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APPLICATION NUMBER:

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OFFICE DIRECTOR MEMO

Summary Basis for Regulatory Action

Date	February 28, 2011
From	Curtis J Rosebraugh, MD, MPH Director, Office of Drug Evaluation II
Subject	Summary Review
NDA/BLA # Supp #	22-522
Applicant Name	Nycomed/Forest Laboratories
Proprietary / Established (USAN) Names	Daliresp roflumilast
Dosage Forms / Strength	Tablet 500 mcg
Proposed Indication(s)	Once daily treatment to reduce exacerbations of COPD associated with chronic bronchitis in patients at risk of exacerbation
Action:	*Approval*

1. Introduction and Discussion

Roflumilast is a new molecular entity, a phosphodiesterase-4 (PDE4) inhibitor, developed for COPD treatment originally submitted on July 15, 2009. During my review for the first cycle of this application, I determined that roflumilast had demonstrated efficacy in decreasing exacerbations in patients with severe COPD associated with chronic bronchitis and a history of exacerbations. However, I also determined that the safety of suicide and psychiatric adverse events, as well as two other issues outlined below, warranted further evaluation. This review will be limited to the sponsor's response to remediate those issues as identified in the Complete Response (CR) action letter of July 17, 2010 which include:

1) Incomplete evaluation of possible roflumilast-induced suicides and psychiatric adverse reactions

(b) (4)

3) Lack of evaluation of roflumilast as a potential P-glycoprotein (P-gp) substrate.

The sponsor has satisfactorily addressed these deficiencies as will be briefly discussed below, and therefore this application should be approved if appropriate labeling can be agreed upon. Please refer to other reviews in the action package and my initial review for further details.

Regarding #1 above, a possible signal suicide and psychiatric events warranted further evaluation to allow for an adequate risk-benefit assessment. To determine if there was a roflumilast associated suicide signal or not, the sponsor was instructed to perform a comprehensive review and evaluation of all roflumilast safety data utilizing an acceptable method, such as the Columbia Classification Algorithm of Suicide Assessment (C-CASA).

The complete response resubmission included analysis of the COPD safety pool and overall pool using the Columbia Classification Algorithm of Suicide Assessment (C-CASA). This analysis included 12,654 patients for the COPD safety pool and 21,623 patients for an overall pool (including data from other diseases for which the drug is or was being developed). The number of possible suicide-related adverse events (PSRAEs) identified was 3 in roflumilast group (2 attempts, 1 completed) and 1 in the control group (suicide ideation) in the COPD pool (and overall pool as well). Suicides occurring 3 weeks after discontinuation of roflumilast were excluded. The new analysis did not identify any new PSRAEs. For the COPD pool, the risk rate (per 1000 patient years) of having PSRAE was 0.793 for roflumilast, and 0.284 for placebo, not statistically significant. A psychiatry consult was obtained from within the FDA who agreed with the methodological aspects of the C-CASA analysis and concluded that there was not a statistically significant difference in suicidal events in patients receiving roflumilast compared to placebo. The psychiatry consultants also felt, given the uncertainty of the association, that a Boxed Warning was not justified.

As with all safety issues which have very few events upon which to draw conclusions, it is hard to exonerate or assign responsibility for PSRAEs to roflumilast. While the psychiatric consultants seemed reassured because this signal did not achieve statistical significance, I am not comforted by this as there were very few events and this was not a safety study powered to reveal a safety signal. A counter-argument could be made however that this was a very large database that one would have expected for a true causation to be demonstrated in a more convincing way. I think at best, we can conclude that if this is a real drug induced event, it is rare (approximately 1 per 2000 patient years), and considering the lack of effective agents, and severity of the disease, a tolerable risk that can be labeled and monitored. I agree that the data at this point would not warrant a boxed warning but this finding should receive prominent labeling.

(b) (4)

Regarding #3 above, the sponsor has submitted in vitro assessments determining that neither roflumilast nor roflumilast N-oxide are substrates for P-gp.

2. Conclusions and Recommendations

As I had stated in my previous review, COPD, particularly of the severity examined for this application, is a devastating disease for which we have few effective therapies. I believe that roflumilast has demonstrated that it decreases exacerbations in patients with severe COPD associated with chronic bronchitis in patients and a history of exacerbations. A safety signal of PSRAE was identified in the original submission that warranted further evaluation for risk/benefit determinations. No further events were identified using a C-CASA protocol. It is difficult to make conclusions regarding causality with few events, but this is a large database,

and the placebo subtracted rate of PSRAE, if due to drug, is low. I believe that roflumilast has an adequate risk/benefit ratio to allow marketing with adequate labeling (e.g. restricting the indication from the broad claim originally made to treatment to reduce risk of COPD exacerbations in patients with severe COPD associated with chronic bronchitis and a history of exacerbation) and a medication guide alerting patients to potential risks. This decision is also in keeping with the advice from a majority of the advisory committee members. I also agree that a post-approval trial of roflumilast as add-on therapy to LABA/ICS therapy would be useful for clinicians.

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/s/

CURTIS J ROSEBRAUGH
02/28/2011