not identified during the review of the original NDA. Forest Laboratories compared the risk between treatment groups using statistical methods and criteria consistent with previous FDA C-CASA analyses. For the COPD pool, the risk rate (per 1000 patient years) of having PSRAE was 0.793 for roflumilast, and 0.284 for placebo. The difference in the risk rates was not statistically significant. The risk rate was lower for the overall pool as a result of greater number of patients being in the pool with no additional events. A psychiatry consult was obtained from within the FDA that agreed with the methodological aspects of the C-CASA analysis and concluded that the risk of suicides with roflumilast is not a major safety concern.

Weight loss

Weight loss was a common adverse event reported in roflumilast clinical studies. Patients from all indication studies (including indications other than COPD) were affected, which suggest a drug specific effect. In the studies 124 and 125, where weights were carefully measured, 62.4% patients in the roflumilast group compared to 37.7% patients in the placebo group had measured weight loss below baseline. Weight loss

reported as adverse event was more common with roflumilast compared to placebo (10.3% vs 2.8%). Patients who had lower body weight at baseline and most severe COPD lost more weight than others. The Applicant submitted a REMS (MedGuide) to inform patients and health care providers about the risks for weight loss with use of roflumilast. The REMS was submitted on April 14, 2010, during review of the original NDA.

Gastrointestinal adverse events

Gastrointestinal adverse events were more common in the roflumilast group compared to the placebo group in the COPD clinical program. Common adverse events under this category were diarrhea (10.1% roflumilast 500 mcg vs 2.6% placebo), and nausea (5.2% roflumilast 500 mcg vs 1.4% placebo). Diarrhea and nausea were also the most common cause of withdrawal after COPD exacerbation. About 90% of gastrointestinal adverse events were mild or moderate in intensity and about 10% met the criteria for severe adverse reactions.

Cancer

Roflumilast was found to cause nasal tumors in rodents. Thus, cancer frequency in humans is a topic of special interest. The overall number of tumors reported as adverse events in the roflumilast group was comparable to that of the placebo group (105 tumors in 6563 roflumilast treated patients vs 80 from 5491 placebo treated patients), but more patients in the roflumilast group compared to the placebo group had lung cancer (29 in 5752 roflumilast treated patients vs 17 in 5505 placebo treated patients), prostate cancer (13 in 5752 roflumilast treated patients vs 5 in 5505 placebo treated patients), and colo-rectal cancer (9 in 5752 roflumilast treated patients vs 2 in 5505 placebo treated patients). Many of these cancers were identified early during treatment suggesting uncovering of existing cancers rather than development of new cancers. Appearance of common cancers more frequently in roflumilast treated patients is difficult to explain. A definite link between roflumilast and human cancers cannot be proven or excluded. The animal findings provide a biological plausibility, but occurrence of cancers early in treatment with short duration of exposure argues against it. The product label will describe the cancer findings and acknowledge this possible risk.

Summary

The roflumilast clinical program has identified safety concerns as noted above, but none rise to the level that would preclude approval or would require demonstration of efficacy above and beyond what is typically expected for a drug for COPD. The safety findings will be noted in the product label with appropriate level of warning and in the required Medication Guide.

c. REMS/RiskMAP

As mentioned above, Forest Pharmaceuticals submitted a Medication Guide only REMS on April 14, 2010, to inform patients of the potential risk associated with the use of roflumilast in COPD patients. The risk of increased psychiatric adverse events including

suicide, and weight loss will be addressed in the Medication Guide. Per the February 2011, Draft Guidance for Industry: Medication Guides – Distribution Requirements and Inclusion in Risk Evaluation and Mitigation Strategies (REMS), in most cases FDA expects to include a Medication Guide as part of a REMS only when the REMS includes elements to assure safe use. Thus, while a Medication Guide is required to communicate the potential risks of roflumilast to patients, a Medication Guide as part of a REMS is not necessary.

9. Advisory Committee Meeting

A Pulmonary-Allergy Drugs Advisory Committee (PADAC) meeting was held on April 7, 2010, during review of the original NDA. Questions were asked about the efficacy, safety, and approvability of roflumilast. The questions were framed against the original broad COPD indication submitted by Nycomed (maintenance treatment of COPD associated with chronic bronchitis in patients with risk of exacerbation), and not the revised more restricted COPD exacerbation indication submitted later by Forest Pharmaceuticals (maintenance treatment to reduce exacerbation of COPD associated with chronic bronchitis in patients at risk of exacerbation). The original indication was used for discussion because the revised indication was submitted late in the review cycle, therefore, there was not sufficient time for review and consideration of potential ramifications of the new proposed indication. Nevertheless, the intention of Forest Pharmaceuticals to change the indication was disclosed in the FDA briefing documents and during presentations at the meeting. The committee voted favorably regarding whether there was substantial evidence of efficacy (9 yes, 6 no), and the safety profile of roflumilast (9 yes, 6 no). Regarding the approvability question, which is essentially the sum of demonstration of efficacy and safety, the results were against approval (5 yes, 10 no). During the deliberation, some Committee members expressed that they would be more favorable on efficacy and approvability with the proposed revised and restricted indication. The Applicant did not present a risk-mitigation strategy as part of the NDA and also in the briefing material for the PADAC meeting. Some Committee members felt that a risk mitigation strategy should be developed for this product and such a plan could have swayed their view on approvability. Some Committee members also had some reservation on the "maintenance treatment" wording in the indication given the possible attenuation of the COPD exacerbation benefit over time and lack of benefit on some other patient reported outcomes, such as SGRQ.

After the PADAC meeting the applicant further modified the indication to remove the "maintenance treatment" wording (the further revised indication reads as: once daily treatment to reduce exacerbations of COPD associated with chronic bronchitis in patients at risk of exacerbation), and submitted a REMS limited to a MedGuide to inform patients and health care providers about the potential risks of psychiatric adverse events including suicide, and weight loss.

10. Pediatric

COPD is an adult disease, therefore, specific pediatric studies would not be required that relate to this action specific to COPD.

11. Other Relevant Regulatory Issues

a. DSI Audits

A DSI audit was requested for 4 clinical study sites based on high enrollment and favorable outcome for roflumilast. Final reports of the DSI inspections revealed adherence to Good Clinical Practices. Minor deficiencies were noted, but these were isolated and deemed unlikely to impact data integrity and patient safety. During review of the submission no irregularities were found that would raise concerns regarding data integrity. No ethical issues were present. All studies were performed in accordance with acceptable ethical standards.

(b) (4) The proposal to market the formulation studied in pivotal studies is acceptable.

b. Financial Disclosure

Forest Pharmaceuticals submitted acceptable financial disclosure statements. Eight investigators had significant financial interest in Forest Pharmaceuticals. The number of subjects that these investigators enrolled was not large enough to alter the outcome of any study. Furthermore, the multi-center nature of the studies makes it unlikely that these financial interests could have influenced or biased the results of these studies.

c. Others

There are no outstanding issues with consults received from DDMAC, DMEPA, or from other groups in CDER.

12. Labeling

a. Proprietary Name

The proposed proprietary name Daxas was tentatively found to be acceptable by DMEPA during review of the original NDA, but during review of this complete response resubmission DMEPA concluded that the name Daxas is no longer acceptable. The reason for finding the Daxas name unacceptable is (b) (4)

(b) (4), which was recently approved by DMEPA for another product. Forest Pharmaceuticals later proposed Daliresp as the proprietary name, which was determined to be acceptable by DMEPA.

b. Physician Labeling

The Applicant submitted a label in the Physician's Labeling Rule format. As noted above in various sections, three versions of label were submitted to the NDA during the original review cycle. The original label submitted by Nycomed was revised by Forest Pharmaceuticals when it took ownership of this NDA effective December 4, 2009. The indication was revised to make it more limited to a COPD exacerbation claim. At the same time, new warning related to psychiatric adverse reactions and suicides were added. On April 14, 2010, after the PADAC meeting, Forest Pharmaceuticals submitted another version of the label where the indication was revised to delete the "maintenance treatment" wording, and a new MedGuide only REMS was proposed. The complete response resubmission contains a proposed label in the PLR formation that generally is similar to what was submitted after the PADAC meeting. The label was reviewed by various disciplines of this Division, DRISK, DMEPA, SEALD, and by DDMAC. Various changes to different sections of the label were done to reflect the data accurately and better communicate the findings to health care providers. The label contains efficacy data from 8 clinical trials (Table 1), including negative findings, to explain the limited indication in a specified COPD population that is supported by the submitted data. Psychiatric adverse events including suicide and weight loos are described in the Warnings and Precautions section as well as in a Medication Guide as mentioned above. The Division and Forest Pharmaceuticals have agreed on the final labeling language.

c. Carton and Immediate Container Labels

These were reviewed by various disciplines of this Division, and DMEPA, and found to be acceptable.

d. Patient Labeling and Medication Guide

A Medication Guide was required as discussed in section 8c above.

13. Action and Risk Benefit Assessment

a. Regulatory Action

The applicant has submitted adequate data to support approval of roflumilast tablets 500 mcg for once daily treatment to reduce risk of COPD exacerbations in patients with severe COPD associated with chronic bronchitis and a history of exacerbation. The recommended action on this application is Approval.

b. Risk Benefit Assessment

The overall risk benefit assessment supports approval of roflumilast 500 mcg. The major safety issues are psychiatric adverse events including suicide, weight loss, malignancy, and gastrointestinal adverse events (discussed in section 8 above). One outstanding safety issue that required further analysis was the psychiatric adverse events. Forest Pharmaceuticals conducted adequate analyses using acceptable methodologies and

submitted the results with the complete response resubmission (discussed in section 8 above). The analysis did not raise new safety concerns. These safety findings will be described in the product label and managed by a Medication Guide (discussed in section 8c above). From an efficacy standpoint, Forest Pharmaceuticals has submitted adequate efficacy data to show reduction of risk of COPD exacerbations in patients with COPD associated with chronic bronchitis and a history of exacerbation. The demonstrated efficacy of reduction of exacerbations is in a limited subgroup of COPD patients (severe COPD associated with bronchitis and a history of exacerbation), which will be reflected in the product label.

c. Post-marketing Risk Management Activities

Forest Pharmaceuticals submitted a Medication Guide only REMS on April 14, 2010, to inform patients of the potential risk associated with the use of roflumilast in COPD patients. The risk of increased psychiatric adverse events including suicide and weight loss will be addressed in the Medication Guide. Per the February 2011, Draft Guidance for Industry: Medication Guides – Distribution Requirements and Inclusion in Risk Evaluation and Mitigation Strategies (REMS), in most cases FDA expects to include a Medication Guide as part of a REMS only when the REMS includes elements to assure safe use. Thus, while a Medication Guide is required to communicate the potential risks of roflumilast to patients, a Medication Guide as part of a REMS is not necessary to ensure the benefits of roflumilast outweigh the risks.

d. Post-marketing Study Commitments

During the course of the review of the original NDA it was decided that obtaining data to assess the efficacy of roflumilast when added to current standard of care for COPD patients, such as use of combination products containing an inhaled corticosteroid plus an inhaled LABA is important and will provide valuable information for the use of roflumilast. Forest Pharmaceuticals has committed to conduct a post-marketing controlled clinical trial to evaluate the efficacy and safety of roflumilast an a add-on therapy to long-acting beta agonist and inhaled corticosteroid fixed dose combination treatment in the population of COPD patients for which roflumilast will be indicated (severe COPD associated with chronic bronchitis and a history of exacerbation).

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/s/

BADRUL A CHOWDHURY
02/25/2011