



NDA 20444/S-018

**SUPPLEMENT APPROVAL**

GlaxoSmithKline LLC  
Attention: Willa B. Phyll, Ph.D.  
Senior Director  
Regulatory Affairs (Mail Code RN0420)  
2301 Renaissance Boulevard  
King of Prussia, PA 19406

Dear Dr. Phyll:

Please refer to your supplemental New Drug Application (sNDA) dated December 13, 2010, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Flolan (epoprostenol sodium) 0.5 and 1.5 mg Injection.

This Prior Approval sNDA provides for the following revisions to the labeling for Flolan (epoprostenol sodium):

**Revisions to labeling**

In **INDICATIONS AND USAGE**, revise the following text

FROM

FLOLAN is indicated for the long-term intravenous treatment of primary pulmonary hypertension and pulmonary hypertension associated with the scleroderma spectrum of disease in NYHA Class III and Class IV patients who do not respond adequately to conventional therapy (see CLINICAL TRIALS IN PULMONARY HYPERTENSION).

TO

FLOLAN is indicated for the treatment of pulmonary arterial hypertension (WHO Group 1) to improve exercise capacity. Studies establishing effectiveness included predominantly patients with NYHA Functional Class III-IV symptoms and etiologies of idiopathic or heritable PAH or PAH associated with connective tissue diseases.

In addition, several other minor modifications to the labeling were made:

In **ADVERSE REACTIONS** Tables 5 and 7, which provided for adverse events occurring in patients with <10% difference between FLOLAN and conventional therapy were deleted; however, several adverse event terms were retained within the labeling text.

In **ADVERSE REACTIONS/Adverse Events During Chronic Administration**, revise the following text

FROM

Interpretation of adverse events is complicated by the clinical features of PPH and PH/SSD, which are similar to some of the pharmacologic effects of FLOLAN (e.g., dizziness, syncope). Adverse events probably related to the underlying disease include dyspnea, fatigue, chest pain, edema, hypoxia, right ventricular failure, and pallor. Several adverse events, on the other hand, can clearly be attributed to FLOLAN. These include headache, jaw pain, flushing, diarrhea, nausea and vomiting, flu-like symptoms, and anxiety/nervousness.

TO

Interpretation of adverse events is complicated by the clinical features of PAH, which are similar to some of the pharmacologic effects of FLOLAN (e.g., dizziness, syncope). Adverse events which may be related to the underlying disease include dyspnea, fatigue, chest pain, edema, hypoxia, right ventricular failure, and pallor. Several adverse events, on the other hand, can clearly be attributed to FLOLAN. These include hypotension, bradycardia, tachycardia, pulmonary edema, bleeding at various sites, thrombocytopenia, headache, abdominal pain, pain (unspecified), sweating, rash, arthralgia, jaw pain, flushing, diarrhea, nausea and vomiting, flu-like symptoms, anxiety/nervousness, and agitation. In addition, chest pain, fatigue, and pallor have been reported during FLOLAN therapy, and a role for the drug in these events cannot be excluded.

In **ADVERSE REACTIONS/Adverse Events Attributable to the Drug Delivery System**, revise the following text

FROM

During controlled PPH trials of up to 12 weeks' duration, up to 21% of patients reported a local infection and up to 13% of patients reported pain at the injection site. During a controlled PH/SSD trial of 12 weeks' duration, 14% of patients reported a local infection and 9% of patients reported pain at the injection site. During long-term follow-up in the clinical trial of PPH, sepsis was reported at least once in 14% of patients and occurred at a rate of 0.32 infections/patient per year in patients treated with FLOLAN.

TO

During controlled PAH trials of up to 12 weeks' duration, the local infection rate was about 18%, and the rate for pain was about 11%. During long-term follow-up, sepsis was reported at a rate of 0.3 infections/patient per year in patients treated with FLOLAN.

Furthermore, minor revisions were made in the labeling to be consistent with the revisions made in **INDICATIONS AND USAGE**. Also, several sentences were changed from passive to active voice.

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We have completed our review of this supplemental application. It is approved, effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling text.

### **CONTENT OF LABELING**

As soon as possible, but no later than 14 days from the date of this letter, submit, using the FDA automated drug registration and listing system (eLIST), the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format, as described at <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>, that is identical to the enclosed labeling (text for the package insert, Medication Guide) and include the labeling changes proposed in any pending "Changes Being Effected" (CBE) supplements. Information on submitting SPL files using eLIST may be found in the guidance for industry titled "SPL Standard for Content of Labeling Technical Qs and As" at <http://www.fda.gov/downloads/DrugsGuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf>.

The SPL will be accessible from publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications for this NDA, including pending "Changes Being Effected" (CBE) supplements, for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 314.50(l)(1)(i)] in MS Word format that includes the changes approved in this supplemental application.

We request that the revised labeling approved today be available on your website within 10 days of receipt of this letter.

## **LETTERS TO HEALTH CARE PROFESSIONALS**

If you decide to issue a letter communicating important safety-related information about this drug product (i.e., a “Dear Health Care Professional” letter), we request that you submit, at least 24 hours prior to issuing the letter, an electronic copy of the letter to this NDA, to CDERMedWatchSafetyAlerts@fda.hhs.gov, and to the following address:

MedWatch Program  
Office of Special Health Issues  
Food and Drug Administration  
10903 New Hampshire Ave  
Building 32, Mail Stop 5353  
Silver Spring, MD 20993

## **REPORTING REQUIREMENTS**

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, please call Dan Brum, PharmD, BCPS, RAC, Regulatory Project Manager, at (301)796-0578.

Sincerely,

*{See appended electronic signature page}*

Norman Stockbridge, M.D., Ph.D.  
Director  
Division of Cardiovascular and Renal Products  
Office of Drug Evaluation I  
Center for Drug Evaluation and Research

Enclosures:

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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NORMAN L STOCKBRIDGE  
03/29/2011