

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

**APPLICATION NUMBER: 20-444/S003**

**CORRESPONDENCE**

## MEMORANDUM OF TELECON

DATE: March 30, 2000

APPLICATION NUMBER: NDA 20-444/S-003; FLOLAN (epoprostenol sodium) for Injection

BETWEEN:

Name: Roger Gaby, Project Director  
Phone: (919) 483-9035  
Representing: Glaxo Wellcome, Inc.

AND

Name: Brian Strongin, Regulatory Health Project Manager  
Division of Gastrointestinal and Coagulation Drug Products, HFD-180

SUBJECT: Clinical Information Requests

### BACKGROUND

NDA 20-444 for FLOLAN (epoprostenol sodium) for Injection was approved September 20, 1995 for long-term intravenous treatment of primary pulmonary hypertension in NYHA Class III and Class IV patients who do not respond adequately to conventional therapy. Efficacy supplement SE1-003 was submitted December 11, 1998 for the treatment of pulmonary hypertension in patients associated with the scleroderma spectrum of disease in NYHA Class III and Class IV patients who do not respond adequately to conventional therapy. A Not Approvable action was taken May 26, 1999. The firm submitted a complete response October 13, 1999. The Medical Officer's Review dated March 23, 2000 recommends approval and includes labeling changes and 3 information requests.

### TODAY'S CALL

The following information requests included in the March 23, 2000 Medical Officer's Review were conveyed to the firm:

1. Provide additional information concerning Case A0106225A (agranulocytosis in a 34-year-old woman with primary pulmonary hypertension).
2. Examine the epoprostenol safety database with regard to neurologic adverse events, particularly for anxiety, nervousness, and depression to determine if modifications to the ADVERSE REACTIONS section of the package insert are warranted.
3. Examine the epoprostenol safety database for all cases of pneumonitis to see if further modifications to the ADVERSE REACTIONS section of the package insert are warranted.

NDA 20-444/S-003

Page 2 of 2

The sponsor was told that a response to these requests was not necessary prior to approval of S-003. The call was then concluded.

           /S/

3/30/00

Brian Strongin  
Regulatory Health Project Manager

cc: Original NDA 20-444/S-003  
HFD-180/Div. File  
HFD-180/Brian Strongin  
HFD-180/K.Robie-Suh

TELECON

APPEARS THIS WAY  
ON ORIGINAL



DEPARTMENT OF HEALTH & HUMAN SERVICES

NDA 20-444/S-003

Food and Drug Administration  
Rockville MD 20857

Glaxo Wellcome, Inc.  
Attention: Roger Gaby  
Project Director, Regulatory Affairs  
Five Moore Drive  
Research Triangle, NC 27709

OCT 21 1999

Dear Mr. Gaby:

We acknowledge receipt on October 14, 1999 of your October 13, 1999 resubmission to your supplemental new drug application for Flolan (epoprostenol sodium) for Injection.

This resubmission contains additional draft labeling and clinical information submitted in response to our May 26, 1999 action letter.

With this amendment, we have received a complete response to our May 26, 1999 action letter.

If you have any questions, contact me at (301) 827-7310.

Sincerely,

*/s/*

Brian Strongin  
Project Manager  
Division of Gastrointestinal and Coagulation Drug  
Products  
Office of Drug Evaluation III  
Center for Drug Evaluation and Research

APPEARS THIS WAY  
ON ORIGINAL

OCT 27 1999  
OCT 27 1999

NDA 20-444/S-003

Glaxo Wellcome, Inc.  
Attention: Roger Gaby  
Project Director, Regulatory Affairs  
Five Moore Drive  
Research Triangle Park, NC 27709

Dear Mr. Gaby:

Please refer to the meeting between representatives of your firm and FDA on Monday, September 27, 1999. The purpose of the meeting was to discuss your response to our May 26, 1999 Not Approvable letter.

A copy of our minutes of that meeting is enclosed. These minutes are the official minutes of the meeting. You are responsible for notifying us of any significant differences in understanding you may have regarding the meeting outcomes.

If you have any questions, contact me at (301) 827-7310.

Sincerely yours,

/S/

Brian Strongin  
Regulatory Health Project Manager  
Division of Gastrointestinal and  
Coagulation Drug Products  
Office of Drug Evaluation III  
Center for Drug Evaluation and Research

cc:

Archival NDA 20-444/S-003  
HFD-180/Division File  
HFD-180/B. Strongin  
HFD-180/M. Kidwell

Drafted by: mk 10/5/99  
Initialed by: B. Strongin 10/5/99  
Final: M. Kidwell 10/5/99  
Filename: \_\_\_\_\_  
GENERAL CORRESPONDENCE (Minutes Sent)



DEPARTMENT OF HEALTH & HUMAN SERVICES

NDA 20-444/S-003

Food and Drug Administration  
Rockville MD 20857

Glaxo Wellcome, Inc  
Attention: Roger Gaby  
Project Director, Regulatory Affairs  
Five Moore Drive  
Research Triangle Park, NC 27709

**APR 23 1999**

Dear Mr. Gaby:

Please refer to your pending December 11, 1998 supplemental new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Flolan (epoprostenol sodium) for Injection.

We are reviewing the Statistical section of your submission and have the following comments and information requests:

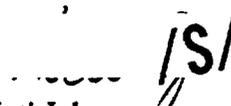
1. Concerning the randomization for Study VA1A4001, entitled, "A Multicenter, Open-Label, Randomized, Parallel Comparison of the Safety and Efficacy of Chronic Flolan (epoprostenol sodium) Infusions Plus Conventional Therapy to Conventional Therapy Alone In Patients with Pulmonary Hypertension Secondary to the Scleroderma Spectrum of Diseases; A Twelve-Week Study":
  - A. Provide the randomization list employed for treatment assignment.
  - B. Explain how patients were allocated to a treatment group.
  - C. Explain the method of randomization (e.g., stratification, blocking).
  - D. Provide information about the predetermined randomization code, block size, the predetermined and actual treatment assignment, and the number of patients screened.
  - E. Section 4.3.4.3.A of the Report for Study VA1A4001 states that, "The code itself was known only to them and unblinding during the Treatment Phase could only be performed by \_\_\_\_\_ staff assigned to the study." Clarify if treatment was blinded in this study and if so, explain how blinding was maintained throughout the study.
2. The protocol attached to the Report for Study VA1A4001 is a revised version. Please resubmit the original protocol and provide the application number (IND or NDA), submission date, and serial number for the original submission.

We would appreciate your prompt written response so we can continue our evaluation of your supplemental application.

These comments are being provided to you prior to completion of our review of the application to give you preliminary notice of issues that have been identified. Per the user fee reauthorization agreements, these comments do not reflect a final decision on the information reviewed and should not be construed to do so. These comments are preliminary and are subject to change as the review of your application is finalized. In addition, we may identify other information that must be provided prior to approval of this application. If you choose to respond to the issues raised in this letter during this review cycle, depending on the timing of your response, as per the user fee reauthorization agreements, we may or may not be able to consider your response prior to taking an action on your application during this review cycle.

If you have any questions, contact me at (301) 827-7310.

Sincerely,

  
Kati Johnson  
Supervisory Consumer Safety Officer  
Division of Gastrointestinal and  
Coagulation Drug Products  
Office of Drug Evaluation III  
Center for Drug Evaluation and Research

APPEARS THIS WAY  
ON ORIGINAL

CSO/Steingard

NDA 20-444/S-003

Glaxo Wellcome, Inc.  
Attention: Roger Gaby  
Project Director, Regulatory Affairs  
Five Moore Drive  
Research Triangle Park, NC 27709

FEB 11 1999

Dear Mr. Gaby:

Please refer to your pending December 11, 1998 supplemental new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Flolan (epoprostenol sodium) for Injection.

We are reviewing the clinical and statistical sections of your submission and have the following information requests:

1. Please provide a presentation of safety and effectiveness data by gender, race, and age subgroups. In addition, identify any modifications of dose or dose interval needed for specific subgroups.
2. Please provide an estimate of the extent of pediatric (birth to 16 years) usage of Flolan for Injection for the proposed indication.
3. Please provide baseline, demographic, efficacy, and safety data for Study VAI.A-4001 in SAS data set format on diskette.

We would appreciate your prompt written response so we can continue our evaluation of your supplemental application.

These comments are being provided to you prior to completion of our review of the application to give you preliminary notice of issues that have been identified. Per the user fee reauthorization agreements, these comments do not reflect a final decision on the information reviewed and should not be construed to do so. These comments are preliminary and are subject to change as the review of your application is finalized. In addition, we may identify other information that must be provided prior to approval of this application. If you choose to respond to the issues raised in this letter during this review cycle, depending on the timing of your response, as per the user fee reauthorization agreements, we may or may not be able to consider your response prior to taking an action on your application during this review cycle.

If you have any questions, contact me at (301) 827-7310.

Sincerely,

/S/ 2/11/99

Kati Johnson  
Supervisory Consumer Safety Officer  
Division of Gastrointestinal and Coagulation Drug Products  
Office of Drug Evaluation III  
Center for Drug Evaluation and Research

CS/K 4/5/99

NDA 20-444/S-003

Glaxo Wellcome, Incorporated  
Attention: Roger Gaby  
Product Director  
Five Moore Drive  
Research Triangle Park, NC 27709

FEF - 8 1998

Dear Mr. Gaby:

We acknowledge receipt of your efficacy supplemental application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product: Flolan (epoprostenol sodium) for Injection

NDA Number: 20-444

Supplement Number: S-003

Therapeutic Classification: Priority (P)

Date of Supplement: December 11, 1998

Date of Receipt: December 14, 1998

This supplement provides for the use of Flolan (epoprostenol sodium) for Injection for the treatment of secondary pulmonary hypertension in patients refractory to conventional therapy.

Unless we notify you within 60 days of our receipt date that the application is not sufficiently complete to permit a substantive review, this application will be filed under section 505(b) of the Act on February 12, 1999 in accordance with 21 CFR 314.101(a). If the application is filed, the user fee goal date will be June 14, 1999.

Please cite the application number listed above at the top of the first page of any communications concerning this application. All communications concerning this supplemental application should be addressed as follows:

U.S. Postal/Courier/Overnight Mail:

Food and Drug Administration  
Center for Drug Evaluation and Research  
Division of Gastrointestinal and Coagulation Drug Products, HFD-180  
Attention: Division Document Room  
5600 Fishers Lane  
Rockville, Maryland 20857

NDA 20-444/S-003  
Page 2

If you have any questions, contact me at (301) 827-7310.

Sincerely,

Brian Strongin  
Project Manager  
Division of Gastrointestinal and Coagulation Drug  
Products  
Office of Drug Evaluation III  
Center for Drug Evaluation and Research

APPEARS THIS WAY  
ON ORIGINAL

## MEMORANDUM OF MEETING MINUTES

**Meeting Date:** September 27, 1999  
**Time:** 2:00PM – 3:30PM  
**Location:** Parklawn Building, Conference Room C  
**Application:** NDA 20-444/SE1-003;  
Flolan (epoprostenol sodium) for Injection  
**Type of Meeting:** End-of-Review Conference  
**Meeting Chair:** Lilia Talarico, M.D.  
**Meeting Recorder:** Brian Strongin

### **FDA Attendees, Titles, and Office/Division:**

#### The Division of Gastrointestinal and Coagulation Drug Products

Lilia Talarico, M.D.	Director
Steve Aurecchia, M.D.	Deputy Director
Kathy Robie-Suh, M.D., Ph.D.	Medical Team Leader, Hematology
Brian Strongin	Regulatory Health Project Manager

#### The Division of Biometrics II

Paul Flyer, Ph.D.	Team Leader, Biometrics
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#### Office of Orphan Products Development

John McCormick, M.D.	Supervisory Medical Officer
Melvin Lessing	Consumer Safety Officer

### **External Constituent Attendees and Titles:**

#### Glaxo Wellcome, Inc.

Richard Kent, M.D.	Vice President, Medical Operations
Katharine Knobil, M.D.	Senior Clinical Research Physician
Mieke Jobsis	Clinical Research Project Manager
Kenneth Kral	Associate Director, Biostatistics
Craig Metz, Ph.D.	Director, Regulatory Affairs
Roger Gaby	Project Director, Regulatory Affairs

Consultant

**Background:**

NDA 20-444 was approved September 20, 1995 for long-term intravenous treatment of primary pulmonary hypertension (PPH) in NYHA Class III and IV patients. Efficacy supplement S-003, submitted December 11, 1998, provided for long-term intravenous treatment of pulmonary hypertension

Safety and efficacy in S-003 is supported by Study VA1A4001, a multicenter, randomized, open-label, parallel group trial of Flolan plus conventional therapy versus conventional therapy alone for 12 weeks in patients having pulmonary hypertension secondary to the scleroderma spectrum of diseases (SPH/SSD). A Not Approvable action was taken May 26, 1999 with the following reasons cited in the action letter:

2. Study VA1A4001, as a single study, failed to adequately support efficacy because it lacked consistency across centers, subsets of patients, and across primary and secondary endpoints.

An additional clinical trial, \_\_\_\_\_ was recommended.

**Objectives:**

1. present and discuss additional information from the firm's clinical research program
2. provide a clinical practice perspective on the relevance of the endpoints evaluated in Study VA1A4001
3. respond to the points raised in the May 26, 1999 Not Approvable letter

**Discussion Points:**

1. \_\_\_\_\_ presented a brief overview of SPH/SSD and the role of epoprostenol in its treatment.
2. The firm's questions were discussed. The questions are italicized below followed by the Division's responses.

A. *Have any of the conditions or agreements established at our September 5, 1996 pre-NDA meeting to secure approval of this application changed?*

*If not, how does the Division feel the conditions established at the September 5, 1996 meeting have not been met?*

None of the conditions or agreements established at the September 5, 1996 pre-efficacy supplement meeting have changed.

The information provided in this application is insufficient to extrapolate from the population studied, patients with SPH/SSD, to the population for which labeling is requested, patients with \_\_\_\_\_. As stated in our May 26, 1999 Not Approvable letter, we lack the necessary data/information to adequately assess the morbidity and mortality consequences and evaluate the benefit/risk of Flolan for Injection in the different \_\_\_\_\_ subpopulations. Some clinical experience in the patient subpopulations within \_\_\_\_\_ is necessary to adequately assess the benefit/risk in these subpopulations. A statistically significant effect in each subpopulation is not necessary.

Due to weaknesses intrinsic to the primary endpoint in Study VA1A4001, exercise capacity as measured by the maximum distance walked during the six minute walk test, and since it is a single study, further support for the internal consistency in Study VA1A4001 is necessary. To further support the internal consistency (within patients both for the treatment effect over time and among primary and secondary endpoints) of Study VA1A4001, provide a list of patients showing outcomes (including baseline values, values and each timepoint, and the change) for all primary and secondary endpoints for each patient. Include any summary tables and descriptive statistics necessary to support both correlation among the efficacy endpoints and internal consistency over time. It may be helpful to provide an analysis of patient perceptions of clinical benefit or other similar measures in a broader secondary pulmonary hypertension population in a future study(s).

It is recommended that your response to our Not Approvable letter include draft labeling listing the PPH and SPH/SSD indications separately. The mortality benefit observed in PPH should be included in your proposed labeling as well as a statement that no mortality benefit has been observed in other patient populations.



NDA 20-444/SE1-003

Page 5 of 5

cc:

Original NDA 20-444/S-003

HFD-180/Div.Files

HFD-180/K.Robie-Suh

HFD-180/B.Strongin

HFD-720/P.Flyer

Drafted by: BKS/September 29, 1999

R/d init: KRS/September 30, 1999

LT/September 30, 1999

Final: BKS/October 1, 1999

Filename: \_\_\_\_\_

MEETING MINUTES

APPEARS THIS WAY  
ON ORIGINAL

**Pulmonary Hypertension  
Secondary to the  
Scleroderma Spectrum of Disease:**

**An Overview of the Disease  
and the Role of Epoprostenol**

[ ]

# Outline

- Pulmonary Hypertension (PH)
- Scleroderma Spectrum of Disease (SSD)
- PH in SSD
- Epoprostenol in the Treatment of PH
- Epoprostenol Trial in PH secondary to SSD
- Clinical Perspective

# **Pulmonary Hypertension (PPH/SPH)**

- **Characterized by progressive elevation of pulmonary artery pressure and vascular resistance**
- **Patients are limited by:**
  - Shortness of breath
  - Dyspnea on exertion
  - Pre-syncope and syncope
  - Chest pain
  - Edema and ascites
- **Often leads to right ventricular failure and death**

# **Scleroderma Spectrum of Disease (SSD)**

- SSD includes:
  - diffuse scleroderma
  - limited scleroderma (the CREST syndrome)
  - overlap syndrome
  - features of scleroderma
- These multi-system diseases are characterized by connective tissue and vascular abnormalities, with vascular lesions being prominent in all affected tissues
- SSD may be an endothelial-based disease, with endothelial dysfunction playing an important pathogenic role

# PH in SSD

- PH occurring in SSD consists of a direct proliferative vascular involvement of small- and medium-sized pulmonary arteries and arterioles
- Pathophysiologic and hemodynamic findings in PH secondary to SSD are very similar to those in PPH
- PH frequently complicates SSD:
  - up to 33% of patients with diffuse scleroderma
  - 10-50% of those with the CREST syndrome
    - A leading cause of mortality in CREST

# PH in SSD

- PH secondary to SSD is very often progressive and fatal
- There are no approved therapies for PH secondary to SSD
- Small numbers of patients have responded to captopril, nifedipine, and prazosin
- PH is widely considered by Rheumatologists to be the most devastating complication of scleroderma, particularly in Limited Scleroderma (CREST)
- Orphan Disease

# UCHSC Pulmonary Hypertension Center Experience

- ~20% of patients have PPH
- ~80% have SPH
  - SSD is among the most common causes of severe SPH
    - Predominantly female population
    - Therapeutic options are very limited in this group
      - Very few (< 20%) are “vasoresponders” and respond to available oral agents such as Ca<sup>2+</sup>-channel blockers

# Goals of Therapy

- Relief of Symptoms
  - Improved ability to conduct day to day activities
  - Improved exercise capacity
  - Improved dyspnea on exertion
- Improvement in cardiopulmonary hemodynamics
- Patient satisfaction with treatment
- Improved survival

# Epoprostenol

- Has both vasodilating and anti-platelet effects
- Is highly effective in the treatment of primary pulmonary hypertension (PPH), improving:
  - Exercise capacity
  - Cardiopulmonary hemodynamics
  - NYHA functional class
  - Quality of life
  - Survival

# Side Effects of Epoprostenol

- Dose-related:
  - Jaw pain with initial mastication
  - Flushing
  - Diarrhea
  - Rash
  - Headache
  - Nausea
- Delivery system-related:
  - Site, tunnel, bloodstream infections
  - Catheter or pump failure

# Dose Adjustment of Epoprostenol (PPH/SPH)

- Indications for a dose increase:
  - Persistent signs & symptoms of PH
  - No intolerable side effects:
    - Severe jaw pain, flushing, diarrhea, nausea, headache, foot pain
    - Will increase the dose if only mild-moderate jaw pain or mild diarrhea
- Indications for a dose decrease:
  - Intolerable side effects:
    - Persistent headache, nausea, severe diarrhea, severe foot pain, severe blotchy erythematous rash, systemic hypotension

# Study VA1A 4001

- **Investigator-initiated study**
  - Enthusiastic support from the Rheumatology community
  - Input from an internationally-recognized expert in the treatment of scleroderma
- The study was done for the following reasons:
  - Poor prognosis of PH due to SSD
  - Epoprostenol's effectiveness in the treatment of PPH
  - The similarities between PPH and SPH due to SSD in terms of:
    - Symptoms
    - Pathophysiology
    - Response to therapy
  - Limited availability of epoprostenol for off-label usage in the treatment of PH due to SSD

# Study VA1A 4001

- Pre-reviewed with FDA, and appropriate changes made
- Involved virtually all of the major pulmonary hypertension referral centers in the US
- It was modeled after the previous trial in PPH
  - Results in SPH corroborated those from the previous study in PPH
- The similarities between the results of these two studies - contributed to the WHO's reclassification of PH

# 44 yo F with CREST

- [ ]
  - Developed breathlessness in 8/94
  - Could not tolerate  $\text{Ca}^{2+}$ -channel blocker therapy
  - Cath 2/95: PA 68/40, mean 50; CO 2.6 L/min; PVR 17.9
  - Evaluated for possible lung transplant
  - Rapidly progressive RV failure
  - Applied for, and received emergency IND from FDA on 7/27/95
  - Died 7/28/95, prior to receiving
-

# 22 yo F with SSD

- Developed DOE and exercise intolerance in spring '95
- In 1/97, due to progressive DOE, she enrolled in the randomized, controlled trial of epoprostenol in PH due to SSD

<u>Date</u>	<u>8/95</u>	<u>1/97</u>	<u>epoprostenol</u> <u>4/97</u>
PAP, (m)	43/20, 29	54/25, 36	36/17, 25
CO	6.3	5.9	6.3
CI	3.3	3.1	3.3
PVR	3.9	4.2	2.4

- Has had several line-related infections
- Works, plays golf, and bowls
  - Despite recent flare of SSD, bowled on 9/17; \_\_\_\_\_

# 22 yo F with SSD

- Developed DOE and exercise intolerance in spring '95
- In 1/97, due to progressive DOE, she enrolled in the randomized, controlled trial of epoprostenol in PH due to SSD

<u>Date</u>	<u>8/95</u>	<u>1/97</u>	epoprostenol <u>4/97</u>
PAP, (m)	43/20, 29	54/25, 36	36/17,25
CO	6.3	5.9	6.3
CI	3.3	3.1	3.3
PVR	3.9	4.2	2.4

- Has had several line-related infections
- She works, plays golf, & bowls  
(Despite recent flare of SSD, bowled on 9/17; \_\_\_\_\_ )

# 44 yo F with Overlap Syndrome

- First seen in PH Clinic 5/99 with:
  - Fatigue
  - Inability to walk even short distances w/o assistance
  - Arrived in a wheelchair
  - Significant LE edema
  - Recent ECHO showing grossly enlarged RA & RV, flattening of IVS, severe PI & TR
  - Recent cath showing: PAP 56/43, 48; CO 3.1 L/min, CI 1.4 L/min/m<sup>2</sup>
- Began on epoprostenol 7/26/99
- Activity tolerance had improved by the first F/U visit to the Clinic on 8/16/99
- Activity tolerance significantly improved by second F/U visit to the Clinic on 9/15/99. Now ambulating into the clinic (as opposed to using a wheelchair). Quite pleased with her progress.

# **Availability of Epoprostenol**

- **Currently available to patients with PPH:**
  - Insurers cover this FDA-approved use
  - Indigent patients receive it through an industry-sponsored assistance program
- **Current availability for patients with PH due to SSD is variable:**
  - Some insurers cover this off-label usage, often after a substantial period of review, resulting in delay of therapy.
  - Some insurers refuse to cover off-label usage, noting an exclusion in their plan
  - Medicare has been covering its usage in this situation, based upon the results of the study as described in abstract form. However, this could change if a final decision is made by FDA to not approve the drug.
  - Other insurers may begin to refuse payment for patients with SSD