CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

022260Orig1s005

Trade Name: **Veletri**

Generic Name: **Epoprostenol sodium**

Sponsor: **Actelion Pharmaceuticals Ltd.**

Approval Date: 06/28/2012

Indications: VELETRI is a prostanoid vasodilator indicated for the treatment of pulmonary arterial hypertension (PAH) (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.

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APPROVAL LETTER

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 22260/S-005

APPROVAL LETTER

Acetelion Clinical Research, Inc.
Attention: Sheila Mathias, Ph.D.
Director, Drug Regulatory Affairs
1820 Chapel Avenue West, Suite 300
Cherry Hill, NJ 08002

Dear Dr. Mathias:

Please refer to your supplemental New Drug Application (sNDA) dated February 28, 2012, received February 29, 2012, submitted under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act, for Veletri (epoprostenol sodium) for Injection, 0.5 mg and 1.5 mg.

We acknowledge receipt of your amendments dated April 11, May 2 (two), June 19 and 22, 2012.

This supplemental new drug application provides for a change in excipient in the sterile diluent from mannitol to sucrose, a change in both drug substance manufacturer and drug product manufacturer, addition of a new strength (0.5 mg epoprostenol per vial), and a change to in-use directions and storage conditions based on new stability data.

We have completed our review of this supplemental new drug application, as amended. This supplement is approved.

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, please call Dan Brum, Pharm.D., 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: package insert and carton and container labeling

CENTER FOR DRUG EVALUATION AND RESEARCH

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LABELING

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use VELETRI safely and effectively. See full prescribing information for VELETRI.

VELETRI (epoprostenol) for Injection
Initial U.S. Approval: 1995

----------RECENT MAJOR CHANGES----------
Dosage and Administration (2.4) 06/2012

----------INDICATIONS AND USAGE----------
VELETRI is a prostanoid vasodilator indicated for the treatment of pulmonary arterial hypertension (PAH) (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. (1)

----------DOSAGE AND ADMINISTRATION----------
- Dosage
  - Infusion of VELETRI should be initiated at 2 ng/kg/min and increased in increments of 2 ng/kg/min every 15 minutes or longer until dose-limiting pharmacologic effects are elicited or until a tolerance limit to the drug is established. (2.1)
  - If symptoms of pulmonary hypertension persist or recur after improving - the infusion should be increased by 1- to 2-ng/kg/min increments at intervals sufficient to allow assessment of clinical response; these intervals should be at least 15 minutes. (2.2)
- Administration
  - VELETRI is administered by continuous intravenous infusion via a central venous catheter using an ambulatory infusion pump. (2.3)
  - Do not mix with any other parenteral medications or solutions prior to or during administration. (2.4)
- Reconstitution
  - Reconstituted in vial with only 5 mL of either Sterile Water for Injection or Sodium Chloride 0.9% Injection.
  - VELETRI solution reconstituted and immediately diluted to the final concentration in the drug delivery reservoir can be administered per the conditions of use as outlined in Table 1. (2.4)
  - Solution for chronic delivery should be prepared in a drug delivery reservoir appropriate for the infusion pump. (2.4)

----------DOSAGE FORMS AND STRENGTHS----------
10 mL vial with 0.5 mg (500,000 ng) or 1.5 mg (1,500,000 ng) VELETRI. (3)

----------CONTRAINDICATIONS----------
- Congestive heart failure due to severe left ventricular systolic dysfunction (4)
- Pulmonary edema (4)
- Hypersensitivity to the drug or to structurally related compounds (4)

----------WARNINGS AND PRECAUTIONS----------
- VELETRI should be used only by clinicians experienced in the diagnosis and treatment of pulmonary hypertension. (5.1)
- Reconstitute only as directed, with Sterile Water for Injection or Sodium Chloride 0.9% Injection.(5.1)
- Do not abruptly lower the dose or withdraw dosing. All dosing initiation and changes should be closely monitored. (5.3, 5.4)

----------ADVERSE REACTIONS----------
- Most common adverse reactions during:
  - Dose Initiation and Escalation: Nausea, vomiting, headache, hypotension, flushing, chest pain, anxiety, dizziness, bradycardia, dyspnea, abdominal pain, musculoskeletal pain, and tachycardia (6.1)
  - Chronic Dosing: Headache, jaw pain, flushing, diarrhea, nausea and vomiting, flu-like symptoms, and anxiety/nervousness (6.1)

To report SUSPECTED ADVERSE REACTIONS, please contact: ACTELION at 1-866-228-3546 or FDA at 1-800-FDA-1088, or http://www fda.gov/medwatch

----------DRUG INTERACTIONS----------
- Diuretics, antihypertensive agents, or other vasodilators: reduction in blood pressure (7)
- Antiplatelet agents or anticoagulants: increase the risk of bleeding (7)
- Patients on digoxin: elevations of digoxin concentrations clinically significant in patients prone to digoxin toxicity (7)

See 17 for PATIENT COUNSELING INFORMATION

Revised: 06/2012

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

VELETRI is indicated for the treatment of pulmonary arterial hypertension (PAH) (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.

2 DOSAGE AND ADMINISTRATION

Important Note: Reconstitute VELETRI only as directed with Sterile Water for Injection, USP, or Sodium Chloride 0.9% Injection, USP. Do not dilute reconstituted solutions of VELETRI or administer it with other parenteral solutions or medications *[see Warnings and Precautions (5.1)]*.

2.1 Dosage

Prepare continuous chronic infusion of VELETRI as directed, and administer through a central venous catheter. Temporary peripheral intravenous infusion may be used until central access is established. Initiate chronic infusion of VELETRI at 2 ng/kg/min and increase in increments of 2 ng/kg/min every 15 minutes or longer until a tolerance limit to the drug is established or further increases in the infusion rate are not clinically warranted. If dose-limiting pharmacologic effects occur, then decrease the infusion rate until VELETRI is tolerated. In clinical trials, the most common dose-limiting adverse events were nausea, vomiting, hypotension, sepsis, headache, abdominal pain, or respiratory disorder (most treatment-limiting adverse events were not serious). If the initial infusion rate of 2 ng/kg/min is not tolerated, use a lower dose.

In the controlled 12-week trial in PAH/SSD, for example, the dose increased from a mean starting dose of 2.2 ng/kg/min. During the first 7 days of treatment, the dose was increased daily to a mean dose of 4.1 ng/kg/min on day 7 of treatment. At the end of week 12, the mean dose was 11.2 ng/kg/min. The mean incremental increase was 2 to 3 ng/kg/min every 3 weeks.

2.2 Dosage Adjustments

Base changes in the chronic infusion rate on persistence, recurrence, or worsening of the patient's symptoms of pulmonary hypertension and the occurrence of adverse events due to excessive doses of VELETRI. In general, expect increases in dose from the initial chronic dose.

Consider increments in dose if symptoms of pulmonary hypertension persist or recur. Adjust the infusion by 1- to 2-ng/kg/min increments at intervals sufficient to allow assessment of clinical response; these intervals should be at least 15 minutes. In clinical trials, incremental increases in dose occurred at intervals of 24 to 48 hours or longer. Following establishment of

new chronic infusion rate, observe the patient, and monitor standing and supine blood pressure and heart rate for several hours to ensure that the new dose is tolerated.

During chronic infusion, the occurrence of dose-limiting pharmacological events may necessitate a decrease in infusion rate, but the adverse event may occasionally resolve without dosage adjustment. Make dosage decreases gradually in 2-ng/kg/min decrements every 15 minutes or longer until the dose-limiting effects resolve. Avoid abrupt withdrawal of VELETRI or sudden large reductions in infusion rates. Except in life-threatening situations (e.g., unconsciousness, collapse, etc.), infusion rates of VELETRI should be adjusted only under the direction of a physician.

In patients receiving lung transplants, doses of epoprostenol were tapered after the initiation of cardiopulmonary bypass.

2.3 Administration

VELETRI, once prepared as directed [see *Reconstitution (2.4)*], is administered by continuous intravenous infusion via a central venous catheter using an ambulatory infusion pump. During initiation of treatment, VELETRI may be administered peripherally.

Infusion sets with an in-line 0.22 micron filter should be used.

The ambulatory infusion pump used to administer VELETRI should: (1) be small and lightweight, (2) be able to adjust infusion rates in 2-ng/kg/min increments, (3) have occlusion, end-of-infusion, and low-battery alarms, (4) be accurate to $\pm$6% of the programmed rate, and (5) be positive pressure-driven (continuous or pulsatile) with intervals between pulses not exceeding 3 minutes at infusion rates used to deliver VELETRI. The reservoir should be made of polyvinyl chloride, polypropylene, or glass. The infusion pump used in the most recent clinical trials was the CADD-1 HFX 5100 (SIMS Deltec). A 60-inch microbore non-DEHP extension set with proximal antisyphon valve, low priming volume (0.9 mL), and in-line 0.22 micron filter was used during clinical trials.

To avoid potential interruptions in drug delivery, the patient should have access to a backup infusion pump and intravenous infusion sets. Consider a multi-lumen catheter if other intravenous therapies are routinely administered.

2.4 Reconstitution

VELETRI is stable only when reconstituted as directed using Sterile Water for Injection, USP, or Sodium Chloride 0.9% Injection, USP. Do not reconstitute or mix VELETRI with any other parenteral medications or solutions prior to or during administration. Each vial is for single use only; discard any unused solution.

Use after reconstitution and immediate dilution to final concentration

Use at room temperature (77°F/25°C)

VELETRI solution reconstituted with 5 mL of Sterile Water for Injection, USP or Sodium Chloride 0.9% Injection**,** and immediately diluted to the final concentration in the drug delivery reservoir can be administered at room temperature per the conditions of use as outlined in Table 1.

Table 1: Maximum duration of administration (hours) at room temperature (77°F/ 25°C) of fully diluted solutions in the drug delivery reservoir*

Final concentration range	**Immediate administration**	**If stored for up to 8 days at 36° to 46°F (2° to 8°C)**
0.5mg vial		
≥3,000 ng/mL and <15,000 ng/mL	48 hours	24 hours
1.5mg vial		
≥15,000 ng/mL and < 60,000 ng/mL	48 hours	48 hours
≥60,000 ng/mL	72 hours	48 hours

∗Short excursions at 104°F (40°C) are permitted for up to:
2 hours for concentrations below15,000 ng/mL
4 hours for concentrations between 15,000 ng/mL and 60,000 ng/mL
8 hours for concentrations above 60,000 ng/mL

Use at higher temperatures >77°F up to 104°F (>25° to 40°C)

Temperatures greater than 77°F and up to 86 °F (>25°C to 30°C): A single reservoir of fully diluted solution of 60 000 ng/mL or above of VELETRI prepared as directed can be administered (either immediately or after up to 8 days storage at 36° to 46°F (2° to 8°C))for up to 48 hours. For diluted solutions of less than 60 000 ng/mL, pump reservoirs should be changed every 24 hours.

Temperatures up to 104°F (40°C**):** Fully diluted solutions of 60,000 ng/mL or above of VELETRI, prepared as directed, can be immediately administered for periods up to 24 hours.

Do not expose this solution to direct sunlight.

A concentration for the solution of VELETRI should be selected that is compatible with the infusion pump being used with respect to minimum and maximum flow rates, reservoir capacity, and the infusion pump criteria listed above. VELETRI, when administered chronically, should be prepared in a drug delivery reservoir appropriate for the infusion pump. Outlined in Table 2 are directions for preparing different concentrations of VELETRI. **Each vial is for single use only; discard any unused solution.**

Table 2: Reconstitution and Dilution Instructions

To make 100 mL of solution with Final Concentration (ng/mL) of:	**Directions:**
Using the 0.5 mg vial	
3,000 ng/ml	Dissolve contents of **one 0.5 mg vial** with 5 mL of Sterile Water for Injection, USP or Sodium Chloride 0.9% Injection, USP. Withdraw 3 mL of the vial contents and add to a sufficient volume of the identical diluent to make a total of 100 mL.
5,000 ng/mL	Dissolve contents of **one 0.5 mg vial** with 5 mL of Sterile Water for Injection, USP, or Sodium Chloride 0.9% Injection, USP. Withdraw entire vial contents and add to a sufficient volume of the identical diluent to make a total of 100 mL.
10,000 ng/ml	Dissolve contents of **two 0.5 mg vials** each with 5 mL of Sterile Water for Injection, USP, or Sodium Chloride 0.9% Injection, USP. Withdraw entire vial contents and add to a sufficient volume of the identical diluent to make a total of 100 mL.
Using the 1.5 mg vial	
15,000 ng/mL*	Dissolve contents of **one 1.5 mg vial** with 5 mL of Sterile Water for Injection, USP, or Sodium Chloride 0.9% Injection, USP. Withdraw entire vial contents and add to a sufficient volume of the identical diluent to make a total of 100 mL.
30,000 ng/mL*	Dissolve contents of **two 1.5 mg vials** each with 5 mL of Sterile Water for Injection, USP, or Sodium Chloride 0.9% Injection, USP. Withdraw entire vial contents and add to a sufficient volume of the identical diluent to make a total of 100 mL.
* Higher concentrations may be prepared for patients who receive VELETRI long-term.	

Infusion rates may be calculated using the following formula:

$$\textbf{Infusion Rate (mL/hr)} = \frac{\textbf{[Dose (ng/kg/min) x Weight (kg) x 60 min/hr]}}{\textbf{Final Concentration (ng/mL)}}$$

Tables 3 to 7 provide infusion delivery rates for doses up to 16 ng/kg/min based upon patient weight, drug delivery rate, and concentration of the solution of VELETRI to be used. These tables may be used to select the most appropriate concentration of VELETRI that will result in an infusion rate between the minimum and maximum flow rates of the infusion pump and that will allow the desired duration of infusion from a given reservoir volume. For infusion/dose rates lower than those listed in Tables 3 to 7, it is recommended that the pump rate be set by a healthcare professional such that steady state is achieved in the patient, keeping in mind the half life of epoprostenol is no more than six minutes. Higher infusion rates, and therefore, more concentrated solutions may be necessary with long-term administration of VELETRI.

Table 3: Infusion Rates for VELETRI at a Concentration of 3,000 ng/mL

Patient weight (kg)	Dose or Drug Delivery Rate (ng/kg/min)			
	2	3	4	5
	Infusion Delivery Rate (mL/hr)			
20	---	1.2	1.6	2.0
30	1.2	1.8	2.4	3.0
40	1.6	2.4	3.2	4.0
50	2.0	3.0	4.0	---
60	2.4	3.6	---	---
70	2.8	---	---	---
80	3.2	---	---	---
90	3.6	---	---	---
100	4.0	---	---	---

Table 4: Infusion Rates for VELETRI at a Concentration of 5,000 ng/mL

Patient weight (kg)	Dose or Drug Delivery Rate (ng/kg/min)						
	2	4	6	8	10	12	14
	Infusion Delivery Rate (mL/hr)						
20	---	1.0	1.4	1.9	2.4	2.9	3.4
30	---	1.4	2.2	2.9	3.6	---	---
40	1.0	1.9	2.9	3.8	---	---	---
50	1.2	2.4	3.6	---	---	---	---
60	1.4	2.9	---	---	---	---	---
70	1.7	3.4	---	---	---	---	---
80	1.9	3.8	---	---	---	---	---
90	2.2	---	---	---	---	---	---
100	2.4	---	---	---	---	---	---

Table 5: Infusion Rates for VELETRI at a Concentration of 10,000 ng/mL

Patient weight (kg)	Dose or Drug Delivery Rate (ng/kg/min)						
	4	6	8	10	12	14	16
	Infusion Delivery Rate (mL/hr)						
20	---	---	1.0	1.2	1.4	1.7	1.9
30	---	1.1	1.4	1.8	2.2	2.5	2.9
40	1.0	1.4	1.9	2.4	2.9	3.4	3.8
50	1.2	1.8	2.4	3.0	3.6	---	---
60	1.4	2.2	2.9	3.6	---	---	---
70	1.7	2.5	3.4	---	---	---	---
80	1.9	2.9	3.8	---	---	---	---
90	2.2	3.2	---	---	---	---	---
100	2.4	3.6	---	---	---	---	---

Table 6: Infusion Rates for VELETRI at a Concentration of 15,000 ng/mL

Patient weight (kg)	Dose or Drug Delivery Rate (ng/kg/min)						
	4	6	8	10	12	14	16
	Infusion Delivery Rate (mL/hr)						
20	---	---	---	---	1.0	1.1	1.3
30	---	---	1.0	1.2	1.4	1.7	1.9
40	---	1.0	1.3	1.6	1.9	2.2	2.6
50	---	1.2	1.6	2.0	2.4	2.8	3.2
60	1.0	1.4	1.9	2.4	2.9	3.4	3.8
70	1.1	1.7	2.2	2.8	3.4	3.9	---
80	1.3	1.9	2.6	3.2	3.8	---	---
90	1.4	2.2	2.9	3.6	---	---	---
100	1.6	2.4	3.2	4.0	---	---	---

Table 7: Infusion Rates for VELETRI at a Concentration of 30,000 ng/mL

Patient weight (kg)	Dose or Drug Delivery Rate (ng/kg/min)					
	6	8	10	12	14	16
30	---	---	---	---	---	1.0
40	---	---	---	1.0	1.1	1.3
50	---	---	1.0	1.2	1.4	1.6
60	---	1.0	1.2	1.4	1.7	1.9
70	---	1.1	1.4	1.7	2.0	2.2
80	1.0	1.3	1.6	1.9	2.2	2.6
90	1.1	1.4	1.8	2.2	2.5	2.9
100	1.2	1.6	2.0	2.4	2.8	3.2

3 DOSAGE FORMS AND STRENGTHS

VELETRI contains epoprostenol sodium equivalent to 0.5 mg (500,000 ng) or 1.5 mg (1,500,000 ng) epoprostenol and is supplied as a sterile lyophilized material in a 10 mL vial.

4 CONTRAINDICATIONS

A large study evaluating the effect of epoprostenol on survival in NYHA Class III and IV patients with congestive heart failure due to severe left ventricular systolic dysfunction was terminated after an interim analysis of 471 patients revealed a higher mortality in patients receiving epoprostenol plus conventional therapy than in those receiving conventional therapy alone. The chronic use of VELETRI in patients with congestive heart failure due to severe left ventricular systolic dysfunction is therefore contraindicated.

Some patients with pulmonary hypertension have developed pulmonary edema during dose initiation, which may be associated with pulmonary veno-occlusive disease. VELETRI should not be used chronically in patients who develop pulmonary edema during dose initiation.

VELETRI is also contraindicated in patients with known hypersensitivity to the drug or to structurally related compounds.

5 WARNINGS AND PRECAUTIONS

5.1 General

Reconstitute VELETRI only as directed using Sterile Water for Injection, USP, or Sodium Chloride 0.9% Injection, USP. Do not mix VELETRI with any other parenteral medications or solutions prior to or during administration.

VELETRI should be used only by clinicians experienced in the diagnosis and treatment of pulmonary hypertension. Carefully establish the diagnosis of idiopathic or heritable PAH or PAH/CTD.

5.2 Dose Initiation

VELETRI is a potent pulmonary and systemic vasodilator. Initiate VELETRI in a setting with adequate personnel and equipment for physiologic monitoring and emergency care. Dose initiation has been performed during right heart catheterization and without cardiac catheterization. During dose initiation, asymptomatic increases in pulmonary artery pressure coincident with increases in cardiac output occurred rarely. In such cases, consider dose reduction, but such an increase does not imply that chronic treatment is contraindicated.

5.3 Chronic Use and Dose Adjustment

During chronic use, deliver VELETRI continuously on an ambulatory basis through a permanent indwelling central venous catheter. Unless contraindicated, administer anticoagulant therapy to patients receiving VELETRI to reduce the risk of pulmonary thromboembolism or systemic embolism through a patent foramen ovale. To reduce the risk of infection, use aseptic technique in the reconstitution and administration of VELETRI and in routine catheter care. Because epoprostenol is metabolized rapidly, even brief interruptions in the delivery of VELETRI may result in symptoms associated with rebound pulmonary hypertension including dyspnea, dizziness, and asthenia. Intravenous therapy with VELETRI will likely be needed for prolonged periods, possibly years, so consider the patient's capacity to accept and care for a permanent intravenous catheter and infusion pump.

Based on clinical trials, the acute hemodynamic response (reduction in pulmonary artery resistance) to epoprostenol did not correlate well with improvement in exercise tolerance or survival during chronic use of epoprostenol. Adjust dosage of VELETRI during chronic use at the first sign of recurrence or worsening of symptoms attributable to pulmonary hypertension or the occurrence of adverse events associated with epoprostenol *[see Dosage and Administration (2)]*. Following dosage adjustments, monitor standing and supine blood pressure and heart rate closely for several hours.

5.4 Withdrawal Effects

Abrupt withdrawal (including interruptions in drug delivery) or sudden large reductions in dosage of VELETRI may result in symptoms associated with rebound pulmonary hypertension, including dyspnea, dizziness, and asthenia. In clinical trials, one Class III primary pulmonary hypertension patient's death was judged attributable to the interruption of epoprostenol. Avoid abrupt withdrawal.

5.5 Sepsis

See ***Adverse Reactions (6.1)***

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

During clinical trials, adverse events were classified as follows: (1) adverse events during dose initiation and escalation, (2) adverse events during chronic dosing, and (3) adverse events associated with the drug delivery system.

Adverse Events during Dose Initiation and Escalation

During early clinical trials, epoprostenol was increased in 2-ng/kg/min increments until the patients developed symptomatic intolerance. The most common adverse events and the adverse events that limited further increases in dose were generally related to vasodilation, the major pharmacologic effect of epoprostenol. The most common dose-limiting adverse events (occurring in ≥1% of patients) were nausea, vomiting, headache, hypotension, and flushing, but also include chest pain, anxiety, dizziness, bradycardia, dyspnea, abdominal pain, musculoskeletal pain, and tachycardia. Table 8 lists the adverse events reported during dose initiation and escalation in decreasing order of frequency.

Table 8: Adverse Events during Dose Initiation and Escalation

Adverse Events Occurring in ≥1% of Patients	Epoprostenol (n = 391)
Flushing	58%
Headache	49%
Nausea/vomiting	32%
Hypotension	16%
Anxiety, nervousness, agitation	11%
Chest pain	11%
Dizziness	8%
Bradycardia	5%
Abdominal pain	5%
Musculoskeletal pain	3%
Dyspnea	2%
Back pain	2%
Sweating	1%
Dyspepsia	1%
Hypesthesia/paresthesia	1%
Tachycardia	1%

Adverse Events during Chronic Administration:

Interpretation of adverse events is complicated by the clinical features of PAH, which are similar to some of the pharmacologic effects of epoprostenol (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 epoprostenol. 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 epoprostenol therapy, and a role for the drug in these events cannot be excluded.

Adverse Events during Chronic Administration for Idiopathic or Heritable PAH:

In an effort to separate the adverse effects of the drug from the adverse effects of the underlying disease, Table 9 lists adverse events that occurred at a rate at least 10% greater on epoprostenol than on conventional therapy in controlled trials for idiopathic or heritable PAH.

Table 9: Adverse Events Regardless of Attribution Occurring in Patients with Idiopathic or Heritable PAH with ≥ 10% Difference between Epoprostenol and Conventional Therapy Alone

Adverse Event	Epoprostenol (n = 52)	Conventional Therapy (n = 54)
Occurrence More Common With Epoprostenol		
General		
Chills/fever/sepsis/flu-like symptoms	25%	11%
Cardiovascular		
Tachycardia	35%	24%
Flushing	42%	2%
Gastrointestinal		
Diarrhea	37%	6%
Nausea/vomiting	67%	48%
Musculoskeletal		
Jaw pain	54%	0%
Myalgia	44%	31%
Nonspecific musculoskeletal pain	35%	15%
Neurological		
Anxiety/nervousness/tremor	21%	9%
Dizziness	83%	70%
Headache	83%	33%
Hypesthesia, hyperesthesia, paresthesia	12%	2%

Thrombocytopenia has been reported during uncontrolled clinical trials in patients receiving epoprostenol.

Adverse Events during Chronic Administration for PAH/SSD

In an effort to separate the adverse effects of the drug from the adverse effects of the underlying disease, Table 10 lists adverse events that occurred at a rate at least 10% greater on epoprostenol in the controlled trial.

Table 10: Adverse Events Regardless of Attribution Occurring in Patients with PAH/SSD With ≥10% Difference Between Epoprostenol and Conventional Therapy Alone

Adverse Event	Epoprostenol (n = 56)	Conventional Therapy (n = 55)
Cardiovascular		
Flushing	23%	0%
Hypotension	13%	0%
Gastrointestinal		
Anorexia	66%	47%
Nausea/vomiting	41%	16%
Diarrhea	50%	5%
Musculoskeletal		
Jaw pain	75%	0%
Pain/neck pain/arthralgia	84%	65%
Neurological		
Headache	46%	5%
Skin and Appendages		
Skin ulcer	39%	24%
Eczema/rash/urticaria	25%	4%

Although the relationship to epoprostenol administration has not been established, pulmonary embolism has been reported in several patients taking epoprostenol and there have been reports of hepatic failure.

Adverse Events Attributable to the Drug Delivery System

Chronic infusions of epoprostenol are delivered using a small, portable infusion pump through an indwelling central venous catheter. 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 epoprostenol. This rate was higher than reported in patients using chronic indwelling central venous catheters to administer parenteral nutrition, but lower than reported

in oncology patients using these catheters. Malfunctions in the delivery system resulting in an inadvertent bolus of or a reduction in epoprostenol were associated with symptoms related to excess or insufficient epoprostenol, respectively.

6.2 Post-Marketing Experience

In addition to adverse reactions reported from clinical trials, the following events have been identified during post-approval use of epoprostenol. Because they are reported voluntarily from a population of unknown size, estimates of frequency cannot be made. These events have been chosen for inclusion due to a combination of their seriousness, frequency of reporting, or potential causal connection to epoprostenol.
Blood and Lymphatic: Anemia, hypersplenism, pancytopenia, splenomegaly.
Endocrine and Metabolic: Hyperthyroidism

7 DRUG INTERACTIONS

Additional reductions in blood pressure may occur when VELETRI is administered with diuretics, antihypertensive agents, or other vasodilators. When other antiplatelet agents or anticoagulants are used concomitantly, there is the potential for VELETRI to increase the risk of bleeding. However, patients receiving infusions of epoprostenol in clinical trials were maintained on anticoagulants without evidence of increased bleeding. In clinical trials, epoprostenol was used with digoxin, diuretics, anticoagulants, oral vasodilators, and supplemental oxygen.

In a pharmacokinetic substudy in patients with congestive heart failure receiving furosemide or digoxin in whom therapy with epoprostenol was initiated, apparent oral clearance values for furosemide (n = 23) and digoxin (n = 30) were decreased by 13% and 15%, respectively, on the second day of therapy and had returned to baseline values by day 87. The change in furosemide clearance value is not likely to be clinically significant. However, patients on digoxin may show elevations of digoxin concentrations after initiation of therapy with epoprostenol, which may be clinically significant in patients prone to digoxin toxicity.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category B. Reproductive studies have been performed in pregnant rats and rabbits at doses up to 100 mcg/kg/day (600 mcg/m^2/day in rats, 2.5 times the recommended human dose, and 1,180 mcg/m^2/day in rabbits, 4.8 times the recommended human dose based on body surface area) and have revealed no evidence of impaired fertility or harm to the fetus due to epoprostenol. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

8.2 Labor and Delivery

The use of epoprostenol during labor, vaginal delivery, or cesarean section has not been adequately studied in humans.

8.3 Nursing Mothers

It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when VELETRI is administered to a nursing woman.

8.4 Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

8.5 Geriatric Use

Clinical studies of epoprostenol in pulmonary hypertension did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger patients. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function and of concomitant disease or other drug therapy.

10 OVERDOSAGE

Signs and symptoms of excessive doses of epoprostenol during clinical trials are the expected dose-limiting pharmacologic effects of epoprostenol, including flushing, headache, hypotension, tachycardia, nausea, vomiting, and diarrhea. Treatment will ordinarily require dose reduction of epoprostenol.

One patient with secondary pulmonary hypertension accidentally received 50 mL of an unspecified concentration of epoprostenol. The patient vomited and became unconscious with an initially unrecordable blood pressure. Epoprostenol was discontinued and the patient regained consciousness within seconds. In clinical practice, fatal occurrences of hypoxemia, hypotension, and respiratory arrest have been reported following overdosage of epoprostenol.

Single intravenous doses of epoprostenol at 10 and 50 mg/kg (2,703 and 27,027 times the recommended acute phase human dose based on body surface area) were lethal to mice and rats, respectively. Symptoms of acute toxicity were hypoactivity, ataxia, loss of righting reflex, deep slow breathing, and hypothermia.

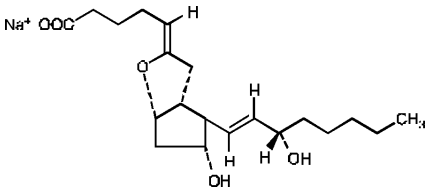
11 DESCRIPTION

Epoprostenol sodium is the sodium salt of epoprostenol, formulated as a sterile lyophilized powder for intravenous (IV) administration. Each vial of VELETRI contains epoprostenol

sodium equivalent to either 0.5 mg (500,000 ng) or 1.5 mg (1,500,000 ng) epoprostenol, 100 mg sucrose, and 50 mg arginine. Sodium hydroxide is added to adjust pH.

Epoprostenol (PGI_2, PGX, prostacyclin), a metabolite of arachidonic acid, is a naturally occurring prostaglandin with potent vasodilatory activity and inhibitory activity of platelet aggregation.

Epoprostenol is (5*Z*,9a,lla,13*E*,15*S*)-6,9-epoxy-11,15-dihydroxyprosta-5,13-dien-l-oic acid. Epoprostenol sodium has a molecular weight of 374.45 and a molecular formula of $C_{20}H_{31}NaO_5$. The structural formula is:



VELETRI is a white to off-white lyophilized powder material. It is reconstituted with Sterile Water for Injection, USP, or Sodium Chloride 0.9% Injection, USP.

The reconstituted solution of VELETRI has a pH ranging from 11 to 13 and is increasingly unstable at a lower pH.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Epoprostenol has 2 major pharmacological actions: (1) direct vasodilation of pulmonary and systemic arterial vascular beds, and (2) inhibition of platelet aggregation.

12.2 Pharmacodynamics

In animals, the vasodilatory effects reduce right- and left-ventricular afterload and increase cardiac output and stroke volume. The effect of epoprostenol on heart rate in animals varies with dose. At low doses, there is vagally mediated bradycardia, but at higher doses, epoprostenol causes reflex tachycardia in response to direct vasodilation and hypotension. No major effects on cardiac conduction have been observed. Additional pharmacologic effects of epoprostenol in animals include bronchodilation, inhibition of gastric acid secretion, and decreased gastric emptying.

12.3 Pharmacokinetics

Epoprostenol is rapidly hydrolyzed at neutral pH in blood and is also subject to enzymatic degradation. Animal studies using tritium-labeled epoprostenol have indicated a high clearance (93 mL/kg/min), small volume of distribution (357 mL/kg), and a short half-life (2.7 minutes).

During infusions in animals, steady-state plasma concentrations of tritium-labeled epoprostenol were reached within 15 minutes and were proportional to infusion rates.

No available chemical assay is sufficiently sensitive and specific to assess the *in vivo* human pharmacokinetics of epoprostenol. The *in vitro* half-life of epoprostenol in human blood at 37°C and pH 7.4 is approximately 6 minutes; therefore, the *in vivo* half-life of epoprostenol in humans is expected to be no greater than 6 minutes. The *in vitro* pharmacologic half-life of epoprostenol in human plasma, based on inhibition of platelet aggregation, was similar for males (n = 954) and females (n = 1,024).

Tritium-labeled epoprostenol has been administered to humans in order to identify the metabolic products of epoprostenol. Epoprostenol is metabolized to 2 primary metabolites: 6-keto-$PGF_{1\alpha}$ (formed by spontaneous degradation) and 6,15-diketo-13,14-dihydro-$PGF_{1\alpha}$ (enzymatically formed), both of which have pharmacological activity orders of magnitude less than epoprostenol in animal test systems. The recovery of radioactivity in urine and feces over a 1-week period was 82% and 4% of the administered dose, respectively. Fourteen additional minor metabolites have been isolated from urine, indicating that epoprostenol is extensively metabolized in humans.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis and Mutagenesis and Impairment of Fertility

Long-term studies in animals have not been performed to evaluate carcinogenic potential. A micronucleus test in rats revealed no evidence of mutagenicity. The Ames test and DNA elution tests were also negative, although the instability of epoprostenol makes the significance of these tests uncertain. Fertility was not impaired in rats given epoprostenol by subcutaneous injection at doses up to 100 mcg/kg/day (600 mcg/m^2/day, 2.5 times the recommended human dose [4.6 ng/kg/min or 245.1 mcg/m^2/day, IV] based on body surface area).

14 CLINICAL STUDIES

14.1 Clinical Trials in Pulmonary Arterial Hypertension (PAH)

Acute Hemodynamic Effects: Acute intravenous infusions of epoprostenol for up to 15 minutes in patients with idiopathic or heritable PAH or PAH associated with scleroderma spectrum of diseases (PAH/SSD) produce dose-related increases in cardiac index (CI) and stroke volume (SV) and dose-related decreases in pulmonary vascular resistance (PVR), total pulmonary resistance (TPR), and mean systemic arterial pressure (SAPm). The effects of epoprostenol on mean pulmonary arterial pressure (PAPm) were variable and minor.

Chronic Infusion in Idiopathic or Heritable PAH:
Hemodynamic Effects: Chronic continuous infusions of epoprostenol in patients with idiopathic or heritable PAH were studied in 2 prospective, open, randomized trials of 8 and 12 weeks' duration comparing epoprostenol plus conventional therapy to conventional therapy alone. Dosage of epoprostenol was determined as described in ***DOSAGE AND ADMINISTRATION (2)*** and averaged 9.2 ng/kg/min at study's end. Conventional therapy

varied among patients and included some or all of the following: anticoagulants in essentially all patients; oral vasodilators, diuretics, and digoxin in one half to two thirds of patients; and supplemental oxygen in about half the patients. Except for 2 New York Heart Association (NYHA) functional Class II patients, all patients were either functional Class III or Class IV. As results were similar in the 2 studies, the pooled results are described.

Chronic hemodynamic effects were generally similar to acute effects. Increases in CI, SV, and arterial oxygen saturation and decreases in PAPm, mean right atrial pressure (RAPm), TPR, and systemic vascular resistance (SVR) were observed in patients who received epoprostenol chronically compared to those who did not. Table 11 illustrates the treatment-related hemodynamic changes in these patients after 8 or 12 weeks of treatment.

Table 11: Hemodynamics during Chronic Administration of Epoprostenol in Patients with Idiopathic or Heritable PAH

	Baseline		**Mean Change from Baseline at End of Treatment Period***	
Hemodynamic Parameter	**Epoprostenol (N = 52)**	**Standard Therapy (N = 54)**	**Epoprostenol (N = 48)**	**Standard Therapy (N = 41)**
CI ($L/min/m^2$)	2.0	2.0	0.3†	-0.1
PAPm (mm Hg)	60	60	-5†	1
PVR (Wood U)	16	17	-4†	1
SAPm (mm Hg)	89	91	-4	-3
SV (mL/beat)	44	43	6†	-1
TPR (Wood U)	20	21	-5†	1

* At 8 weeks: Epoprostenol N = 10, conventional therapy N = 11
(N is the number of patients with hemodynamic data).
At 12 weeks: Epoprostenol N = 38, conventional therapy N = 30
(N is the number of patients with hemodynamic data).

† Denotes statistically significant difference between Epoprostenol and conventional therapy groups. CI = cardiac index, PAPm = mean pulmonary arterial pressure, PVR = pulmonary vascular resistance, SAPm = mean systemic arterial pressure, SV = stroke volume, TPR = total pulmonary resistance.

These hemodynamic improvements appeared to persist when epoprostenol was administered for at least 36 months in an open, nonrandomized study.

Clinical Effects: Statistically significant improvement was observed in exercise capacity, as measured by the 6-minute walk test in patients receiving continuous intravenous epoprostenol plus conventional therapy (N = 52) for 8 or 12 weeks compared to those receiving conventional therapy alone (N = 54). Improvements were apparent as early as the first week of therapy. Increases in exercise capacity were accompanied by statistically significant improvement in dyspnea and fatigue, as measured by the Chronic Heart Failure Questionnaire and the Dyspnea Fatigue Index.

Survival was improved in NYHA functional Class III and Class IV patients with idiopathic or heritable PAH treated with epoprostenol for 12 weeks in a multicenter, open, randomized, parallel study. At the end of the treatment period, 8 of 40 (20%) patients receiving conventional therapy alone died, whereas none of the 41 patients receiving epoprostenol died (p = 0.003).

Chronic Infusion in PAH/Scleroderma Spectrum of Diseases (SSD):
Hemodynamic Effects: Chronic continuous infusions of epoprostenol in patients with PAH/SSD were studied in a prospective, open, randomized trial of 12 weeks' duration comparing epoprostenol plus conventional therapy (N = 56) to conventional therapy alone (N = 55). Except for 5 NYHA functional Class II patients, all patients were either functional Class III or Class IV. Dosage of epoprostenol was determined as described in ***DOSAGE AND ADMINISTRATION (2)*** and averaged 11.2 ng/kg/min at study's end. Conventional therapy varied among patients and included some or all of the following: anticoagulants in essentially all patients, supplemental oxygen and diuretics in two thirds of the patients, oral vasodilators in 40% of the patients, and digoxin in a third of the patients. A statistically significant increase in CI, and statistically significant decreases in PAPm, RAPm, PVR, and SAPm after 12 weeks of treatment were observed in patients who received epoprostenol chronically compared to those who did not. Table 12 illustrates the treatment-related hemodynamic changes in these patients after 12 weeks of treatment.

Table 12: Hemodynamics during Chronic Administration of Epoprostenol in Patients with PAH/SSD

	Baseline		Mean Change from Baseline at 12 Weeks	
Hemodynamic Parameter	**Epoprostenol (N = 56)**	**Conventional Therapy (N = 55)**	**Epoprostenol (N = 50)**	**Conventional Therapy (N = 48)**
CI ($L/min/m^2$)	1.9	2.2	0.5*	-0.1
PAPm (mm Hg)	51	49	-5*	1
RAPm (mm Hg)	13	11	-1*	1
PVR (Wood U)	14	11	-5*	1
SAPm (mm Hg)	93	89	-8*	-1

*	Denotes statistically significant difference between Epoprostenol and conventional therapy groups (N is the number of patients with hemodynamic data). CI = cardiac index, PAPm = mean pulmonary arterial pressure, RAPm = mean right atrial pressure, PVR = pulmonary vascular resistance, SAPm = mean systemic arterial pressure.

Clinical Effects: Statistically significant improvement was observed in exercise capacity, as measured by the 6-minute walk, in patients receiving continuous intravenous epoprostenol plus conventional therapy for 12 weeks compared to those receiving conventional therapy alone. Improvements were apparent in some patients at the end of the first week of therapy. Increases in exercise capacity were accompanied by statistically significant improvements in dyspnea and fatigue, as measured by the Borg Dyspnea Index and Dyspnea Fatigue Index. At week 12, NYHA functional class improved in 21 of 51 (41%) patients treated with epoprostenol compared to none of the 48 patients treated with conventional therapy alone. However, more patients in both treatment groups (28/51 [55%] with epoprostenol and 35/48 [73%] with conventional therapy alone) showed no change in functional class, and 2/51 (4%) with epoprostenol and 13/48 (27%) with conventional therapy alone worsened. Of the patients randomized, NYHA functional class data at 12 weeks were not available for 5 patients treated with epoprostenol and 7 patients treated with conventional therapy alone.

No statistical difference in survival over 12 weeks was observed in PAH/SSD patients treated with epoprostenol as compared to those receiving conventional therapy alone. At the end of the treatment period, 4 of 56 (7%) patients receiving epoprostenol died, whereas 5 of 55 (9%) patients receiving conventional therapy alone died.

No controlled clinical trials with epoprostenol have been performed in patients with pulmonary hypertension associated with other diseases.

16 HOW SUPPLIED / STORAGE AND HANDLING

16.1 How Supplied

VELETRI is supplied as a sterile lyophilized material in 10 mL vials.
10 mL vial with a white flip-off seal containing epoprostenol sodium equivalent to 0.5 mg (500,000 ng) epoprostenol, is packaged in carton of 1 vial (**NDC 66215-403-01)**.
10 mL vial with a red flip-off seal containing epoprostenol sodium equivalent to 1.5 mg (1,500,000 ng) epoprostenol, is packaged in carton of 1 vial (**NDC 66215-402-01**).

Store the vials of VELETRI at 68° to 77°F (20° to 25°C) [see USP Controlled Room Temperature].

16.2 Storage and Stability

Unopened vials of VELETRI are stable until the date indicated on the package when stored at **68° to 77°F (20° to 25°C).** The unopened vial should be kept in the carton and not exposed to direct sunlight.

Use after reconstitution and immediate dilution to final concentration can be found in ***DOSAGE AND ADMINISTRATION (2.4)*** Reconstitution, Table 1: Maximum duration of administration (hours) at room temperature (77°F /25°C) of fully diluted solutions in the drug delivery reservoir.

Inspect parenteral drug products for particulate matter and discoloration prior to administration whenever solution and container permit. If either occurs, do not administer.

17 PATIENT COUNSELING INFORMATION

Patients receiving VELETRI should receive the following information.

VELETRI must be reconstituted as directed using only Sterile Water for Injection, USP, or Sodium Chloride 0.9% Injection, USP. VELETRI is infused continuously through a permanent indwelling central venous catheter via a small, portable infusion pump. Thus, therapy with VELETRI requires commitment by the patient to drug reconstitution, drug administration, and care of the permanent central venous catheter. Patients must adhere to sterile technique in preparing the drug and in the care of the catheter, and even brief interruptions in the delivery of VELETRI may result in rapid symptomatic deterioration. A patient's decision to receive VELETRI should be based upon the understanding that there is a high likelihood that therapy with VELETRI will be needed for prolonged periods, possibly years. The patient's ability to accept and care for a permanent intravenous catheter and infusion pump should also be carefully considered.

Manufactured for:
Actelion Pharmaceuticals US, Inc.
5000 Shoreline Court, Ste. 200
South San Francisco, CA 94080

Manufactured by:
Patheon S.p.A
Viale G.B. Stucchi 110, 20900 Monza MB
Italy

ACT20120628

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

022260Orig1s005

CHEMISTRY REVIEW(S)

QUALITY (CMC) REVIEW #2	1. ORGANIZATION ONDQA Div 1, Branch 3 HFD-110	2. NDA NUMBER 022-260

3. NAME AND ADDRESS OF APPLICANT	4. COMMUNICATION, DATE
Actelion Pharmaceuticals Ltd. Gewerbestrasse 16 CH-4123 Allschwil SWITZERLAND	S-005 Resubmission (SDN 164) PAS PDUFA Date: Jun. 29, 2012

5. PROPRIETARY	6. NAME OF THE DRUG	7. AMENDMENTS, REPORT, DATE
Veletri®	Epoprostenol sodium	Amendment: 5/2/2012 (SDN 179 and 180); 6/19/2012 (SDN 182); 7/9/2012 (SDN 188)

8. COMMUNICATION PROVIDES FOR:

Proposed changes in 1) New formulation to replace mannitol with sucrose, 2) Addition of a new (lower) strength of 0.5 mg/vial, 3) New drug substance manufacturer- (b) (4), 4) New drug product manufacturer—Patheon Italia, and 5) Various label and labeling changes.

9. PHARMACOL. CATEGORY	10. HOW DISPENSED	11. RELATED IND, NDA, DMF
Prostacyclin agonist/Hypertension	Rx only	(b) (4)
12. DOSAGE FORM	**13. POTENCY**	
lyophilized powder, for intravenous solution	1.5 mg/vial 0.5 mg/vial (new)	

14. CHEMICAL NAME AND STRUCTURE

Chemical Name: (5*Z*,9α,11α,13*E*,15*S*)-6,9-epoxy-11,15-dihydroxyprosta-5,13-dien-1-oic acid, sodium salt

Code Name: ACT-385781A

Empirical Formula: $C_{20}H_{31}O_5Na$

Molecular Weight: 374.45

CASRN: 61849-14-7 (b) (4)

Chemical Structure: (b) (4)

Indication: Long-term treatment of pulmonary arterial hypertension (PAH).

15. COMMENTS

This supplement was submitted as a PAS which is appropriate. The supplemental application S005 Resubmission, dated Feb. 28, 2012, was recommended for approval, from the CMC perspective, with one post-approval agreement—to lower the acceptance criteria for two new drug substance impurities (b) (4) On Jul. 9, 2012 the company submitted the post-approval amendment and the agreement is deemed fulfilled. There are no other outstanding deficiencies.

16. CONCLUSION AND RECOMMENDATION

From the CMC perspective this supplemental application, as amended, is approved.

17. REVIEWER NAME	18. REVIEWERS SIGNATURE	19. DATE COMPLETED
Huai T. (Ted) Chang	See appended electronic signature sheet	Jul. 11, 2012

DISTRIBUTION: ORIGINAL JACKET, CSO, REVIEWER, DIVISION FILE

Review Note—Chemistry, Manufacturing and Controls

BACKGROUND—DRUG SUBSTANCE AND DRUG PRODUCT

The drug product—Veletri® (epoprostenol) for injection—is a sterile epoprostenol sodium salt formulated as lyophilized powder for reconstitution for intravenous (IV) infusion. The powder is white to off-white. It is reconstituted with sterile Water for Injection (WFI), USP, or Sodium Chloride 0.9% Injection, USP, and further diluted to the final concentration with the same diluent as used for reconstitution. Each 10-mL glass vial of Veletri contains respectively (b) (4) epoprostenol sodium (equivalent to respectively 0.5 and 1.5 mg epoprostenol). Each vial also contains excipients 50 mg arginine, and 100 mg sucrose. Sodium hydroxide is added, if needed, to adjust the pH. Veletri, once prepared as directed, is administered by continuous intravenous infusion via a central venous catheter using an ambulatory infusion pump.

Epoprostenol (PGI_2, PGX, prostacyclin)—a metabolite of arachidonic acid—is a naturally occurring prostanoid vasodilator indicated for the treatment of pulmonary arterial hypertension (PAH) (WHO Group 1) to improve exercise capacity.

Veletri®—a 505(b)(2) new drug application—was initially approved by FDA in 2008. The RLD is Flolan® (epoprostenol sodium) for Injection of NDA 020-444 of GlaxoSmithKline which was approved by FDA in 1995.

POST-APPROVAL AGREEMENT AND COMPANY RESPONSE

The supplemental application S005 Resubmission, dated Feb. 28, 2012, was recommended for approval, from CMC perspective, with one Agency requested post-approval agreement (H.T. Chang, Jun. 28, 2012). The agreement was to lower the acceptance criteria for two impurities—(b) (4)—newly listed in the drug substance specification. On Jul. 9, 2012 Actelion submitted an amendment to fulfill the agreement. A snapshot of the company's cover letter is presented below.

(b) (4)

CMC ASSESSMENT, CONCLUSION AND RECOMMENDATION

The company has submitted the amendment to lower the acceptance criterion for each of the two impurities. The post-approval agreement is deemed fulfilled. The revised drug substance impurities specification is summarized in the table below.

Acceptance Criteria for Impurity in Drug Substance Specification—Actelion

	(b) (4)

There are no other outstanding deficiencies. The changes proposed in S005 will not impact adversely the identity, strength, purity and quality of the drug product. From the CMC perspective supplemental application S005, as amended, is approved.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

HUAI T CHANG
07/11/2012

HASMUKH B PATEL
07/11/2012

QUALITY (CMC) REVIEW #1	1. ORGANIZATION ONDQA Div 1, Branch 3 HFD-110	2. NDA NUMBER 022-260

3. NAME AND ADDRESS OF APPLICANT	4. COMMUNICATION, DATE
Actelion Pharmaceuticals Ltd. Gewerbestrasse 16 CH-4123 Allschwil SWITZERLAND	S-005 Resubmission (SDN 164) PAS PDUFA Date: Jun. 29, 2012

5. PROPRIETARY	6. NAME OF THE DRUG	7. AMENDMENTS, REPORT, DATE
Veletri®	Epoprostenol sodium	May 2, 2012 (SDN 179) May 2, 2012 (SDN 180) Jun. 19, 2012 (SDN 182)

8. COMMUNICATION PROVIDES FOR:

Proposed changes in 1) New formulation to replace mannitol with sucrose, 2) Addition of a new (lower) strength of 0.5 mg/vial, 3) New drug substance manufacturer– (b) (4), 4) New drug product manufacturer—Patheon Italia, and 5) Various label and labeling changes.

9. PHARMACOLOGICAL CATEGORY	10. HOW DISPENSED	11. RELATED IND, NDA, DMF
Prostacyclin agonist/Hypertension	Rx only	(b) (4)
12. DOSAGE FORM	**13. POTENCY**	
lyophilized powder, for reconstitution for intravenous infusion	1.5 mg/vial 0.5 mg/vial (new)	

14. CHEMICAL NAME AND STRUCTURE

Chemical Name: (5*Z*,9α,11α,13*E*,15*S*)-6,9-epoxy-11,15-dihydroxyprosta-5,13-dien-1-oic acid, sodium salt

Code Name: ACT-385781A

Empirical Formula: $C_{20}H_{31}O_5Na$

Molecular Weight: 374.45

CASRN: 61849-14-7

(b) (4)

Chemical Structure:

(b) (4)

Indication: Long-term treatment of pulmonary arterial hypertension (PAH).

15. COMMENTS

This supplement was submitted as a PAS which is appropriate. The original S005 received a CR due to deficiencies in the lack of information for the new DS and DP manufacturers. The new EFI2 formulation uses sucrose, in stead of mannitol in EFI1, [redacted] (b) (4) [redacted]. The proposed new DS [redacted] (b) (4) [redacted] and DP (Patheon Italia) manufacturers are deemed acceptable—supported adequately by batch and stability data. The supplement has received an overall recommendation of acceptable from the Office of Compliance, and a recommendation of approval from Microbiology Review. The changes proposed for Package Insert DOSAGE AND ADMINISTRATION at different concentrations and temperatures are supported adequately by in-use stability data. **Post-Approval Commitment**: The company has agreed to lower the acceptance criteria for two new impurities in DS [redacted] (b) (4) [redacted] The company has committed to amend the supplement accordingly. The proposed changes will not impact adversely the identity, strength, purity and quality of the drug substance and drug product.

16. CONCLUSION AND RECOMMENDATION

From the CMC perspective this supplemental application, as amended per post-approval commitment, is recommended for APPROVAL.

17. REVIEWER NAME	18. REVIEWERS SIGNATURE	19. DATE COMPLETED
Huai T. (Ted) Chang	See appended electronic signature sheet	Jun. 28, 2012

DISTRIBUTION: ORIGINAL JACKET, CSO, REVIEWER, DIVISION FILE

Review Notes—Chemistry, Manufacturing and Controls

BACKGROUND—DRUG SUBSTANCE AND DRUG PRODUCT

The drug product—Veletri® (epoprostenol) for injection—is a sterile epoprostenol sodium salt formulated as lyophilized powder for reconstitution for intravenous (IV) infusion. The powder is white to off-white. It is reconstituted with sterile Water for Injection (WFI), USP, or Sodium Chloride 0.9% Injection, USP, and further diluted to the final concentration with the same diluent as used for reconstitution. Each 10-mL glass vial of Veletri contains respectively (b) (4) epoprostenol sodium (equivalent to respectively 0.5 and 1.5 mg epoprostenol). Each vial also contains excipients 50 mg arginine, and 100 mg sucrose. Sodium hydroxide is added, if needed, to adjust the pH. Veletri, once prepared as directed, is administered by continuous intravenous infusion via a central venous catheter using an ambulatory infusion pump.

Epoprostenol (PGI_2, PGX, prostacyclin)—a metabolite of arachidonic acid—is a naturally occurring prostanoid vasodilator indicated for the treatment of pulmonary arterial hypertension (PAH) (WHO Group 1) to improve exercise capacity.

Veletri®—a 505(b)(2) new drug application—was initially approved by FDA in 2008. The RLD is Flolan® (epoprostenol sodium) for Injection of NDA 020-444 of GlaxoSmithKline which was approved by FDA in 1995.

CMC Review Note: S005 was initially submitted Jan. 28, 2011 and then withdrawn May 27, 2011 after receiving a CR from the Agency. The original S005 proposed the following changes:

- a new formulation (change the excipient mannitol to sucrose).
- a new lower strength (add a 0.5 mg/vial strength).
- new carton and container labeling.
- revised prescribing information including changes to DOSAGE AND ADMINISTRATION, DOSAGE FORMS AND STRENGTHS, DESCRIPTION, and HOW SUPPLIED/STORAGE AND HANDLING.
- new manufacturing facilities for both the drug substance and the drug product.

The original S005 was found deficient for the new drug substance manufacturer (name and DMF number not provided) and in-use storage stability.

PROPOSED CHANGE

This Prior Approval Supplement (S005) proposed the following changes in the cover letter:

- The EFI2 formulation has the same qualitative and quantitative composition in active substance and has the same pharmaceutical form for the 1.5 mg/vial strength as that of

EFI1. The change in excipient (from mannitol to sucrose) in EFI2 was found (b) (4)

- A quantitative change in composition is proposed with the additional 0.5 mg/vial strength developed for convenience for dilution of the drug product. The composition of the drug product includes the excipient sucrose as proposed above.

- A change in drug substance manufacturer is proposed with this application (b) (4)

- A change in drug product manufacturer is proposed with this application from Jubilant Hollister-Stier LLC to Patheon Italia S.p.A. in Monza, ITALY

- Based on the in-use stability data with the new formulation EFI2 and the availability of a 0.5 mg additional strength, changes to the Prescribing Information are as follows:

  - The proposed changes in the Dosage and Administration, and How Supplied sections of the Veletri label provide additional recommendations regarding the use at room temperature and higher (>77°F up to 104°F (25°C to 40°C)) prior to administration of the diluted solutions.

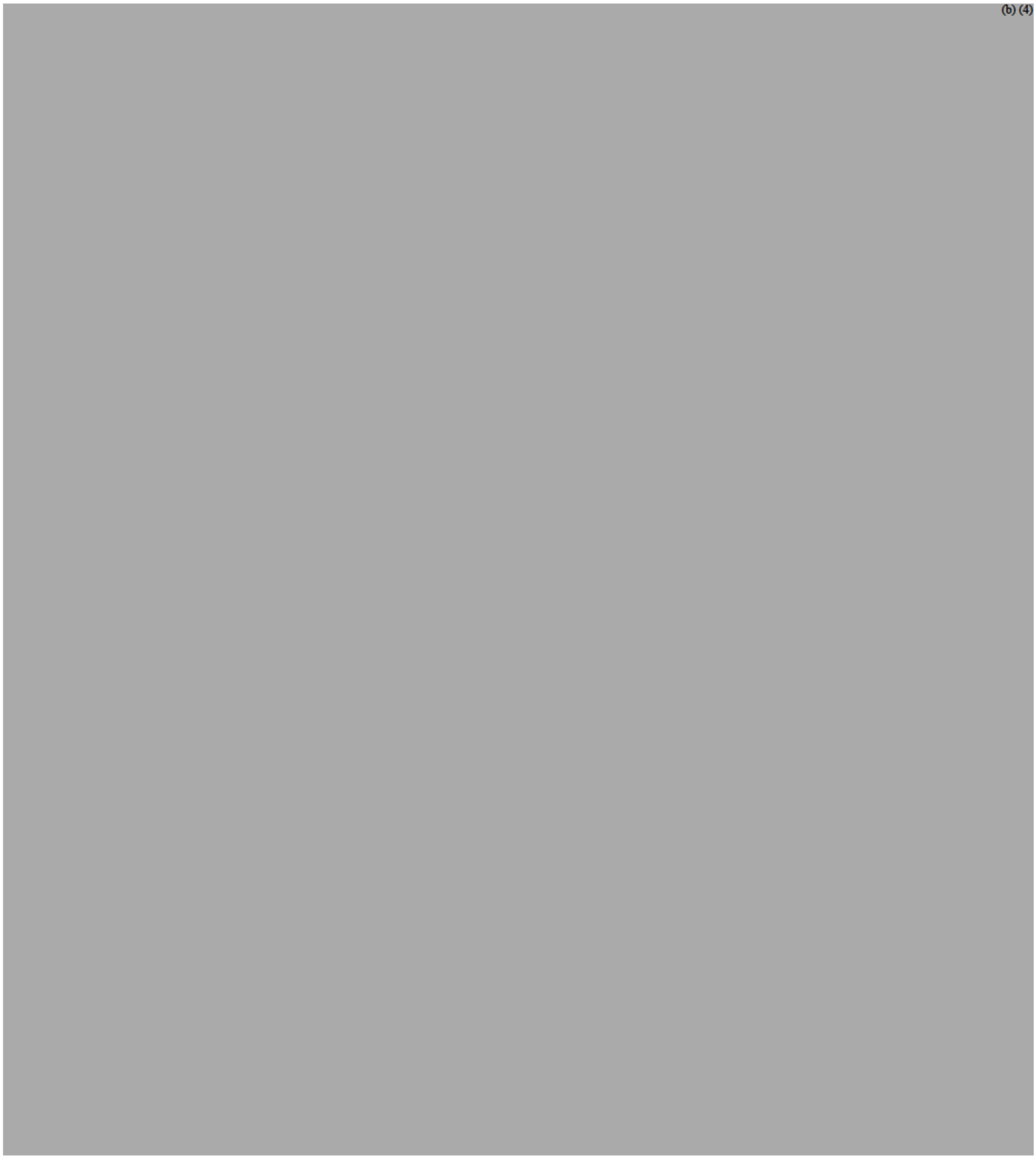
  - In addition, the current recommendations which allow the reconstituted solution in the vial to be kept under refrigerated conditions for as long as 5 days, have been removed. Those changes reflect the current medical practice with Veletri in the US since the introduction of the 7-day refrigerated stability in the cassette (for the diluted solution). The storage of the reconstituted solution in the refrigerator for up to 5 days increases the possibility of multiple dosing from a single vial.

- Changes to current packaging (carton and vial labeling) have been proposed to take into account the additional 0.5 mg strength and to clearly differentiate Veletri strengths.

Actelion intends to withdraw the current formulation (EFI1) of Veletri and replace it with the proposed changed EFI2 formulation upon approval of this prior approval supplement.

18 Page(s) has been Withheld in Full as b4 (CCI/TS) immediately following this page

(b) (4)



ENVIRONMENTAL ASSESSMENT (EA)

The applicant provided a calculation of the Expected Introduction Concentration (EIC) of epoprostenol into the Aquatic Environment according to 21 CFR 25.30 and 25.31 Environmental Impact Considerations. The EIC of epoprostenol into the aquatic environment is below 1 µg/L.

The applicant stated that if no extraordinary circumstances occur, epoprostenol is subject to categorical exclusion and an environmental assessment (EA) ordinarily is not required. The applicant has provided revised calculation to show that the amount of active ingredient entering the aquatic environment to be 0.004 μg/L (which is <1 μg/L).

LABELING REVIEW

The applicant proposed to delete a statement which allows the reconstituted solution in the vial to be kept under refrigerated conditions for as long as 5 days. The storage of the reconstituted solution in the refrigerator for up to 5 days increases the possibility of multiple dosing from a single vial.

The new strength 0.5 mg is added to the section Dosage Forms and Strengths.

The section Description is updated in accord with the proposed changes of adding a new strength of 0.5 mg and new excipient "100 mg sucrose", and the deletion of "50 mg mannitol".

The section How Supplied/Storage and Handling is updated with the new strength of 0.5 mg.

The manufacturer section is updated with the name and address of proposed new drug product manufacturer—Patheon S.p.A.

MICROBIOLOGY CONSULT/REVIEW

Amendment #3 (Response on Jun. 19, 2012 to Agency's IR Jun. 13, 2012): Actelion provides both a narrative description as well as validation summary reports for the processes used to reduce and control [redacted] (b) (4) during production of the drug product.

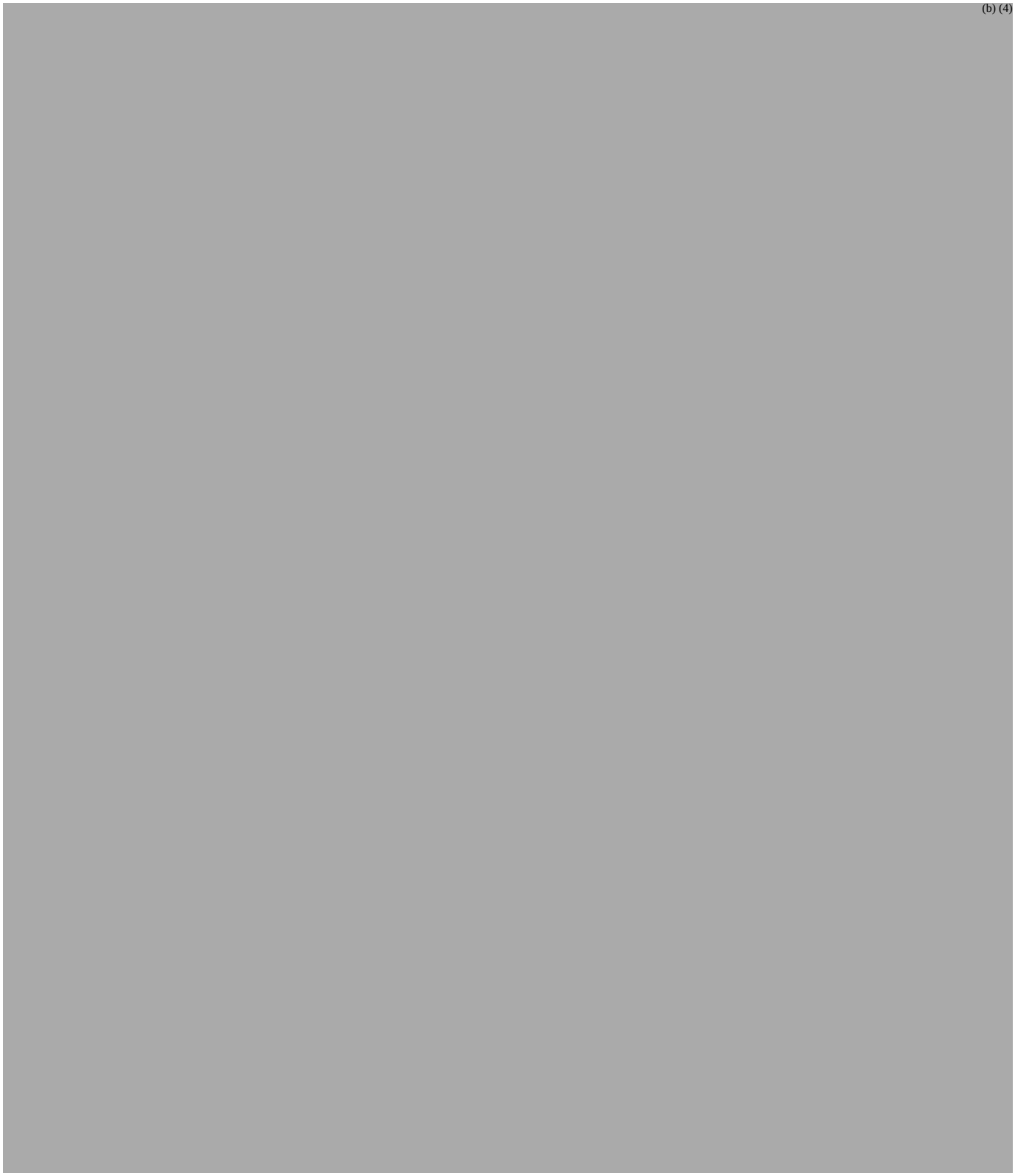
The supplement has been recommended for approval from the Microbiology Review perspective (R. J. Mello, Jun. 21, 2012).

PHARMACOLOGY/TOXICOLOGY REVIEW

Recommendation by J. M. Willard, Jun. 15, 2012: "Already approved and no changes are needed for the labeling".

Additional comments from PharmTox (email from J. M. Willard, 6/27/2012):

(b) (4)



ESTABLISHMENT EVALUATION

This supplement has received an overall recommendation of "ACCEPTABLE" from the Office of Compliance for the proposed manufacturing sites for drug substance and drug product.

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Application:	NDA 22260/005	**Sponsor:**	ACTELION
Org. Code:	110		1820 CHAPEL AVE WEST STE 300
Priority:	5S		CHERRY HILL, NJ 08002
Stamp Date:	28-JAN-2011	**Brand Name:**	Veletri
PDUFA Date:	29-JUN-2012	**Estab. Name:**	
Action Goal:		**Generic Name:**	EPOPROSTENOL SODIUM
District Goal:	25-MAY-2012	**Product Number; Dosage Form; Ingredient; Strengths**	001; INJECTABLE; EPOPROSTENOL SODIUM; EQ 1.5MG BASE/1VIL

FDA Contacts:	T. BOUIE	Project Manager	3017961649
	H. CHANG	Review Chemist	3017961974
	K. SRINIVASACHAR	Team Leader	3017961760

Overall Recommendation:	ACCEPTABLE	on 05-MAR-2012	by M. STOCK	(HFD-320)	3017964753
	PENDING	on 01-MAR-2012	by EES_PROD		

Establishment:	(b) (4)
DMF No:	**AADA:**
Responsibilities:	DRUG SUBSTANCE MANUFACTURER
Profile:	(b) (4) **OAI Status:** NONE
Last Milestone:	OC RECOMMENDATION
Milestone Date:	01-MAR-2012
Decision:	ACCEPTABLE
Reason:	BASED ON PROFILE

Establishment:	**CFN:** **FEI:** 3003065803 PATHEON ITALIA S.P.A. VIALE GB STUCCHI 110 MONZA, MILANO, ITALY
DMF No:	**AADA:**
Responsibilities:	FINISHED DOSAGE MANUFACTURER FINISHED DOSAGE PACKAGER FINISHED DOSAGE RELEASE TESTER FINISHED DOSAGE STABILITY TESTER
Profile:	STERILE-FILLED SMALL VOLUME PARENTERAL DRUGS **OAI Status:** NONE
Last Milestone:	OC RECOMMENDATION
Milestone Date:	05-MAR-2012
Decision:	ACCEPTABLE
Reason:	DISTRICT RECOMMENDATION

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/s/

HUAI T CHANG
06/28/2012

NALLAPERUM CHIDAMBARAM
06/28/2012
for Dr. Hasmukh Patel

QUALITY (CMC) REVIEW #1	1. ORGANIZATION	2. NDA NUMBER
	ONDQA Div 1, Branch 3 HFD-110	022-260

3. NAME AND ADDRESS OF APPLICANT	4. COMMUNICATION, DATE
Actelion Pharmaceuticals Ltd. Gewerbestrasse 16 Allschwil, CH-4123 SWITZERLAND **US Agent**: Catherine L. Kohler, Regulatory Affairs (856-773-5723)	S-005 (Jan. 28, 2011) PAS PDUFA Date: May 28, 2011

5. PROPRIETARY	6. NAME OF THE DRUG	7. AMENDMENTS, REPORT, DATE
VELETRI®	Epoprostenol sodium	N/A

8. COMMUNICATION PROVIDES FOR:

1. New formulation—replacing mannitol with sucrose.
2. Addition of a new (lower) strength at 0.5 mg/vial.
3. Various label and labeling changes.

9. PHARMACOLOGICAL CATEGORY	10. HOW DISPENSED	11. RELATED IND, NDA, DMF
Anti-hypertension	Rx only	N/A

12. DOSAGE FORM	13. POTENCY
lyophilized powder, for reconstitution for intravenous infusion	1.5 mg/vial

14. CHEMICAL NAME AND STRUCTURE

(5*Z*,9a,11a,13*E*,15*S*)-6,9-epoxy-11,15-dihydroxyprosta-5,13-dien-1-oic acid

Code Name: ACT-385781A

Empirical Formula: $C_{20}H_{31}O_5Na$

Molecular Weight: 374.45

CASRN: 61849-14-7

(b) (4)

Chemical Structure:

(b) (4)

Indication: Treatment of pulmonary hypertension.

15. COMMENTS

This supplement was submitted as a PAS which is appropriate. The applicant did not list, in the cover letter, the "new/proposed" manufacturers for both drug substance and drug product.

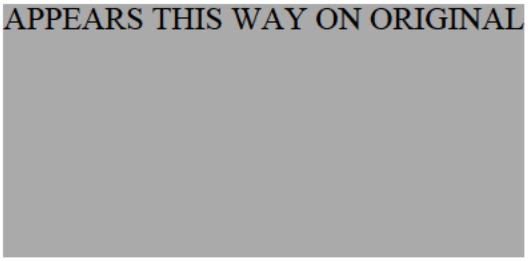
16. CONCLUSION AND RECOMMENDATION

From the CMC perspective this supplemental application is deemed deficient and is recommended for NON-APPROVAL/COMPLETE RESPONSE.

17. REVIEWER NAME	18. REVIEWERS SIGNATURE	19. DATE COMPLETED
Huai T. (Ted) Chang	See appended electronic signature sheet	May 17, 2011

DISTRIBUTION: ORIGINAL JACKET, CSO, REVIEWER, DIVISION FILE

APPEARS THIS WAY ON ORIGINAL



Chemistry Review Notes

BACKGROUND—DRUG PRODUCT AND DRUG SUBSTANCE

The drug product—VELETRI (epoprostenol) for injection—is a sterile epoprostenol salt formulated as lyophilized powder for reconstitution for intravenous (IV) administration. Each 10-mL glass vial of VELETRI contains (b) (4) epoprostenol sodium (equivalent to 1.5 mg epoprostenol), 50 mg arginine, and 50 mg mannitol. Sodium hydroxide is added to adjust pH. Epoprostenol (PGI_2, PGX, prostacyclin), a metabolite of arachidonic acid, is a naturally occurring prostaglandin with potent vasodilatory activity and inhibitory activity of platelet aggregation.

VELETRI is a white to off-white lyophilized material that may be translucent. It is reconstituted with sterile Water for Injection, USP, or Sodium Chloride 0.9% Injection, USP. The reconstituted solution of VELETRI has a pH of >11.0 and is increasingly unstable at a lower pH.

Epoprostenol for injection was initially approved in 1995. The RLD is FLOLAN (epoprostenol sodium) for Injection of NDA 020-444 of GlaxoSmithKline.

PROPOSED CHANGES

The applicant proposed two changes in the cover letter:

- Change in formulation, i.e. replacing mannitol with sucrose. (Note: The applicant sometimes refers to the new formulation as Epoprostenol for Injection 2 (EFI2).)
- Addition of a new (lower) strength at 0.5 mg/vial.

The applicant also stated that based on the newly generated in-use stability data with new EFI2 and the availability of a 0.5 mg additional strength, changes to the Prescribing Information are proposed as follows:

- The proposed changes in the Dosage and Administration, and How Supplied sections of the Veletri label provide additional recommendations regarding the use at room temperature and higher (>77°F up to 104°F) prior to administration of the diluted solutions.
- In addition, the current recommendations which allow the reconstituted solution in the vial to be kept under refrigerated conditions for as long as 5 days, have been removed. Those changes reflect the current medical practice with Veletri in the US since the introduction of the 7- day refrigerated stability in the cassette (for the diluted solution). The storage of the reconstituted solution in the fridge for up to 5 days increases the possibility of multiple dosing from a single vial.
- Changes to the current Packaging have been proposed to take into account the additional 0.5 mg strength and to differentiate from the current Veletri formulation for the 1.5 mg strength.

- To introduce and highlight the new strength, second formulation and changes to the stability, (b) (4)

The EFI2 formulation similarly to VELETRI, has the same qualitative and quantitative composition in active substance (i.e. epoprostenol sodium) and has the same pharmaceutical form. The change in excipient (from mannitol to sucrose) was found (b) (4)

DETAILS OF PROPOSED CHANGE AND REVIEW

3.2.P.1 DESCRIPTION AND COMPOSITION OF THE DRUG PRODUCT (ALL, MONZA)

Table 2.1. Composition for Epoprostenol for Injection 0.5 mg/vial

Ingredient	Declaration	Actual Amount*	% (m/m)	Function
Epoprostenol (as epoprostenol sodium)	0.500 mg (b) (4)	(b) (4)	(b) (4)	Drug substance
Sucrose	100.0 mg			(b) (4)
(b) (4) arginine	50.0 mg			
Sodium hydroxide	(b) (4)			pH adjustment
				(b) (4)

* (b) (4)

q.s: quantity sufficient

Table 2.2. Composition for Epoprostenol for Injection 1.5 mg/vial

Ingredient	Declaration	Actual Amount*	% (m/m)	Function
Epoprostenol (as epoprostenol sodium)	1.500 mg (b) (4)	(b) (4)	1.0%	Drug substance
Sucrose	100.0 mg		66.0%	(b) (4)
(b) (4) arginine	50.0 mg		33.0%	
Sodium hydroxide	(b) (4)		/	pH adjustment
				(b) (4)

(b) (4)

q.s: quantity sufficient

CMC Notes: The currently approved 1.5 mg strength formulation contains 50.0 mg of mannitol and no sucrose.

3.2.P.3 MANUFACTURE

Batch Formula for Epoprostenol for Injection

(b) (4)

[redacted]

Manufacturing, testing and packaging site:

Patheon S.p.A.
Viale G.B. Stucchi 110
20900 Monza MB
ITALY

The contact person at Patheon S.p.A. is:
Maria Di Cillo
Quality Assurance Manager
Phone: (+39) 039 2047 509
Fax: (+39) 039 2047 314
Email: maria.dicillo@patheon.com

A cGMP certificate from Patheon S.p.A. is provided (latest acceptable inspection conducted on Nov. 27, 2008).

CMC Evaluation: DEFICIENT.

The applicant has listed the following establishment information in form FDA 356h:

Manufacturer

Drug Product	Drug Substance
Hollister-Stier Laboratories LLC 525 North Regal Street Spokane, WA 99207 CFN: 3010477	(b) (4)

These company establishment sites are different from those listed in the body of text/supplement. It appears that the applicant intended to change the manufacturer/supplier of drug product as well as the manufacturer of drug substance. However, the applicant did not list the names and addresses of the new manufacturers in the Cover Letter. According to 21 CFR 314.70(a)(6), "A supplement or annual report must include a list of all changes contained in the supplement or annual report. For supplements, this list must be provided in the cover letter."

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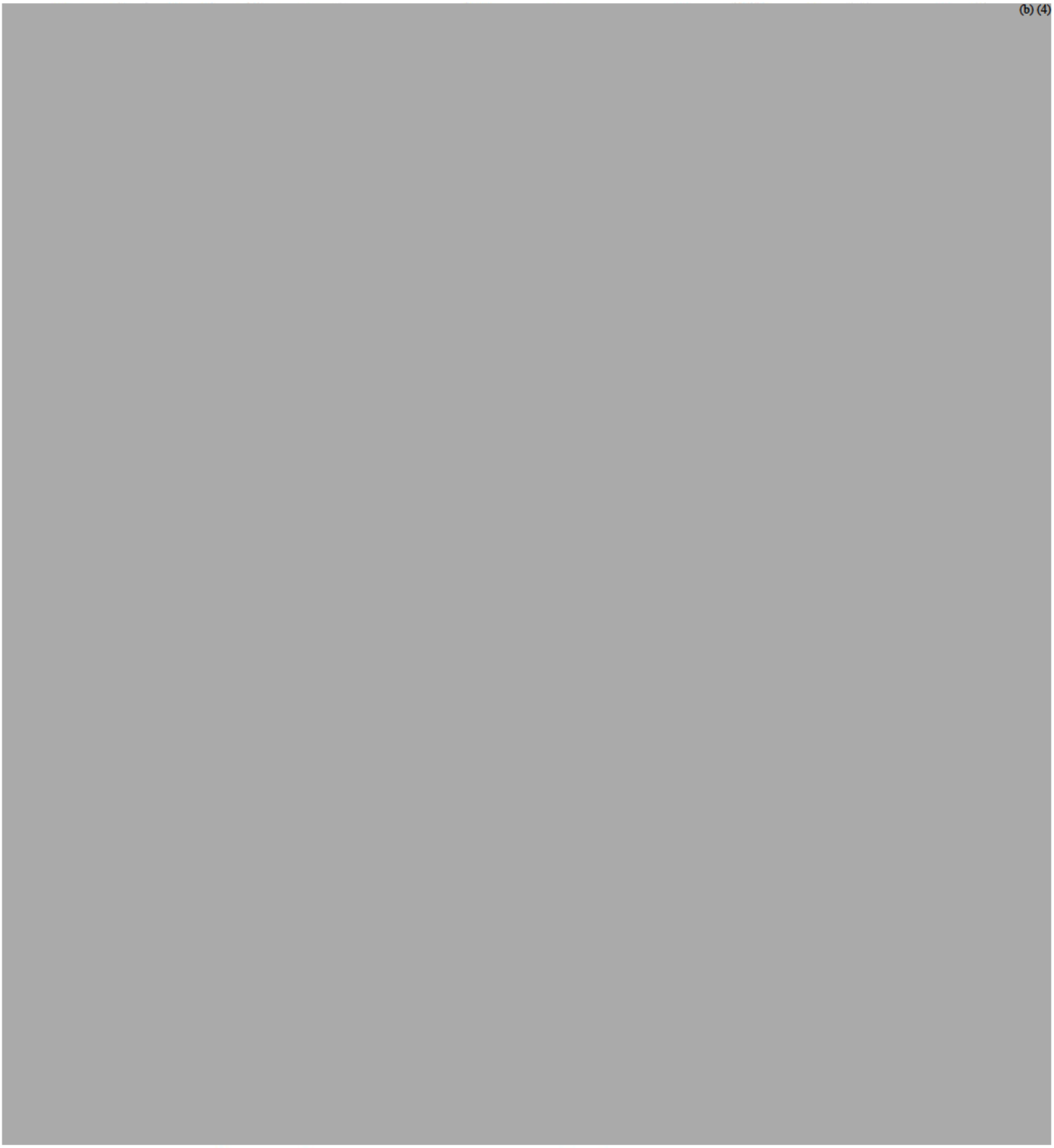

ENVIRONMENTAL ASSESSMENT (EA) OF HUMAN DRUG AND BIOLOGICS APPLICATIONS

The applicant provided a calculation of the Expected Introduction Concentration (EIC) of epoprostenol into the Aquatic Environment according to the Code of Federal Regulations Title 21 Part 25 Environmental Impact Considerations. The EIC of epoprostenol into the aquatic environment is below 1 μg/L. The applicant stated that if no extraordinary circumstances occur, epoprostenol is subject to categorical exclusion and an environmental assessment (EA) ordinarily is not required.

LABELS AND LABELING

The applicant modified the PI and labels to accommodate the added lower strength vial—0.5 mg.

1. In package insert Section 2.4 Reconstitution, the applicant proposed to modify/simplify (from 5 to 3 concentration ranges) the table for maximum duration for storage and administration for fully diluted solution. The proposed in-use duration, up to 72 hours for ≥60,000 ng/mL for Immediate Administration, should be supported by in-use stability data. The in-use stability data and/or rationale for the proposed modifications are not provided in this submission.

2. Added Instructions for Reconstitution and Dilution for 0.5 mg strength vial are acceptable.

3. Proposed changes to Section 11 Description include adding 0.5-mg strength and sucrose (in excipient list) is acceptable.

4. Proposed changes to Section 16 How Supplied/Storage and Handling include adding 0.5 mg strength package and modification of table for storage duration for reconstituted solution. The package descriptions for 0.5 mg and 1.5 mg are acceptable. The modification of storage duration (same as Item 1) should be supported by in-use stability data.

5. The container and carton labels for the 0.5-mg strength are acceptable from CMC perspective. Additional review comments are provided in Label and Labeling Review by DMEPA.

DEFICIENCY

1. It appears that the applicant intended to change the drug substance manufacturer. If the change is indeed intended in this supplement, please provide:

   - In the cover letter, complete name and address of the drug substance manufacturer.
   - Letter of authorization to reference the drug substance DMF, if needed.

   The applicant was contacted on Apr. 6, 2011 regarding the above deficiencies. However, the applicant chose not to submit an amendment to address the deficiencies.

2. In package insert Section 2.4 Reconstitution, the applicant proposed to modify/simplify (from 5 to 3 concentration ranges) the table for maximum duration for storage and administration for fully diluted solution. The proposed in-use duration, up to 72 hours for ≥60,000 ng/mL for Immediate Administration, should be supported by in-use stability data. The in-use stability data and/or rationale for the proposed modifications are not provided in this submission. (CMC Note: The applicant claimed "The change in excipient (from mannitol to sucrose) was found (b) (4)).

CMC ASSESSMENT, CONCLUSION AND RECOMMENDATION

From the CMC perspective this supplemental application is deemed deficient and is recommended for NON-APPROVAL/COMPLETE RESPONSE.

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/s/

HUAI T CHANG
05/17/2011

HASMUKH B PATEL
05/17/2011

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

022260Orig1s005

PHARMACOLOGY REVIEW(S)

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PHARMACOLOGY/TOXICOLOGY NDA REVIEW AND EVALUATION

Application Number: NDA022260

Submission Number/code: S-005

CDER Stamp Date: 2/8/2012

PDUFA Date: 6/29/2012

Product: Epoprostenol

Drug Class: Prostacyclin agonist

Indication: Treatment of Pulmonary Arterial Hypertension

Applicant: Actelion Pharmaceuticals, Ltd.

Review Division: Cardiovascular and Renal Products

Reviewer: James M. Willard, Ph.D.

Supervisor/Team Leader: Albert DeFelice, Ph.D.

Division Director: Norman Stockbridge, M.D.

Project Manager: Dan Brum

Review Completion Date: 6/15/2012

Disclaimer: Some of the Methods information in this report are taken directly from the Sponsor's submission.

TABLE OF CONTENTS

1. Executive Summary

1.1. Recommendations

1.1.1. Approvability

- already approved

1.1.2. Additional nonclinical studies

– Although there is sufficient information in the study to reduce concerns of hemolytic risks, the study was poorly executed and poorly edited, making it difficult to ascertain exactly what had been done. Sponsor should repeat the study with appropriate controls and editing of the text.

1.1.3. Labeling

– no changes needed

1.2. Integrated Evaluation and Discussion of Nonclinical Findings

1.2.1. Basis of Recommendation

– Epoprostenol did not hemolyze red blood cells in a short-term *in vitro* study. A positive control such as saponin, rather than an inadequate volume of distilled water, should have been used. However, the free hemoglobin concentrations used to generate the optical density vs free Hgb conc. calibration curve were appropriate to detect up to approx. 3% hemolysis, and on that basis the sensitivity of the assay could be considered adequate.

1.2.2. Clinical Implication

Under the conditions of the assay, results forecast a clinically insignificant amount of hemolysis, if any, with infusion of epoprostenol. Although only 0.07 mL of epoprostenol was tested in a total assay volume of 5 mL, the concentration was 10,000 ng/ml.

2. Drug Information

2.1. Drug: **Veletri**
2.2. Route of administration: **injection**

2.3. Proposed clinical dose: **N/A**

2.4. Regulatory history: **Drug was approved in 2008 for long-term treatment of pulmonary hypertension**

10 Special toxicology study - Hemolysis:

The *In-vitro* Haemolytic Compatibility of
Epoprostenol in Human Peripheral Blood

Key study findings: 5 ml of whole blood were mixed with 0.07 ml of test article, control agent (normal saline) or positive control (distilled water), and observed for signs of hemolysis after a 20 minute incubation at 37 deg. C. Samples were then centrifuged and plasma was read in a Hemacue Plasma Haemoglobinometer to quantify. No samples gave a reading for hemoglobin above the negative control, which was physiological saline. The positive control, distilled water, was in too small an amount to cause hypotonic hemolysis in this assay system.

Study no.: T-10.529
Study report location: Actelion Pharmaceuticals, Gewerbestrasse 16, CH-4123 Allschwil, Switzerland
Conducting laboratory and location: [redacted] (b) (4)

Date of study initiation: April 29, 2010
GLP compliance: No
QA report: yes ( ) no (x)
Drug, lot #, and % purity: The test article is identified as Epoprostenol for injection (ACT-38578 1A) batch number TT2 11 and was supplied on 29 April 2010. Epoprostenol for injection (ACT-385781A) is a sterile, lyophilized powder for reconstitution, packaged in a 10 mL vial with a 20 mm rubber stopper and white overseal. One vial contained 0.5 mg of epoprostenol base ([redacted] (b) (4) epoprostenol sodium)

Methods:

Test condition	Test condition Volume physiological saline (ml)	Volume ofBlood(ml)
Negative control	0.07	5
Negative control	Vehicle control 0.07	5
TA1	Test Atticle 0.07 ml	5
TA2	Test Article –0.07 ml	5
Positive control	Distilled water 0.07	5

TAl: One vial of finished drug product was reconstituted with 5 ml vehicle. After complete dissolution, the whole content of the vial was further diluted to 50 ml with vehicle to prepare a 10000 ng/ml concentration.
TA2: One vial of finished drug product was reconstituted with 5 ml vehicle. After complete dissolution 3 ml of the content of the vial was withdrawn and further diluted to 100 ml with vehicle to prepare a 3000 ng/ml concentration.

Fresh blood was obtained from human donors who had taken no medication during the previous 7 days. Blood was collected in Sodium Heparin Vacutainer Blood Collection Tubes (BD Vacutainer NH 170 I.U. 10mL, ref 368480).

Whole blood was used on the day of collection.

Conclusions and Summary:

Sponsor resorted to a very simple assay to assess hemolytic potential of epoprostenol. The choice of positive control showed a lack of forethought by the investigators since a small amount of distilled water would not be anticipated to have an effect on an approximately 70-fold excess of whole blood. Probably a hemolyzing detergent would have been more appropriate. The assay reported here would not be acceptable by the usual standards due to the lack of a positive control. However, it can be considered informative. Additionally, information on whether epoprostenol changed the osmolarity would be of interest in the assay results, although the red blood cell is considered rather resistant to hemolysis due to decreases in osmolality per se.

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/s/

JAMES M WILLARD
08/06/2012

ALBERT F DEFELICE
08/06/2012

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PHARMACOLOGY/TOXICOLOGY NDA REVIEW AND EVALUATION

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/s/

JAMES M WILLARD
06/15/2012

ALBERT F DEFELICE
06/15/2012

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

022260Orig1s005

MICROBIOLOGY REVIEW(S)

Product Quality Microbiology Review

20 June 2012

NDA: 22-260/S-005

Drug Product Name
Proprietary: Veletri
Non-proprietary: Epoprostenol for Injection

Review Number: 2

Dates of Submission(s) Covered by this Review

Submit	Received	Review Request	Assigned to Reviewer
28 February 2012	29 February 2012	01 March 2012	01 March 2012
19 June 2012	19 June 2012	n/a	n/a

Submission History (for amendments only)

Submit Date(s)	Microbiology Review #	Review Date(s)
28 January 2011	1	26 May 2011

Applicant/Sponsor

Name: Actelion Pharmaceuticals Ltd.
Address: Gewerbestrasse 16
Allschwil, CH-4123
SWITZERLAND

Representative: Frances Duffy-Warren, Ph.D.
(US Agent) VP, US Drug Regulatory Affairs
Actelion Clinical Research, Inc.
1820 Chapel Avenue West, Suite 300,
Cherry Hill, NJ 08002 USA
Telephone: 856-773-5723

Name of Reviewer: Robert J. Mello, Ph.D.

Conclusion: The application is recommended for approval from microbiology product quality standpoint.

Product Quality Microbiology Data Sheet

A. 1. TYPE OF SUBMISSION: Prior Approval Supplement

2. SUBMISSION PROVIDES FOR:

- A change to the drug product formulation
- An addition of an additional drug product strength (0.5 mg epoprostenol/vial)
- A change in the labeled reconstitution, storage and use instructions
- A new drug substance manufacturing site
- A new drug product manufacturing site

3. MANUFACTURING SITE:

Drug Product:

Current:	Proposed:
Hollister-Stier-Laboratories LLC 525 North Regal Street Spokane, WA 99207	Patheon S.p.A Viale G.B. Stucchi 110 20900 Monza MB ITALY

Drug Substance:

Current:	Proposed:
(b) (4)	

4. DOSAGE FORM, ROUTE OF ADMINISTRATION AND STRENGTH/POTENCY: Sterile lyophilized powder in a 10 mL glass vial; Intravenous injection; 1.5 mg epoprostenol/vial and 0.5 mg epoprostenol/vial

5. METHOD(S) OF STERILIZATION: (b) (4)

6. PHARMACOLOGICAL CATEGORY: GI prostaglandins

B. SUPPORTING/RELATED DOCUMENTS:

- Microbiology Review #1 dated 26 May 2011 (DARRTS date: 27 May 2011)

C. REMARKS:

- The submission is electronic and in eCTD format.
- The original Supplement 005 was submitted on 28 January 2011. The initial microbiology review of Supplement 005 was entered into DARRTS on 27 May 2011. However, due to multiple deficiencies, the Applicant withdrew that submission on 27 May 2011. In a letter dated 21 June 2011, the Agency acknowledged the withdrawal and submitted a list of deficiencies. Subsequently, the Applicant re-submitted Supplement 005 on 28 February 2012 to address those deficiencies. The current review is an assessment of the Applicant's responses to

those deficiencies. All other review categories not addressed here were found to be acceptable in the initial Microbiology Review #1 dated 26 May 2011.

- An information request concerning (b) (4) was transmitted to the Applicant on 13 June 2012. The Applicant's response was received via email on 14 June 2012 and was officially submitted as an amendment to the submission on 19 June 2012. This response was incorporated into the body on the current review.

Filename: N022260S005R2.doc

Executive Summary

I. Recommendations

A. Recommendation on Approvability – Recommend Approval

B. Recommendations on Phase 4 Commitments and/or Agreements, if Approvable – N/A

II. Summary of Microbiology Assessments

A. Brief Description of the Manufacturing Processes that relate to Product Quality Microbiology - (b) (4)

[redacted]

B. Brief Description of Microbiology Deficiencies –None

C. Assessment of Risk Due to Microbiology Deficiencies – N/A

III. Administrative

A. Reviewer's Signature: _____

Robert J. Mello, Ph.D.
Senior Microbiology Reviewer

B. Endorsement Block: _____

Bryan S. Riley, Ph.D.
Acting Team Leader
New Drug Microbiology Staff

C. CC Block

NDA 22-260

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2. REVIEW OF COMMON TECHNICAL DOCUMENT-QUALITY (CTD-Q)
MODULE 1

A. **PACKAGE INSERT** - Acceptable - See Microbiology Review #1. The package insert was revised concerning the in-use reconstituted and diluted hold times. The preservative effectiveness studies reviewed under section P.2.5 of Microbiology Review #1 supported the Applicant's premise that the reconstituted and diluted drug product is self-preserving under conditions of use. The labeling is consistent with these studies.

- Acceptable -

3. LIST OF MICROBIOLOGY DEFICIENCIES AND COMMENTS:

None.

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/s/

ROBERT J MELLO
06/21/2012

BRYAN S RILEY
06/21/2012
I concur.

Product Quality Microbiology Review

26 MAY 2011

NDA: 22-260/S-005

Drug Product Name
Proprietary: Veletri
Non-proprietary: Epoprostenol for Injection

Review Number: 1

Dates of Submission(s) Covered by this Review

Submit	Received	Review Request	Assigned to Reviewer
28 January 2011	28 January 2011	31 January 2011	03 February 2011
13 April 2011	13 April 2011	-	-

Submission History (for amendments only): N/A

Applicant/Sponsor
Name: Actelion Pharmaceuticals Ltd.
Address: Gewerbestrasse 16
Allschwil, CH-4123
SWITZERLAND

Representative: Frances Duffy-Warren, Ph.D.
(US Agent) VP, US Drug Regulatory Affairs
Actelion Clinical Research, Inc.
1820 Chapel Avenue West, Suite 300,
Cherry Hill, NJ 08002 USA
Telephone: 856-773-5723

Name of Reviewer: Robert J. Mello, Ph.D.

Conclusion: The application is APPROVABLE pending receipt of additional information.

Product Quality Microbiology Data Sheet

A. 1. TYPE OF SUBMISSION: Prior Approval Supplement

2. SUBMISSION PROVIDES FOR:

- A change to the drug product formulation
- An addition of an additional drug product strength (0.5 mg epoprostenol/vial)
- A change in the labeled reconstitution, storage and use instructions
- A new drug substance manufacturing site
- A new drug product manufacturing site

3. MANUFACTURING SITE:

Drug Product:

Current:	Proposed:
Hollister-Stier-Laboratories LLC 525 North Regal Street Spokane, WA 99207	Patheon S.p.A Viale G.B. Stucchi 110 20900 Monza MB ITALY

Drug Substance:

Current:	Proposed:
(b) (4)	

4. DOSAGE FORM, ROUTE OF ADMINISTRATION AND STRENGTH/POTENCY: Sterile lyophilized powder in a 10 mL glass vial; Intravenous injection; 1.5 mg epoprostenol/vial and 0.5 mg epoprostenol/vial

5. METHOD(S) OF STERILIZATION: (b) (4)

6. PHARMACOLOGICAL CATEGORY: GI prostaglandins

B. SUPPORTING/RELATED DOCUMENTS:

- Microbiology Review #1 of NDA 22-260 dated 28 January 2008
- Microbiology Review #2 of NDA 22-260(BI) dated 07 May 2008
- Microbiology Review #1 of NDA 22-260/S-003 dated 12 August 2010
- Microbiology Review #2 of NDA 22-260/S-003 dated 28 January 2011

C. REMARKS:

- The submission is electronic and in eCTD format.
- Throughout the document the drug product is referred to as "*epoprostenol for injection 2*" to differentiate the proposed new formulation from the currently approved formulation.

Filename: N022260S005R1.doc

Executive Summary

I. Recommendations

A. Recommendation on Approvability – APPROVABLE pending receipt of additional information.

B. Recommendations on Phase 4 Commitments and/or Agreements, if Approvable – N/A

II. Summary of Microbiology Assessments

A. Brief Description of the Manufacturing Processes that relate to Product Quality Microbiology – (b) (4)

B. Brief Description of Microbiology Deficiencies –

- Inadequate container closure integrity studies.
- Lack of any descriptions of the new drug product manufacturing facility or its environmental monitoring program.
- Lack of descriptions and validations for the control of (b) (4)
- Lack of any description of the actions taken concerning products manufactured (b) (4)
- Lack of validation of the (b) (4) used for the drug product.
- Qualification of the bioburden, sterility and endotoxin assays are either inadequate or completely lacking.

C. Assessment of Risk Due to Microbiology Deficiencies – The risk to the patient is high since the sterility of the drug product cannot be assured.

III. Administrative

A. Reviewer's Signature: _____
Robert J. Mello, Ph.D., Senior Microbiology Reviewer

B. Endorsement Block: _____
James L. McVey, Microbiology Team Leader

C. CC Block: NDA 22-260

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2. REVIEW OF COMMON TECHNICAL DOCUMENT-QUALITY (CTD-Q)
MODULE 1

A. **PACKAGE INSERT** The package insert was revised concerning the in-use reconstituted and diluted hold times. The preservative effectiveness studies reviewed under section P.2.5 of this report supported the applicant's premise that the reconstituted and diluted drug product is self-preserving under conditions of use. The labeling is consistent with these studies.

- ACCEPTABLE -

3. LIST OF MICROBIOLOGY DEFICIENCIES AND COMMENTS:

DEFICIENCIES:

1. The studies supporting container closure integrity were inadequate. (b) (4) [redacted]

2. Please provide floor plans or narrative descriptions summarizing the facility layout, equipment locations, the flow of materials, product and personnel and the air quality in the manufacturing areas used to manufacture this drug product.

3. Please provide a narrative description of the methods or procedures used to control the (b) (4) [redacted] used during production of the drug product. Also, provide the validation protocols and summary reports supporting these procedures.

4. Please provide a description of the facility's environmental monitoring program. This description should include the areas monitored, area air classifications, frequency of monitoring, monitoring methods and media used, and the alert/action levels for each area.

5. Please provide a description of the actions that are taken concerning products manufactured (b) (4) [redacted].

6. Please provide copies of the protocol and summary report for the validation (b) (4) [redacted]

7. The qualification of the (b) (4) [redacted] bioburden assay is inadequate in that the sample volume used is insufficient to reliably determine if the specification has been met. A count of 0 CFU may simply represent an inability of the assay method to accurately quantitate growth in the 0-10 CFU range. The assay should be re-qualified using a larger sample volume such as 100ml.

8. The formulation change necessitates a re-qualification of the sterility and bacterial endotoxin assays. Please provide such requalifications of both of these drug product release assays for review. Include full details of the protocol and the final reports to include the summary data.

COMMENTS:

9. The drug substance microbial limits acceptance criterion of [redacted] (b) (4) [redacted]

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/s/

ROBERT J MELLO
05/27/2011

JAMES L MCVEY
05/27/2011
I concur.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

022260Orig1s005

OTHER REVIEW(S)

RPM Review

Applications:	NDA 22260/S-005 Veletri (epoprostenol sodium) 0.5 mg and 1.5 mg Injection
Applicant:	Actelion
Submission Type:	Prior approval CMC supplement
Supplement receipt date:	February 29, 2012
Reviewer:	Dan Brum, Pharm.D., BCPS, RAC
Date of Review:	June 28, 2012

Background

Cycle 1
Actelion submitted a prior approval CMC supplement on January 18, 2011.
This supplemental application proposed the following changes

- a new formulation (change the excipient mannitol to sucrose)
- a new lower strength (add a 0.5 mg/vial strength)
- new carton and container labeling
- revised prescribing information including changes to **DOSAGE AND ADMINISTRATION, DOSAGE FORMS AND STRENGTHS, DESCRIPTION**, and **HOW SUPPLIED/STORAGE AND HANDLING**
- new manufacturing facilities for both the drug substance and the drug product. to provide for the following:

Prior to sending a Complete Response letter, Actelion withdrew the supplement. The "Acknowledge Withdrawal – Pending Supplement" letter to the sponsor listed several approvability issues including CMC, microbiology, and labeling deficiciencies (letter dated June 21, 2011).

Cycle 2
The sponsor's resubmission was received on February 29, 2012.

Reviews
Microbiology: Robert Mello (May 27, 2011 and June 21, 2012) – recommends approval

CMC: Huai T. Chang (May 17, 2011 and June 28, 2012) – recommends approval

DMEPA: Lubna Merchant and Forest "Ray" Ford (April 1, 2011 and May 25, 2012, respectively) – recommends approval (note: the sponsor addressed all deficiencies described in the DR letter dated June 11, 2012)

Pharm/tox: James Willard (June 15, 2012) – Dr. Willard had some concerns regarding study design but Dr. Stockbridge discussed the issues with the nonclinical team and decided not to request a repeat hemolysis assay.

Dr. Willard also raised the following issue:

(b) (4)

On June 28, 2012, I sent the following email to Dr. Frances Duffy-Warren of Actelion:

(b) (4)

Please provide a written response (email is OK for now) by 3 p.m. today but in any case please let me know prior to 3 p.m. how you expect to proceed.

Dr. Duffy-Warren provided the following response:

(b) (4)

In conclusion, this issue has been resolved.

Revisions to labeling

Modifications to the labeling were made in **DOSAGE AND ADMINISTRATION (2.3 and 2.4), DOSAGE FORMS AND STRENGTHS (3), DESCRIPTION (11), and HOW SUPPLIED/STORAGE AND HANDLING (16)**. (see enclosure for details)

Action
An approval letter will be drafted for Dr. Stockbridge's signature.

Dan Brum, Pharm.D., BCPS
Regulatory Project Manager
June 28, 2012

Enclosure: tracked version of labeling

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/s/

DANIEL BRUM
06/28/2012

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management

Label, Labeling, and Packaging Review

Date:	June 11, 2012
Reviewer:	Ray Ford, RPh Division of Medication Error Prevention and Analysis
Team Leader:	Irene Z. Chan, PharmD, BCPS Division of Medication Error Prevention and Analysis
Associate Director:	Scott Dallas, RPh Division of Medication Error Prevention and Analysis
Division Director:	Carol Holquist, RPh Division of Medication Error Prevention and Analysis
Drug Name and Strength(s):	Veletri (Epoprostenol) for Injection 0.5 mg and 1.5 mg
Application Type/Number:	NDA 22260/S-005
Applicant/sponsor:	Actelion
OSE RCM #:	2012-545

*** This document contains proprietary and confidential information that should not be released to the public.***

Contents

1 INTRODUCTION

This review evaluates the revised labels and labeling for Veletri (Epoprostenol) for Injection, NDA 22260/S-005, for areas of vulnerability that could lead to medication errors. This supplement specifies a change in composition, including a change in excipient from mannitol to sucrose, a change in both drug substance manufacturer and drug product manufacturer, addition of a new strength (0.5 mg per vial), and changes to in-use directions and storage conditions based on new stability data. Actelion intends to withdraw the current formulation of Veletri and replace it with the proposed new formulation upon approval of this supplement. Actelion submitted an amendment dated and received on April 11, 2012. The only change was one digit in the NDC for the carton labeling and container label for 0.5 mg and 1.5 mg and the highlighting of the strengths which maintains the differentiation of the strengths.

1.1 BACKGROUND

Veletri (Epoprostenol) for Injection, 1.5 mg per vial, was approved under NDA 22260 on June 27 2008. Actelion submitted a prior approval CMC supplement (S-005) on January 28, 2011, and subsequently withdrew the supplement on May 27, 2011. On February 28, 2012, Actelion resubmitted supplement 005. DMEPA previously reviewed labels and labeling for this supplement in OSE-RCM #2011-273 dated March 31, 2011.

1.2 PRODUCT INFORMATION

The following product information is provided in the February 29, 2012 container label, carton and insert labeling.

- Active Ingredient: Epoprostenol
- Indication of Use: Pulmonary arterial hypertension (PAH) (World Health Organization Group 1) to improve exercise capacity.
- Route of Administration: Intravenous
- Dosage Form: Sterile lyophilized material in a 10 mL vial
- Strength: 1.5 mg (currently marketed) and 0.5 mg (proposed)
- Dose and Frequency: Infusion of Veletri should be initiated at 2 ng/kg/min and increased in increments of 2 ng/kg/min every 15 minutes or longer until dose-limiting pharmacologic effects are elicited or until a tolerance limit to the drug is established. If symptoms of pulmonary hypertension persist or recur after improving - the infusion should be increased by 1 ng/kg/min to 2 ng/kg/min increments at intervals sufficient to allow assessment of clinical response; these intervals should be at least 15 minutes. Veletri is administered by continuous intravenous infusion via a central venous catheter using an ambulatory infusion pump.

Table 1: Maximum duration of administration (hours) at room temperature (77°F/ 25°C) of fully diluted solutions in the drug delivery reservoir (Short excursions at 104°F (40°C) are permitted for up to: 2 hours for concentrations below 15,000 ng/mL and 4 hours for concentrations between 15,000 ng/mL and 60,000 ng/mL)

Final concentration range after dilution	**Immediate administration**	**If stored for up to 8 days at 36°F to 46°F (2°C to 8°C)**
0.5 mg vial		
Greater than or equal to 3,000 ng/mL and less than 15,000 ng/mL	48 hours	24 hours
1.5 mg vial		
Greater than or equal to 15,000 ng/mL and less than 60,000 ng/mL	48 hours	48 hours
Greater than or equal to 60,000 ng/mL	72 hours	48 hours

- How Supplied: 1.5 mg per vial (currently marketed) and 0.5 mg per vial (proposed).
- Storage: Unopened vials of Veletri are stable until the date indicated on the package when stored at 68°F to 77°F (20°C to 25°C). The unopened vial should be kept in the carton and not exposed to direct sunlight. Maximum duration of administration (hours) at room temperature (77°F /25°C) of fully diluted solutions in the drug delivery reservoir is listed in table 1.
- Container and Closure System: Single Use Vial

2 METHODS AND MATERIALS REVIEWED

DMEPA searched the FDA Adverse Event Reporting System (AERS) for Veletri medication error reports. We also reviewed the Veletri labels and package insert labeling submitted by the Applicant.

2.1 SELECTION OF MEDICATION ERROR CASES

We searched the FDA Adverse Event Reporting System (AERS) database using the strategy listed in Table 2.

Table 2: AERS Search Strategy	
Date	April 2, 2012
Drug Names	(Veletri) (Veletr%)
MedDRA Search Strategy	Medication Errors (HLGT) Product Quality Issue (HLGT) March 2, 2011 (date of last AERS search) to April 2, 2012

The AERS database search identified two reports, respectively. Each report was reviewed for relevancy and duplication. After individual review, one report was not included in the final analysis because it described an incident of pump priming difficulty (device issue). This issue was forwarded to the Center for Devices and Radiological Health for evaluation

The remaining report described an overdose error which is discussed in further detail in Section 3.

2.2 LITERATURE SEARCH

We searched PubMed and the Maude Database on April 2, 2012 for additional cases and actions concerning Veletri (Epoprostenol) for Injection. This search yielded no cases.

2.3 LABELS AND LABELING

Using the principals of human factors and Failure Mode and Effects Analysis,[1] along with post marketing medication error data, the Division of Medication Error Prevention and Analysis (DMEPA) evaluated the following:

- Container Labels submitted February 29, 2012 (Appendix B)
- Carton Labeling submitted February 29, 2012 (Appendix C)
- Insert Labeling submitted February 29, 2012

2.4 PREVIOUSLY COMPLETED REVIEWS

DMEPA had previously reviewed OSE-RCM #2011-273. We compared the recommendations in the review against the revised labels and labeling to ensure all our recommendations were implemented. All of the recommendations were implemented. (b) (4)

3 INTEGRATED MEDICATION ERROR RISK ASSESSMENT

The Sponsor proposes a change in the excipient for the diluent from mannitol to sucrose in the Veletri formulation (b) (4). The

[1] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

second change is the addition of a 0.5 mg/vial strength. The 0.5 mg/vial strength is already available by other manufacturers of epoprostenol. The Sponsor will also have a change in the drug substance manufacturer and this revision will be evaluated by ONDQA. It should have no impact on medication errors. In addition, the new formulation increases the in use stability by allowing longer use at room temperature and limited use under temperatures from greater than 77°F up to 104°F. The Sponsor intends to withdraw the current formulation Veletri and replace it with the revised formulation of Veletri upon approval of supplement. There will be no overlap time where both formulations are marketed according to the Sponsor.

Below are the findings of our postmarketing review of AERS cases and review of proposed revisions.

3.1 MEDICATION ERROR CASES

Following exclusions as described in section 2.1, one relevant medication error case remained for our detailed analysis. This case reported an overdose error where a patient realized that the hospital reconstituted the cassette at a concentration of 45,000 ng/mL instead of 30,000 ng/mL and still infused it at the rate for the 30,000 ng/mL concentration. The outcome of the event was not reported. The cause of the error was not able to be determined from the information provided in the case.

We reviewed the proposed package insert instructions to ensure it is clear with regards to preparing all concentrations. The proposed package insert does provide adequate instructions for preparation of each concentration and the vial required to prepare that concentration.

3.2 MEDICATION ERROR EVALUATION OF PROPOSED REVISIONS

We evaluated the proposed revisions and have the following comments:

- **Excipient change from Mannitol to Sucrose:**

The Sponsor proposes to change an excipient for the diluent from mannitol to sucrose in the Veletri formulation. (b) (4) This will not effect how the product is used and will allow longer administration at room temperature. The inactive ingredients are listed on the container label and the applicant has a flag warning about the new revision. This is adequate labeling to this change in excipients.

- **Addition of 0.5 mg/vial Strength:**

The Sponsor proposes the addition of a 0.5 mg/vial strength. The 0.5 mg/vial strength is available by other manufacturers of epoprostenol. The other manufacturers of epoprostenol have a similar strength statement on their container label and carton labeling. Each vial of epoprostenol is reconstituted with 5 mL of diluent. The amount of reconstituted epoprostenol required to prepare each final concentration varies and is shown in Table 2: Reconstitution and Dilution Instructions. The 0.5 mg/vial strength allows for less waste and fewer concentration ranges located in Table 2: Reconstitution and Dilution Instructions. Since this product is distributed only through the Accredo Specialty Pharmacy, the patient will receive education on reconstitution, and storage when receiving a refill or new prescription for Veletri. Having a single distributor of

Veletri will help mitigate medication errors and ensure patients are educated about any changes. Therefore, adding the proposed strength is appropriate and the sponsor use of a single distributor minimizes confusion and medication errors related to use of the proposed strength. Additionally, the concentration of drug per mL is the same as the currently marketed products.

- **Change in Storage:**

The new formulation of Veletri increases the in use stability by allowing longer time for administration at room temperature. This new storage information for the formulation change is highlighted on the proposed carton labeling PDP for each strength. The maximum duration for administration after being stored for up to eight (8) days at 36°F to 46°F (2°C to 8°C) is increased to at least 24 hours for all concentrations. This change simplifies storage and increases administration time for Veletri. If a patient were to continue to store and use the reconstituted Veletri according to the previous storage conditions, no drug deterioration would occur. Therefore, we do not believe that the increase in administration duration and storage stability time will contribute to medication errors.

- **Insert Labeling:**

In section 2 Dosage and Administration of the package insert, section 2.3 Administration is placed before section 2.4 Reconstitution. This placement is counter to how the drug is reconstituted and administered. Despite the reversal of this information, we did not retrieve any errors attributed to this placement of the Reconstitution section before the Administration section. Therefore, we will not request any revisions to the insert at this time.

- **Proposed Carton Labeling and Container Labels:**

We compared the recommendations in our previous review against the revised labels and labeling and determined that all of the recommendations were implemented. (b) (4)

Additionally, the container labels can be improved by adding stability after reconstitution information to the side display panel of the 0.5 mg and 1.5 mg strength.

- **Addition of New Storage Requirement to the PDP:**

The sponsor has added a flag warning to the carton labeling to highlight the new storage information presented in table 1. Trying to highlight or flag this information is appropriate, but it should be removed from the labeling after the product has been on the market for six (6) months. The information can also be improved to reflect the storage of Veletri following reconstitution.

- **Educating Patients:**

Accredo Specialty Pharmacy is the only distributor of Veletri. The transition of adding the 0.5 mg strength, reconstitution, and storage education will be provided by Accredo. Nurses from Accredo Specialty Pharmacy trained in reconstitution and administration provide initial training to the patient to ensure competency as well as monitoring continued adherence while the patient in receiving Veletri. In addition, their National Customer Support Center is available 24 hours a day, 7 days a week to help patients manage critical aspects Veletri therapy. Therefore, we think the sponsor provides a reasonable way to educate patients on any changes in order to minimize confusion.

4 CONCLUSIONS

DMEPA concludes that the proposed container label, carton and insert labeling can be improved to increase the prominence of important information on the carton labeling to promote the safe use of the product.

5 RECOMMENDATIONS

Based on this review, DMEPA recommends the following be implemented prior to approval of this NDA supplement:

Carton Labeling (0.5 mg per vial, 1.5 mg per vial)

1. (b) (4)
2. Revise the storage statement on the PDP from 'New Storage Requirement' to read 'New Storage Requirement Following Reconstitution.' Ensure this storage requirement statement is removed from the carton labeling not later than 6 months after the new labeling has been introduced into the marketplace.

Container Label (0.5 mg per vial, 1.5 mg per vial)

- (b) (4) Add the statement "After reconstitution, immediately withdraw correct dose, and dilute to final concentration in reservoir. Discard unused portion remaining in vial." to the side panel.

Package Insert:

- In section 2.4 Reconstitution revise "Use after reconstitution and immediate dilution to final concentration" to read "After reconstitution, immediately withdraw correct dose, and dilute to final concentration in reservoir. Discard unused portion of solution remaining in vial." This statement conveys the actual process of reconstitution ensuring unused Veletri is discarded.

If you have further questions or need clarifications, please contact Nina Ton, project manager, at 301-796-1648.

APPENDICES

APPENDIX A. DATABASE DESCRIPTIONS

Adverse Event Reporting System (AERS)

The Adverse Event Reporting System (AERS) is a computerized information database designed to support the FDA's post-marketing safety surveillance program for drug and therapeutic biologic products. The FDA uses AERS to monitor adverse events and medication errors that might occur with these marketed products. The structure of AERS complies with the international safety reporting guidance (ICH E2B) issued by the International Conference on Harmonisation. Adverse events in AERS are coded to terms in the Medical Dictionary for Regulatory Activities terminology (MedDRA).

AERS data do have limitations. First, there is no certainty that the reported event was actually due to the product. FDA does not require that a causal relationship between a product and event be proven, and reports do not always contain enough detail to properly evaluate an event. Further, FDA does not receive all adverse event reports that occur with a product. Many factors can influence whether or not an event will be reported, such as the time a product has been marketed and publicity about an event. Therefore, AERS cannot be used to calculate the incidence of an adverse event in the U.S. population.

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/s/

FOREST R FORD

06/11/2012

Updated review has change in section 5 to reflect that the applicant is removing the storage of reconstituted vials under this supplement.

IRENE Z CHAN

06/11/2012

SCOTT M DALLAS

06/13/2012

CAROL A HOLQUIST

06/13/2012

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management

Label, Labeling, and Packaging Review

Date:	May 24, 2012
Reviewer:	Ray Ford, RPh Division of Medication Error Prevention and Analysis
Team Leader:	Irene Z. Chan, PharmD, BCPS Division of Medication Error Prevention and Analysis
Associate Director:	Scott Dallas, RPh Division of Medication Error Prevention and Analysis
Division Director:	Carol Holquist, RPh Division of Medication Error Prevention and Analysis
Drug Name and Strength(s):	Veletri (Epoprostenol) for Injection 0.5 mg and 1.5 mg
Application Type/Number:	NDA 22260/S-005
Applicant/sponsor:	Actelion
OSE RCM #:	2012-545

*** This document contains proprietary and confidential information that should not be released to the public.***

Contents

1 INTRODUCTION

This review evaluates the revised labels and labeling for Veletri (Epoprostenol) for Injection, NDA 22260/S-005, for areas of vulnerability that could lead to medication errors. This supplement specifies a change in composition, including a change in excipient from mannitol to sucrose, a change in both drug substance manufacturer and drug product manufacturer, addition of a new strength (0.5 mg per vial), and changes to in-use directions and storage conditions based on new stability data. Actelion intends to withdraw the current formulation of Veletri and replace it with the proposed new formulation upon approval of this supplement. Actelion submitted an amendment dated and received on April 11, 2012. The only change was one digit in the NDC for the carton labeling and container label for 0.5 mg and 1.5 mg and the highlighting of the strengths which maintains the differentiation of the strengths.

1.1 BACKGROUND

Veletri (Epoprostenol) for Injection, 1.5 mg per vial, was approved under NDA 22260 on June 27 2008. Actelion submitted a prior approval CMC supplement (S-005) on January 28, 2011, and subsequently withdrew the supplement on May 27, 2011. On February 28, 2012, Actelion resubmitted supplement 005. DMEPA previously reviewed labels and labeling for this supplement in OSE-RCM #2011-273 dated March 31, 2011.

1.2 PRODUCT INFORMATION

The following product information is provided in the February 29, 2012 container label, carton and insert labeling.

- Active Ingredient: Epoprostenol
- Indication of Use: Pulmonary arterial hypertension (PAH) (World Health Organization Group 1) to improve exercise capacity.
- Route of Administration: Intravenous
- Dosage Form: Sterile lyophilized material in a 10 mL vial
- Strength: 1.5 mg (currently marketed) and 0.5 mg (proposed)
- Dose and Frequency: Infusion of Veletri should be initiated at 2 ng/kg/min and increased in increments of 2 ng/kg/min every 15 minutes or longer until dose-limiting pharmacologic effects are elicited or until a tolerance limit to the drug is established. If symptoms of pulmonary hypertension persist or recur after improving - the infusion should be increased by 1 ng/kg/min to 2 ng/kg/min increments at intervals sufficient to allow assessment of clinical response; these intervals should be at least 15 minutes. Veletri is administered by continuous intravenous infusion via a central venous catheter using an ambulatory infusion pump.

Table 1: Maximum duration of administration (hours) at room temperature (77°F/ 25°C) of fully diluted solutions in the drug delivery reservoir (Short excursions at 104°F (40°C) are permitted for up to: 2 hours for concentrations below 15,000 ng/mL and 4 hours for concentrations between 15,000 ng/mL and 60,000 ng/mL)

Final concentration range after dilution	**Immediate administration**	**If stored for up to 8 days at 36°F to 46°F (2°C to 8°C)**
0.5 mg vial		
Greater than or equal to 3,000 ng/mL and less than 15,000 ng/mL	48 hours	24 hours
1.5 mg vial		
Greater than or equal to 15,000 ng/mL and less than 60,000 ng/mL	48 hours	48 hours
Greater than or equal to 60,000 ng/mL	72 hours	48 hours

- How Supplied: 1.5 mg per vial (currently marketed) and 0.5 mg per vial (proposed).
- Storage: Unopened vials of Veletri are stable until the date indicated on the package when stored at 68°F to 77°F (20°C to 25°C). The unopened vial should be kept in the carton and not exposed to direct sunlight. Maximum duration of administration (hours) at room temperature (77°F /25°C) of fully diluted solutions in the drug delivery reservoir is listed in table 1.
- Container and Closure System: Single Use Vial

2 METHODS AND MATERIALS REVIEWED

DMEPA searched the FDA Adverse Event Reporting System (AERS) for Veletri medication error reports. We also reviewed the Veletri labels and package insert labeling submitted by the Applicant.

2.1 SELECTION OF MEDICATION ERROR CASES

We searched the FDA Adverse Event Reporting System (AERS) database using the strategy listed in Table 2.

Table 2: AERS Search Strategy	
Date	April 2, 2012
Drug Names	(Veletri) (Veletr%)
MedDRA Search Strategy	Medication Errors (HLGT) Product Quality Issue (HLGT) March 2, 2011 (date of last AERS search) to April 2, 2012

The AERS database search identified two reports, respectively. Each report was reviewed for relevancy and duplication. After individual review, one report was not included in the final analysis because it described an incident of pump priming difficulty (device issue). This issue was forwarded to the Center for Devices and Radiological Health for evaluation

The remaining report described an overdose error which is discussed in further detail in Section 3.

2.2 LITERATURE SEARCH

We searched PubMed and the Maude Database on April 2, 2012 for additional cases and actions concerning Veletri (Epoprostenol) for Injection. This search yielded no cases.

2.3 LABELS AND LABELING

Using the principals of human factors and Failure Mode and Effects Analysis,[1] along with post marketing medication error data, the Division of Medication Error Prevention and Analysis (DMEPA) evaluated the following:

- Container Labels submitted February 29, 2012 (Appendix B)
- Carton Labeling submitted February 29, 2012 (Appendix C)
- Insert Labeling submitted February 29, 2012

2.4 PREVIOUSLY COMPLETED REVIEWS

DMEPA had previously reviewed OSE-RCM #2011-273. We compared the recommendations in the review against the revised labels and labeling to ensure all our recommendations were implemented. All of the recommendations were implemented. (b) (4)

3 INTEGRATED MEDICATION ERROR RISK ASSESSMENT

The Sponsor proposes a change in the excipient for the diluent from mannitol to sucrose in the Veletri formulation (b) (4) The

[1] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

second change is the addition of a 0.5 mg/vial strength. The 0.5 mg/vial strength is already available by other manufacturers of epoprostenol. The Sponsor will also have a change in the drug substance manufacturer and this revision will be evaluated by ONDQA. It should have no impact on medication errors. In addition, the new formulation increases the in use stability by allowing longer use at room temperature and limited use under temperatures from greater than 77°F up to 104°F. The Sponsor intends to withdraw the current formulation Veletri and replace it with the revised formulation of Veletri upon approval of supplement. There will be no overlap time where both formulations are marketed according to the Sponsor.

Below are the findings of our postmarketing review of AERS cases and review of proposed revisions.

3.1 MEDICATION ERROR CASES

Following exclusions as described in section 2.1, one relevant medication error case remained for our detailed analysis. This case reported an overdose error where a patient realized that the hospital reconstituted the cassette at a concentration of 45,000 ng/mL instead of 30,000 ng/mL and still infused it at the rate for the 30,000 ng/mL concentration. The outcome of the event was not reported. The cause of the error was not able to be determined from the information provided in the case.

We reviewed the proposed package insert instructions to ensure it is clear with regards to preparing all concentrations. The proposed package insert does provide adequate instructions for preparation of each concentration and the vial required to prepare that concentration.

3.2 MEDICATION ERROR EVALUATION OF PROPOSED REVISIONS

We evaluated the proposed revisions and have the following comments:

- **Excipient change from Mannitol to Sucrose:**

The Sponsor proposes to change an excipient for the diluent from mannitol to sucrose in the Veletri formulation. (b) (4) This will not effect how the product is used and will allow longer administration at room temperature. The inactive ingredients are listed on the container label and the applicant has a flag warning about the new revision. This is adequate labeling to this change in excipients.

- **Addition of 0.5 mg/vial Strength:**

The Sponsor proposes the addition of a 0.5 mg/vial strength. The 0.5 mg/vial strength is available by other manufacturers of epoprostenol. The other manufacturers of epoprostenol have a similar strength statement on their container label and carton labeling. Each vial of epoprostenol is reconstituted with 5 mL of diluent. The amount of reconstituted epoprostenol required to prepare each final concentration varies and is shown in Table 2: Reconstitution and Dilution Instructions. The 0.5 mg/vial strength allows for less waste and fewer concentration ranges located in Table 2: Reconstitution and Dilution Instructions. Since this product is distributed only through the Accredo Specialty Pharmacy, the patient will receive education on reconstitution, and storage when receiving a refill or new prescription for Veletri. Having a single distributor of

Veletri will help mitigate medication errors and ensure patients are educated about any changes. Therefore, adding the proposed strength is appropriate and the sponsor use of a single distributor minimizes confusion and medication errors related to use of the proposed strength. Additionally, the concentration of drug per mL is the same as the currently marketed products.

- **Change in Storage:**

The new formulation of Veletri increases the in use stability by allowing longer time for administration at room temperature. This new storage information for the formulation change is highlighted on the proposed carton labeling PDP for each strength. The maximum duration for administration after being stored for up to eight (8) days at 36°F to 46°F (2°C to 8°C) is increased to at least 24 hours for all concentrations. This change simplifies storage and increases administration time for Veletri. If a patient were to continue to store and use the reconstituted Veletri according to the previous storage conditions, no drug deterioration would occur. Therefore, we do not believe that the increase in administration duration and storage stability time will contribute to medication errors.

- **Insert Labeling:**

In section 2 Dosage and Administration of the package insert, section 2.3 Administration is placed before section 2.4 Reconstitution. This placement is counter to how the drug is reconstituted and administered. Despite the reversal of this information, we did not retrieve any errors attributed to this placement of the Reconstitution section before the Administration section. Therefore, we will not request any revisions to the insert at this time.

- **Proposed Carton Labeling and Container Labels:**

We compared the recommendations in our previous review against the revised labels and labeling and determined that all of the recommendations were implemented. (b) (4)

Additionally, the container labels can be improved by adding stability after reconstitution information to the side display panel of the 0.5 mg and 1.5 mg strength.

- **Addition of New Storage Requirement to the PDP:**

The sponsor has added a flag warning to the carton labeling to highlight the new storage information presented in table 1. Trying to highlight or flag this information is appropriate, but it should be removed from the labeling after the product has been on the market for six (6) months. The information can also be improved to reflect the storage of Veletri following reconstitution.

- **Educating Patients:**

Accredo Specialty Pharmacy is the only distributor of Veletri. The transition of adding the 0.5 mg strength, reconstitution, and storage education will be provided by Accredo. Nurses from Accredo Specialty Pharmacy trained in reconstitution and administration provide initial training to the patient to ensure competency as well as monitoring continued adherence while the patient in receiving Veletri. In addition, their National Customer Support Center is available 24 hours a day, 7 days a week to help patients manage critical aspects Veletri therapy. Therefore, we think the sponsor provides a reasonable way to educate patients on any changes in order to minimize confusion.

4 CONCLUSIONS

DMEPA concludes that the proposed container label, carton and insert labeling can be improved to increase the prominence of important information on the carton labeling to promote the safe use of the product.

5 RECOMMENDATIONS

Based on this review, DMEPA recommends the following be implemented prior to approval of this NDA supplement:

Carton Labeling (0.5 mg per vial, 1.5 mg per vial)

1. (b) (4)
2. Revise the storage statement on the PDP from 'New Storage Requirement' to read 'New Storage Requirement Following Reconstitution.' Ensure this storage requirement statement is removed from the carton labeling not later than 6 months after the new labeling has been introduced into the marketplace.
3. (b) (4)

Container Label (0.5 mg per vial, 1.5 mg per vial)

- Add stability after reconstitution information to the side display panel of the 0.5 mg and 1.5 mg strength.

If you have further questions or need clarifications, please contact Nina Ton, project manager, at 301-796-1648.

APPENDICES

APPENDIX A. DATABASE DESCRIPTIONS

Adverse Event Reporting System (AERS)

The Adverse Event Reporting System (AERS) is a computerized information database designed to support the FDA's post-marketing safety surveillance program for drug and therapeutic biologic products. The FDA uses AERS to monitor adverse events and medication errors that might occur with these marketed products. The structure of AERS complies with the international safety reporting guidance (ICH E2B) issued by the International Conference on Harmonisation. Adverse events in AERS are coded to terms in the Medical Dictionary for Regulatory Activities terminology (MedDRA).

AERS data do have limitations. First, there is no certainty that the reported event was actually due to the product. FDA does not require that a causal relationship between a product and event be proven, and reports do not always contain enough detail to properly evaluate an event. Further, FDA does not receive all adverse event reports that occur with a product. Many factors can influence whether or not an event will be reported, such as the time a product has been marketed and publicity about an event. Therefore, AERS cannot be used to calculate the incidence of an adverse event in the U.S. population.

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/s/

FOREST R FORD
05/24/2012

IRENE Z CHAN
05/24/2012

SCOTT M DALLAS
05/25/2012

CAROL A HOLQUIST
05/25/2012

Department of Health and Human Services

Public Health Service

Food and Drug Administration

Center for Drug Evaluation and Research

Office of Surveillance and Epidemiology

Date:	March 31, 2011
Application Type/Number:	NDA 022260/S-005
To:	Norman Stockbridge, MD, Director Division of Cardiovascular and Renal Products
Through:	Melina Griffis, RPh, Team Leader Kellie Taylor, PharmD, MPH, Associate Director Carol Holquist, RPh, Director Division of Medication Error Prevention and Analysis
From:	Lubna Merchant, M.S., Pharm.D, Safety Evaluator Division of Medication Error Prevention and Analysis
Subject:	Label and Labeling Review
Drug Name(s) and Strengths:	Veletri (Epoprostenol) for Injection, 0.5 mg and 1.5 mg per vial
Applicant/sponsor:	Actelion Pharmaceuticals Ltd.
OSE RCM #:	2011-273

CONTENTS

1 INTRODUCTION

This review summarizes the Division of Medication Error Prevention and Analysis evaluation of the proposed labels and labeling for Veletri (Epoprostenol) Injection, for areas of vulnerabilities that could lead to medication errors. These labels were submitted by the Applicant on January 28, 2011, as part of a CMC supplement which provides for a new formulation of Veletri for injection that has been developed to provide enhanced convenience for patients with respect to storage and administration at room temperature and above. An additional 0.5 mg/vial strength has also been proposed by the Applicant. Veletri is currently available in a strength of 1.5 mg/vial. We note that the proposed new strength is consistent with the approved dosing range specification in the product labeling.

2. METHODS AND MATERIALS

Since Veletri is currently marketed, the Division of Medication Error Prevention and Analysis (DMEPA) conducted a search of the FDA Adverse Event Reporting System (AERS) database to identify any medication errors relevant to the labels or labeling of Veletri. Additionally, we evaluated the proposed container labels, and carton labeling submitted by the Applicant.

2.1. ADVERSE EVENT REPORTING SYSTEM (AERS) SELECTION OF CASES

An AERS search conducted on March 3, 2011 used the tradename "Veletri," active ingredient 'Epoprostenol, and verbatim term "Veletr%," and "Epoprosteno%." The reactions used include: HLGT term, "Medication Errors," and the PT term, "Product Quality Issue."

Reports were manually reviewed to determine if a medication error occurred. Duplicate reports were combined into cases. Reports that did not describe a medication error or did not describe an error applicable to this review (e.g. adverse events related to Veletri or other medications, accidental exposure, overdose, no medication errors, errors due to knowledge or performance deficit) were excluded from further analysis. If an error occurred, the reports were categorized by type of error and evaluated for contributing factors to the medication errors. Additionally the reports were reviewed to determine if the error could be applicable to the labels and labeling of Veletri and thus pertinent to this review.

2.2 LABELS AND LABELING

Using Failure Mode and Effects Analysis (FMEA),[1] the Division of Medication Error Prevention and Analysis (DMEPA) evaluated the container labels, and carton labeling. This review focuses on labels and labeling submitted as part of January 28, 2011 submission. See Appendices A-B for images of the proposed container labels and carton labeling.

[1] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

3. RESULTS

The following section describes the results of AERS and our label and labeling review.

3.1 AERS RESULTS

A total of 10 cases were retrieved in the AERS search, however after excluding cases as described in section 2.1, only 2 cases involved a medication error. These cases are categorized below:

- Wrong route error (n=1). This case involved the product Flolan (Epoprostenol sodium) being administered as a continuous aerosol nebulizer instead of continuous intravenous infusion.
- Wrong dose error (n=1), In this case, Flolan (Epoprostenol sodium) 50 mg in 50 mL was prescribed instead of 50 mcg.

3.2 LABELS AND LABELING

The container label risk assessment findings indicate the presentation of information on the label does introduce vulnerability to confusion that can lead to medication errors. It was determined that the labels and labeling need improved differentiation between the available strengths. We provide labeling recommendations in section 5 to address this deficiency.

4. DISCUSSION

The Applicant has proposed a new formulation of Veletri (Epoprostenol) for injection that has been developed to provide enhanced stability at room temperature and above. The previous formulation required refrigeration. The new formulation provides for a change in excipient from mannitol to sucrose, (b) (4) .

Based on the updated stability, changes to the Dosage and Administration, and How Supplied sections are proposed by the Applicant to provide additional recommendations regarding the use at room temperature and higher *(>77°F up to 104°F)* prior to administration of the diluted solutions. In addition, the current recommendations, which allow the reconstituted solution in the vial to be kept under, refrigerated conditions for as long as 5 days, have been removed. The new storage conditions only recommends the reconstituted and diluted solutions to be kept under refrigerated conditions.

To introduce and highlight the new strength, second formulation, and changes to the stability, (b) (4)

An additional 0.5 mg/vial (500,000 ng/vial) strength has also been proposed. This strength is appropriate for the doses described in the dosage and administration section. Our evaluation of the proposed labels identified the following deficiencies: (1) There is inadequate differentiation between the two strengths. (b) (4) .

(b) (4) We provide label and labeling recommendations in section 5 below to help differentiate the two strengths.

5. CONCLUSION AND RECOMMENDATIONS

Our evaluation of the proposed labels and labeling identified areas of needed improvement in order to minimize the potential for medication errors. We provide recommendations for communication to the Applicant prior to approval in Section 5.2 Comments to the Applicant for the container labels and carton labeling.

Please copy the Division of Medication Error Prevention and Analysis on any communication to the Applicant with regard to this review. If you have further questions or need clarifications on this review, please contact the OSE Regulatory Project Manager, Nina Ton at 301-796-1648

5.2 COMMENTS TO THE APPLICANT:

A. Proposed Container Label (0.5 mg/vial and 1.5 mg/vial)

1. The proposed labels for the 0.5 mg/vial are very similar in appearance to the labels proposed for the 1.5 mg/vial. (b) (4)
2. Revise the dosage form statement "for Injection" so that it is presented in the same size and font as the established name.
3. Revise the statement "Single Dose Vial" to state "Single Dose Vial- Discard Unused Portion."

B. Proposed Carton Labeling (0.5 mg/vial and 1.5 mg/vial)

1. See comment A1-A3.
2. (b) (4) Revise the statement to read to "New storage requirement" or "New temperature storage requirement." (b) (4) Ensure that this statement is not more prominent than the strength presentation.

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/s/

LUBNA A MERCHANT
04/01/2011

MELINA N GRIFFIS
04/01/2011

CAROL A HOLQUIST
04/01/2011

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

022260Orig1s005

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 22260/S-005

DISCIPLINE REVIEW LETTER

Acetelion Clinical Research, Inc.
Attention: Sheila Mathias, Ph.D.
Director, Drug Regulatory Affairs
1820 Chapel Avenue West, Suite 300
Cherry Hill, NJ 08002

Dear Dr. Mathias:

Please refer to your supplemental New Drug Application (sNDA) dated February 28, 2012, received February 29, 2012, submitted under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act, for Veletri (epoprostenol sodium) for Injection, 0.5 mg and 1.5 mg.

The Division of Medication Error Prevention and Analysis (DMEPA) review of the proposed label and labeling section of your submission is complete, and we have identified the following deficiencies:

Carton Labeling (0.5 mg per vial, 1.5 mg per vial)

1. [redacted] (b) (4)
2. Revise the storage statement on the Principal Display Panel from 'New Storage Requirement' to read 'New Storage Requirement Following Reconstitution.' Ensure this storage requirement statement is removed from the carton labeling not later than 6 months after the new labeling has been introduced into the marketplace.

Container Label (0.5 mg per vial, 1.5 mg per vial)

- [redacted] (b) (4) Add the statement "After reconstitution, immediately withdraw correct dose, and dilute to final concentration in reservoir. Discard unused portion remaining in vial." to the side panel.

Package Insert:

- In section 2.4 Reconstitution revise "Use after reconstitution and immediate dilution to final concentration" to read "After reconstitution, immediately withdraw correct dose, and dilute to final concentration in reservoir. Discard unused portion of

solution remaining in vial." This statement conveys the actual process of reconstitution ensuring unused Veletri is discarded.

We are providing these comments to you before we complete our review of the entire application to give you preliminary notice of issues that we have identified. In conformance with the prescription drug 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 subject to change as we finalize our review of your application. In addition, we may identify other information that must be provided before we can approve this application. If you respond to these issues during this review cycle, depending on the timing of your response, and in conformance with the user fee reauthorization agreements, we may not be able to consider your response before we take an action on your application during this review cycle.

If you have any questions, please call Dan Brum, Pharm.D., 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

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/s/

NORMAN L STOCKBRIDGE
06/11/2012

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR CONSULTATION

TO *(Office/Division)*:	FROM (*Name, Office/Division, and Phone Number of Requestor)*:
Vera Viehmann, OPS/ New Drug Microbiology	Teshara G. Bouie, ONDQA, Division of Post-Marketing Assessment, 301-796-1649

DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
March 1, 2012		22-260	S-005	February 28, 2012

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
Veletri Injection			May 29, 2012

NAME OF FIRM: Acetlion

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☒ MANUFACTURING CHANGE / ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE-NDA MEETING
- ☐ END-OF-PHASE 2a MEETING
- ☐ END-OF-PHASE 2 MEETING
- ☐ RESUBMISSION
- ☐ SAFETY / EFFICACY
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☐ OTHER *(SPECIFY BELOW)*:

II. BIOMETRICS

- ☐ PRIORITY P NDA REVIEW
- ☐ END-OF-PHASE 2 MEETING
- ☐ CONTROLLED STUDIES
- ☐ PROTOCOL REVIEW
- ☐ OTHER (SPECIFY BELOW):
- ☐ CHEMISTRY REVIEW
- ☐ PHARMACOLOGY
- ☐ BIOPHARMACEUTICS
- ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE 4 STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL - BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG SAFETY

- ☐ PHASE 4 SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE, e.g., POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

- ☐ CLINICAL
- ☐ NONCLINICAL

COMMENTS / SPECIAL INSTRUCTIONS: This resubmission proposes changes to the formulation, the addition of a new 0.5 mg strength, labeling and storage condition changes. Please review. The supplement is located in DARRTS.

SIGNATURE OF REQUESTOR	METHOD OF DELIVERY (Check one)
Teshara G. Bouie	☒ DARRTS ☐ EMAIL ☐ MAIL ☐ HAND
PRINTED NAME AND SIGNATURE OF RECEIVER	PRINTED NAME AND SIGNATURE OF DELIVERER

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/s/

TESHARA G BOUIE
03/01/2012

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADM NISTRATION

REQUEST FOR CONSULTATION

TO *(Division/Office)*: **Mail: OSE/DMEPA cc: Nina Ton**			FROM: Dan Brum x60578 DCRP/ODE I	
DATE March 1, 2012	IND NO.	NDA NO. 22260/s-005	TYPE OF DOCUMENT CMC prior approval supplement (resubmission after withdrawal)	DATE OF DOCUMENT letter date February 28, 2012 received date February 29, 2012
NAME OF DRUG Veletri (epoprostenol)	PRIORITY CONSIDERATION 4-month PDUFA goal date		CLASSIFICATION OF DRUG prostacyclin	DESIRED COMPLETION DATE April 30, 2012

NAME OF FIRM: Actelion

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- X MANUFACTURING CHANGE/ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE--NDA MEETING
- ☐ END OF PHASE II MEETING
- ☐ RESUBMISSION
- ☐ SAFETY/EFFICACY
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- X OTHER *(SPECIFY BELOW)*:

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
☐ TYPE A OR B NDA REVIEW ☐ END OF PHASE II MEETING ☐ CONTROLLED STUDIES ☐ PROTOCOL REVIEW ☐ OTHER (SPECIFY BELOW):	☐ CHEMISTRY REVIEW ☐ PHARMACOLOGY ☐ BIOPHARMACEUTICS ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE IV STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL-BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG EXPERIENCE

- ☐ PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

- ☐ CLINICAL
- ☐ PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS:

We received a resubmission of a prior approval CMC supplement with labeling that requires review by ONDQA, micro, and DMEPA. The sponsor has proposed 1) a new formulation (replacing an inactive ingredient) and 2) a new (lower) strength, 3) new manufacturers, etc. The new formulation involves change in excipient (from mannitol to sucrose) [redacted] (b) (4). An additional 0.5 mg/vial strength has also been developed.
Draft labeling with proposed changes is available for review (eCTD that can be assessed via DARRTS). The entire submission is electronic.
Draft carton labels are also included.
I would like to ask DMEPA to review the proposed changes in conjunction with the reviewer in ONDQA. Please let me know what questions or concerns you may have.

SIGNATURE OF REQUESTER	METHOD OF DELIVERY (Check one) ☐ MAIL ☐ HAND
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

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/s/

DANIEL BRUM
03/01/2012

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 22-260/S-005

ACKNOWLEDGE WITHDRAWAL – PENDING SUPPLEMENT

Actelion Ltd.
Attention: Dr. Frances Duffy-Warren
VP Regulatory Affairs US
1820 Chapel Ave. West, Suite 300
Cherry Hill, NJ 08002

Dear Dr. Duffy-Warren:

We acknowledge receipt of your May 27, 2011 correspondence notifying us that you are withdrawing your January 28, 2011 supplemental new drug application for Veletri (epoprostenol sodium) 1.5 mg Injection. This supplemental new drug application was filed on March 28, 2011.

This supplemental application proposed the following changes

- a new formulation (change the excipient mannitol to sucrose)
- a new lower strength (add a 0.5 mg/vial strength)
- new carton and container labeling
- revised prescribing information including changes to **DOSAGE AND ADMINISTRATION, DOSAGE FORMS AND STRENGTHS, DESCRIPTION**, and **HOW SUPPLIED/STORAGE AND HANDLING**
- new manufacturing facilities for both the drug substance and the drug product.

In accordance with 21 CFR 314.65, this supplemental application is withdrawn as of May 27, 2011. If you decide to resubmit this application, this withdrawal will not prejudice any future decisions on filing. You may reference information contained in this withdrawn application in any resubmission. However, because we retain only the archival copy of a withdrawn application in our files, you should resubmit appropriate review copies of all information. Retain the above NDA number for the resubmitted application.

In addition, the resubmitted application should address the following deficiencies identified during our preliminary review of the withdrawn application:

Chemistry, Manufacturing and Controls

1. According to 21 CFR 314.70(a)(6), "A supplement or annual report must include a list of all changes contained in the supplement or annual report. For supplements, this list must be provided in the cover letter." We acknowledge that you included some information about the proposed manufacturing facilities in the body of the application; however, the cover letter, submitted January 28, 2011, does not make reference to any new manufacturing facilities. Furthermore, Form FDA 356h, submitted January 28, 2011,

references previously approved manufacturing facilities and does not reference the newly proposed manufacturing facilities. If you choose to resubmit your sNDA, include in the cover letter the following information for each new proposed manufacturing site:

a. establishment name
b. complete address
c. full contact information, including contact person, phone number, fax number and email address
d. FEI#

Also, include new establishment information on Form FDA 356h as well as full establishment information in the body of the application.

2. The studies supporting container closure integrity were inadequate. [redacted]
3. Provide floor plans or narrative descriptions summarizing the facility layout, equipment locations, the flow of materials, product and personnel and the air quality in the manufacturing areas used to manufacture this drug product.
4. Provide a narrative description of the methods or procedures used to control the [redacted] during production of the drug product. Also, provide the validation protocols and summary reports supporting these procedures.
5. Provide a description of the facility's environmental monitoring program. This description should include the areas monitored, area air classifications, frequency of monitoring, monitoring methods and media used, and the alert/action levels for each area.
6. Provide a description of the actions that are taken concerning products manufactured [redacted]
7. Provide copies of the protocol and summary report for the validation [redacted]
8. The qualification of the [redacted] bioburden assay is inadequate in that the sample volume used is insufficient to reliably determine if the specification has been met. A count of 0 CFU may simply represent an inability of the assay method to accurately quantitate growth in the 0-10 CFU range. The assay should be re-qualified using a larger sample volume such as 100ml.
9. The formulation change necessitates a re-qualification of the sterility and bacterial endotoxin assays. Please provide such re-qualifications of both of these drug product release assays for review. Include full details of the protocol and the final reports to include the summary data.
10. The drug substance microbial limits acceptance criterion of [redacted]

11. There is no in-use stability data to support your proposed modification of table for Maximum Duration for Storage and Administration in package insert section 2.4 Reconstitution.

Labeling

A. Proposed Container Label (0.5 mg/vial and 1.5 mg/vial)

1. The proposed labels for the 0.5 mg/vial are very similar in appearance to the labels proposed for the 1.5 mg/vial. (b) (4) [redacted]

2. Revise the dosage form statement "for Injection" so that it is presented in the same size and font as the established name.

3. Revise the statement "Single Dose Vial" to state "Single Dose Vial - Discard Unused Portion."

B. Proposed Carton Labeling (0.5 mg/vial and 1.5 mg/vial)

1. See comment A1-A3.

2. (b) (4) [redacted] Revise the statement to read "New storage requirement" or "New temperature storage requirement." (b) (4) [redacted] Ensure that this statement is not more prominent than the strength presentation.

If you have any questions, call Don Henry, Regulatory Project Manager, at (301) 796-4227.

Sincerely,

{See appended electronic signature page}

Hasmukh B. Patel, Ph.D.
Branch Chief
Division of New Drug Quality Assessment I
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

HASMUKH B PATEL
06/21/2011

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADM NISTRATION

REQUEST FOR CONSULTATION

TO *(Division/Office)*: **Mail: OSE/DMEPA cc: Nina Ton**			FROM: Dan Brum x60578 DCRP/ODE I	
DATE February 7, 2011	IND NO.	NDA NO. 22260/s-005	TYPE OF DOCUMENT CMC prior approval supplement	DATE OF DOCUMENT January 28, 2011
NAME OF DRUG Veletri (epoprostenol)	PRIORITY CONSIDERATION 4-month PDUFA goal date		CLASSIFICATION OF DRUG prostacyclin	DESIRED COMPLETION DATE April 4, 2011

NAME OF FIRM: Actelion

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- X MANUFACTURING CHANGE/ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE--NDA MEETING
- ☐ END OF PHASE II MEETING
- ☐ RESUBMISSION
- ☐ SAFETY/EFFICACY
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- X OTHER *(SPECIFY BELOW)*:

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
☐ TYPE A OR B NDA REVIEW ☐ END OF PHASE II MEETING ☐ CONTROLLED STUDIES ☐ PROTOCOL REVIEW ☐ OTHER (SPECIFY BELOW):	☐ CHEMISTRY REVIEW ☐ PHARMACOLOGY ☐ BIOPHARMACEUTICS ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE IV STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL-BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG EXPERIENCE

- ☐ PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

- ☐ CLINICAL
- ☐ PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS:

We received a new prior approval CMC supplement with labeling that requires review by ONDQA, micro, DMEPA, and clinical. The sponsor has proposed 1) a new formulation (replacing an inactive ingredient) and 2) a new (lower) strength. The new formulation involves change in excipient (from mannitol to sucrose) (b) (4). An additional 0.5 mg/vial strength has also been developed.

Draft labeling with proposed changes should be reviewed along with the sponsor's proposal to introduce and highlight the new strength (b) (4)

Draft carton labels are also included.

I, Dan Brum, the DCRP RPM, will help to coordinate review of this supplement. I would like to ask DMEPA to review the proposed changes in conjunction with the reviewer in ONDQA. Please let me know what questions or concerns you may have. The entire submission is electronic (EDR).

SIGNATURE OF REQUESTER	METHOD OF DELIVERY (Check one) ☐ MAIL ☐ HAND
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

DANIEL BRUM
02/07/2011