**Review Report**

January 18, 2017
Pharmaceuticals and Medical Devices Agency

The following are the results of the review of the following pharmaceutical product submitted for marketing approval conducted by the Pharmaceuticals and Medical Devices Agency (PMDA).

| | |
|---|---|
| **Brand Name** | Epoprostenol ACT 0.5 mg<br>Epoprostenol ACT 1.5 mg |
| **Non-proprietary Name** | Epoprostenol Sodium (JAN*) |
| **Applicant** | Actelion Pharmaceuticals Japan Ltd. |
| **Date of Application** | March 04, 2016 |
| **Dosage Form/Strength** | Powder for solution for injection: Each vial contains 0.5 mg or 1.5 mg of epoprostenol. |
| **Application Classification** | Prescription drug, (6) Drug with a new dosage |
| **Items Warranting Special Mention** | None |
| **Reviewing Office** | Office of New Drug II |

**Results of Review**

On the basis of the data submitted, PMDA has concluded that the product has efficacy in the treatment of pulmonary arterial hypertension in children, and that the product has acceptable safety in view of its benefits (see Attachment).

As a result of its review, PMDA has concluded that the product may be approved for the indication and dosage and administration shown below.

**Indication**

Pulmonary arterial hypertension

(Unchanged)

**Dosage and administration**

Adults

Dosage (at the start of treatment)

After reconstitution with the solvent provided (saline), the reconstituted solution (epoprostenol) is administered by continuous intravenous infusion via an electronic infusion device for continuous infusion (a syringe pump or an infusion pump). Usually, infusion of epoprostenol should be initiated in adults at the infusion rate of 2 ng/kg/min. The dosage should be increased by increments of 1 to 2

ng/kg/min every ≥15 minutes, with careful monitoring of the patient's condition (e.g., symptoms, blood pressure, heart rate, and hemodynamics). The optimum infusion rate should be determined within a range not exceeding 10 ng/kg/min.

The onset of adverse reactions, such as flushing (excluding slight one), headache, and queasy, after an increase in the infusion rate is an important factor for determining the optimum infusion rate. If such symptoms (even mild ones) occur, further increases in the dosage should be avoided. If the symptom persists, the dosage should be gradually decreased by decrements of 2 ng/kg/min every ≥15 minutes.

Continuous infusion

The administration should be maintained at the optimum rate thereafter. The patient should be monitored regularly for dosage ajustment. The dosage should be adjusted by increments or decrements of 1 to 2 ng/kg/min every ≥15 minutes according to the patient's condition (e.g., symptoms, blood pressure, heart rate, and hemodymanics).

Children

Dosage (at the start of treatment)

After reconstitution with the solvent provided (saline), the reconstituted solution (epoprostenol) is administered by continuous intravenous infusion via an electronic infusion device for continuous infusion (a syringe pump or an infusion pump). Usually, infusion of epoprostenol should be initiated in children at an infusion rate of 0.5 to 2 ng/kg/min. In principle, the dosage should be increased by increments of 0.5 to 2 ng/kg/min every 1 to 4 weeks, with careful monitoring of the patient's condition (e.g., symptoms, blood pressure, heart rate, and hemodynamics). The optimum infusion rate should be determined within a range from 20 to 40 ng/kg/min. Flushing (excluding slight one), headache, or queasy may occurr after an increase in the infusion rate. If such symptoms (even mild ones) occur, further increases in the dosage should be avoided. If the symptom persists, the dosage should be gradually decreased by decrements of 0.5 to 2 ng/kg/min.

Continuous infusion

The infusion should be continued at the optimum infusion rate thereafter. The patient should be monitored regularly for dosage ajustment. The dosage should be adjusted by increments or decrements of 0.5 to 2 ng/kg/min according to the patient's condition (e.g., symptoms, blood pressure, heart rate, and hemodymanics).

(Underline denotes additions)

**Japanese Accepted Name (modified INN)*

**Attachment**

**Review Report (1)**

November 17, 2016

The following is an outline of the data submitted by the applicant and content of the review conducted by the Pharmaceuticals and Medical Devices Agency.

**Product Submitted for Approval**

| | |
|---|---|
| **Brand Name** | Epoprostenol ACT 0.5 mg<br>Epoprostenol ACT 1.5 mg |
| **Non-proprietary Name** | Epoprostenol Sodium |
| **Applicant** | Actelion Pharmaceuticals Japan Ltd. |
| **Date of Application** | March 04, 2016 |
| **Dosage Form/Strength** | Powder for solution for injection: Each vial contains 0.5 mg or 1.5 mg of epoprostenol. |
| **Proposed Indication** | Pulmonary arterial hypertension |

**Proposed Dosage and Administration**

Adults

Dosage (at the start of treatment)

After reconstitution with the solvent provided (saline), the reconstituted solution (epoprostenol) is administered by continuous intravenous infusion via an electronic infusion device for continuous infusion (a syringe pump or an infusion pump). Usually, infusion of epoprostenol should be initiated in adults at the infusion rate of 2 ng/kg/min. The dosage should be increased by increments of 1 to 2 ng/kg/min every ≥15 minutes, with careful monitoring of the patient's condition (e.g., symptoms, blood pressure, heart rate, and hemodynamics). The optimum infusion rate should be determined within a range not exceeding 10 ng/kg/min.

The onset of adverse reactions, such as flushing (excluding slight one), headache, and queasy, after an increase in the infusion rate is an important factor for determining the optimum infusion rate. If such symptoms (even mild ones) occur, further increases in the dosage should be avoided. If the symptom persists, the dosage should be gradually decreased by decrements of 2 ng/kg/min every ≥15 minutes.

Continuous infusion

The infusion should be continued at the optimum infusion rate thereafter. The patient should be monitored regularly for dosage ajustment. The dosage should be adjusted by increments or decrements of 1 to 2 ng/kg/min

every ≥15 minutes according to the patient's condition (e.g., symptoms, blood pressure, heart rate, and hemodymanics).

Children

Dosage (at the start of treatment)

After reconstitution with the solvent provided (saline), the reconstituted solution (epoprostenol) is administered by continuous intravenous infusion via an electronic infusion device for continuous infusion (a syringe pump or an infusion pump). Usually, infusion of epoprostenol should be initiated in children at an infusion rate of 0.5 to 2 ng/kg/min. In principle, the dosage should be increased by increments of 0.5 to 2 ng/kg/min every 1 to 4 weeks, with careful monitoring of the patient's condition (e.g., symptoms, blood pressure, heart rate, and hemodynamics). The optimum infusion rate should be determined within a range from 20 to 40 ng/kg/min. Flushing (excluding slight one), headache, or queasy may occurr after an increase in the infusion rate. If such symptoms (even mild ones) occur, further increases in the dosage should be avoided. If the symptom persists, the dosage should be gradually decreased by decrements of 0.5 to 2 ng/kg/min.

Continuous infusion

The infusion should be continued at the optimum infusion rate thereafter. The patient should be monitored regularly for dosage ajustment. The dosage should be adjusted by increments or decrements of 0.5 to 2 ng/kg/min according to the patient's condition (e.g., symptoms, blood pressure, heart rate, and hemodymanics).

(Note: Application for the approval for the partial change to add the dosage and administration for children to that for adults)

**Table of Contents**

**List of Abbreviations**

| | |
|---|---|
| AHA/ATS Guidelines | Pediatric Pulmonary Hypertension Guidelines From the American Heart Association and American Thoracic Society |
| CHD-PAH | Congenital heart disease pulmonary arterial hypertension |
| CI | Confidence interval |
| Epoprostenol ACT | Epoprostenol ACT 0.5 mg and 1.5 mg |
| Epoprostenol | Epoprostenol sodium |
| ERA | Endotheline receptor antagonist |
| ESC/ERS Guidelines | The European Society of Cardiology and the European Respiratory Society Guidelines for the diagnosis and treatment of pulmonary hypertension |
| FAS | Full analysis set |
| HPAH | Heritable pulmonary arterial hypertension |
| IPAH | Idiopathic pulmonary arterial hypertension |
| mPAP | Mean Pulmonary Arterial Pressure |
| NYHA-FC | New York Heart Association functional class |
| PAH | Pulmonary arterial hypertension |
| PDE | Phosphodiesterase |
| $PGE_1$ | Prostaglandin $E_1$ |
| $PGE_2$ | Prostaglandin $E_2$ |
| $PGI_2$ | Prostacyclin |
| $PGI_2$ preparations | Preparations of prostacycline and its derivatives |
| PH | Pulmonary hypertension |
| PMDA | Pharmaceuticals and Medical Devices Agency |
| PPH | Primary pulmonary hypertension |
| PPHN | Persistent pulmonary hypertension of the newborn |
| PVRI | Pulmonary vascular resistance index |
| QOL | Quality of life |
| sGC | Soluble guanylate cyclase |
| WHO-FC | World Health Organization functional class |

## 1. Origin or History of Discovery, Use in Foreign Countries, and Other Information

Epoprostenol is an endogenous, physiologically active substance. It is an inhibitor of platelet aggregation and a vasodilator. In Japan, a powder for solution for injection containing Epoprostenol Sodium (hereinafter referred to as "epoprostenol") as an active ingredient (brand name, Flolan for Injection 0.5 mg) was approved for the indication of "primary pulmonary hypertension" in 1999 (approval for import of the product was obtained by Nippon Wellcome K.K. [now GlaxoSmithKline K.K.]). Partial change application for a new indication, "pulmonary arterial hypertension," was approved in 2004. Epoprostenol ACT was developed as a generic formulation of epoprostenol by Actelion Pharmaceuticals Japan Ltd. and was approved in 2013.

Pulmonary arterial hypertension (PAH) is a progressive, fatal disease, and its pathology is similar in adults and children. However published literature reports that pediatric PAH progress more rapidly, resulting in a poorer prognosis (*J Am Coll Cardiol.* 1995;25:466-474, *Circulation.* 2011;124:1755-1764). In clinical settings, physicians use the drugs approved for treatment of PAH in adults to treat pediatric patients with PAH by adjusting the dosage based on the efficacy and safety data from adult patients. In Japan, only "Tracleer 32 mg dispersible tablets for pediatric" (bosentan) is approved for the dosage and administration for pediatric patients with PAH.

On the basis of the results from Japanese clinical studies, an application for the approval for partial change to add the dosage and administration for pediatric patients with PAH has recently been filed. As of November 2016, no overseas countries or regions have approved epoprostenol for the indication or the dosage and administration for pediatric patients with PAH.

## 2. Data Relating to Quality and Outline of the Review Conducted byPMDA

The current application is intended for the approval of a new dosage. No data relating to quality were submitted in the current application.

## 3. Non-clinical Pharmacology and Outline of the Review Conducted by PMDA

The current application is intended for the approval of a new dosage for pediatric use. No new data from non-clinical pharmacology studies were submitted in the current application because the non-clinical pharmacology of epoprostenol had been evaluated for the previous application.

## 4. Non-clinical Pharmacokinetics and Outline of the Review Conducted by PMDA

The current application is intended for the approval of a new dosage for pediatric use. No new data from non-clinical pharmacokinetics studies were submitted in the current application because new pharmacokinetics studies were considered unnecessary for the following reasons: (i) The non-clinical pharmacokinetics of epoprostenol had been evaluated for the previous application and (ii) epoprostenol is rapidly hydrolyzed in plasma and thus differences in pharmacokinetics by age are unlikely to affect the efficacy and safety of epoprostenol [see Section "6.R.1 Influence of age on the pharmacokinetics of epoprostenol"].

## 5. Toxicity and Outline of the Review Conducted by PMDA

The current application is intended for the approval of a new dosage for pediatric use. No new data from toxicity studies were submitted in the current application because toxicity studies in juvenile animals were considered unnecessary for the following reasons: (i) Epoprostenol has already been used in many pediatric patients with PAH in and outside Japan [see Sections "7.2 Japanese and foreign clinical reports" and "7.3 Reports from Japanese post-marketing surveillance"] and (ii) the results of the use-results surveys and the Japanese clinical studies have revealed no major problems with the use of epoprostenol in children [see Section "7.R.4 Safety"].

## 6. Summary of Biopharmaceutic Studies and Associated Analytical Methods, Clinical Pharmacology, and Outline of the Review Conducted by PMDA

The current application is intended for the approval of a new dosage for pediatric use. No new data relating to biopharmaceutic studies or associated analytical methods, or clinical pharmacology were submitted in the current application because the pharmacokinetics of epoprostenol had been evaluated for the previous application.

## 6.R Outline of the review conducted by PMDA

### 6.R.1 Influence of age on pharmacokinetics of epoprostenol

PMDA asked the applicant to explain the justification for selecting the same dosage and administration for pediatric patients with PAH regardless of age by referring to differences in the pharmacokinetics between adults and children and the influence of age.

The applicant's response:

Because epoprostenol is administered intravenously, the influence of age on the distribution, metabolism, and excretion of epoprostenol was investigated. According to reports on distribution, serum protein levels generally vary depending on age (*Pharmaceutics*. 2011;3:53-72, *Nutrition in Pediatrics.* 2nd ed. B.C. Decker Inc;1997:44-62). However, the plasma albumin concentration[1] is approximately $6.0 \times 10^{-4}$ mol/L in adults and approximately $4.6 \times 10^{-4}$ mol/L in 0-year-old infants. This indicates that albumin is excessively present in plasma compared with the main metabolite of epoprostenol (whose plasma concentration was approximately $4.8 \times 10^{-9}$ mol/L after administration of epoprostenol at 40 ng/kg/min). Furthermore, the percentage of epoprostenol bound to protein was approximately 52% (*Prostaglandins*. 1981;21:165-175), which is not very high. Therefore, differences in serum protein levels by age are considered to have little influence on the pharmacokinetics of epoprostenol. While the volume of distribution (total body water and body weight) has also been reported to vary depending on age (*Nutrition in Pediatrics.* 2nd ed. B.C. Decker Inc; 1997:44-62), differences in the volume of distribution by age are likely to have little impact on the pharmacokinetics of epoprostenol because the dosage of epoprostenol is determined on a body weight basis. According to reports on metabolism and excretion, epoprostenol was rapidly hydrolyzed in plasma (*in vitro* elimination half-life, approximately 6 minutes) and predominantly excreted renally as metabolites. The renal function (glomerular filtration rate and

[1] Calculated by dividing the lower limit of normal of serum albumin (adult, 4.0 g/dL; neonate [0months of age], 3.02 g/dL) (*Clinical Laboratory Reference Value Pocket Guide.* Jiho; 2009:34-35) by the molecular weight of albumin (66,241)

tubular secretion) is immature in neonates and infants and reach the similar level to that in adults at around 1 year of age (*Regulatory Toxicol Pharmacol*. 2008;51:66-86, *Principles of Clinical Pharmacology.* 3rd ed. 2012;417-436, and other articles); the pharmacokinetics of epoprostenol may differ between toddlers/older children and neonates/infants. However, the bioactivity of the metabolite(s) of epoprostenol is extremely low as compared with that of unchanged epoprostenol (*Br J Pharmacol*. 1978;62:125-130, *Eur J Pharmacol*. 1981;75:127-130, and other articles). Differences in renal function by age are likely to have no major impacts on the efficacy or safety of epoprostenol.

On the basis of the above, differences in pharmacokinetics according to age are unlikely to affect the efficacy or safety of epoprostenol in light of the pharmacokinetics profile and dosage regimen of epoprostenol. Therefore, the same dosage regimen can be selected for children regardless of age.

PMDA's view:
Considering the applicant's explanation, there should be no major differences in the pharmacokinetics between adults and toddlers/older children. On the other hand, in light of the fact that epoprostenol undergoes renal excretion and that renal function is reportedly immature in neonates and infants, the pharmacokinetics of epoprostenol may differ between neonates/infants and toddlers/older children. However, taking account that the bioactivity of the metabolite(s) of epoprostenol is very low as compared with that of unchanged epoprostenol, the differences in pharmacokinetics among these patient populations are unlikely to affect the efficacy or safety of epoprostenol. On the basis of the above, PMDA has concluded that the same dosage regimen can be selected for children regardless of age. The final decision on the dosage regimen of epoprostenol should be made after evaluation of the results from Japanese clinical studies, the specified use-results survey of epoprostenol, and other data [see Section "7.R.6 Dosage and administration"].

## 7. Clinical Efficacy and Safety and Outline of the Review Conducted by PMDA

### 7.1 Japanese phase III study (Study AC-066A308, CTD 5.3.5.2.1, [redacted] to [redacted]) and Japanese phase III long-term extension study (Study AC-066A309, CTD 5.3.5.2.2, 5.3.2.6, continued since [redacted]; data cut-off on [redacted])

An open-label, uncontrolled study (Study AC-066A308) was conducted at 6 sites in Japan to evaluate the efficacy, safety, and tolerability of epoprostenol in Japanese pediatric patients with PAH (target sample size, ≥3 subjects). An open-label, uncontrolled study (Study AC-066A309) was conducted at 3 sites in Japan to evaluate the long-term efficacy, safety, and tolerability of epoprostenol in the patients who completed Study AC-066A308 (target sample size, 3 subjects).

In Study AC-066A308, the duration of efficacy evaluation was the 12 weeks after the start of treatment. The continuous intravenous infusion of epoprostenol was initiated at 0.5 to 2.0 ng/kg/min and the infusion rate was to be increased according to the patient's condition (e.g., symptoms, blood pressure, heart rate, and hemodynamics) by increments of 0.5 to 2.0 ng/kg/min every 1 to 4 weeks in principle.

After completing the 12-week efficacy evaluation period, subjects were to participate in the long-term extension study (Study AC-066A309) to receive epoprostenol until the approval of Epoprostenol ACT or the termination of the development program. In Study AC-066A309, the infusion of epoprostenol was to be started at the final infusion rate employed in the Study AC-066A308 and the dosage was to be increased to the optimum infusion rate according to the patient's condition (e.g., symptoms, blood pressure, heart rate, and hemodynamics) by increments of 0.5 to 2.0 ng/kg/min every 1 to 4 weeks in principle. The optimum rate of administration ranged from 20 to 40 ng/kg/min.

Throughout the duration of these studies, in the cases where symptoms, such as flushing (excluding slight one), headache, and queasy, even mild ones, occurred after an increase in the infusion rate, further increases in the infusion rate was avoided. The infusion rate was to be decreased in the event of the onset of clinical signs due to excessive dose or symptoms suggestive of a steep increase in cardiac output (e.g., dyspnoea, fatigue, decreased weight, tachycardia, and vomiting). In principle, the infusion rate was to be decreased by decrements of 0.5 to 2.0 ng/kg/min.

The key inclusion criteria were as follows:

- Patients ≥0 years and <15 years of age
- Patients with PAH in World Health Organization functional class (WHO-FC) II, III, or IV
- Patients with idiopathic pulmonary arterial hypertension (IPAH), heritable pulmonary arterial hypertension (HPAH), or pulmonary arterial hypertension associated with congenital heart disease (CHD-PAH) (patients who have persistent or recurrent symptoms of PAH for ≥6 months after surgical repair, or patients with Eisenmenger's syndrome)
- Patients who have a diagnosis of PAH and whose right-heart catheterization results meet the following criteria during the screening period (the 30 days before the start of the study treatment):
  - Mean Pulmonary Arterial Pressure (mPAP) ≥25 mmHg at rest
  - Pulmonary vascular resistance index (PVRI) ≥3 Wood units·$m^2$
  - Pulmonary artery wedge pressure or left ventricular end-diastolic pressure ≤15 mmHg
- Arterial oxygen saturation ≥ 88% (≥ 70% in patients with Eisenmenger's syndrome)

In Study AC-066A308, the use of concomitant endotheline receptor antagonists (ERAs) (bosentan hydrate, ambrisentan) or phosphodiesterase-5 (PDE-5) inhibitors (sildenafil citrate, tadalafil) was allowed as long as the concomitant drug was increased or decreased within the range not exceeding the dose at screening, although the dose had to remain unchanged whenever possible. In the cases where the above medications were discontinued before the start of the study treatment, they had to be discontinued ≥30 days before the right-heart catheterization during the screening period. Although the protocols of the studies allowed the use of concomitant antihypertensive agents (e.g., calcium channel blockers, angiotensin-converting enzyme inhibitors, and diuretics), anticoagulants (e.g., warfarin potassium), thrombolytic agents (e.g., urokinase), antiplatelet agents (e.g., aspirin, ticlopidine hydrochloride, prostaglandin $E_1$ [$PGE_1$], prostaglandin $E_2$ [$PGE_2$] derivatives, and nonsteroidal anti-inflammatory drugs), digoxin, or oxygen therapy, the dose of the concomitant drug had to remain

unchanged whenever possible. The intravenous administration of concomitant cardiotonic agents (e.g., dobutamine hydrochloride and catecholamine) was prohibited throughout the study treatment period. The use of prostacyclin ($PGI_2$) preparations, soluble guanylate cyclase (sGC) stimulants (riociguat), and macitentan was prohibited from 7 days before the right-heart catherterization during the screening period to the end of the study treatment.

In Study AC-066A309, the dose of concomitant ERAs (bosentan hydrate, ambrisentan) or PDE-5 inhibitors (sildenafil citrate, tadalafil) had to remain unchanged whenever possible. The use of $PGI_2$ preparations, sGC stimulants (riociguat), and macitentan was prohibited throughout the study treatment period.

The results of Studies AC-066A308 and AC-066A309 are presented below.

(a) Study AC-066A308

All the 3 subjects enrolled in the study received the study drug and were included in the safety analysis set and full analysis set (FAS). The FAS was the efficacy analysis population. No subjects were withdrawn from the study.

The infusion rate in each subject at Week12 is shown in Table 1.

Efficacy analysis was performed using data from the study. The change in PVRI from baseline to Week 12 (the primary endpoint) is shown in Table 1.

Table 1. Infusion rate at Week 12 and change in PVRI from baseline to Week 12 (FAS)

| | Underlying disease | WHO-FC | Age (years) | Weight (kg) | Infusion rate[a] (ng/kg/min) | PVRI (Wood·m$^2$) | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | | Baseline | Week 12 | Change | Percent change |
| Subject 1 | IPAH | II | 14 | 49.5 | 22.44 | 11.69 | 9.26 | −2.43 | −20.8% |
| Subject 2 | IPAH | III | 8 | 25.8 | 14.83 | 20.88 | 17.64 | −3.24 | −15.5% |
| Subject 3 | IPAH | II | 10 | 27.1 | 12.91 | 8.20 | 5.61 | −2.59 | −31.5% |

a Calculated from the latest body weight that was measured prior to the date of dosage change (flow rate for the infusion pump, concentration of the reconstituted solution, or infusion rate)

Table 2 shows the changes in mPAP and WHO-FC from baseline to Week12, which were the secondary endpoints.

Table 2. Changes from baseline in mPAP and WHO-FC to Week 12 (FAS)

| | mPAP (mmHg) | | | WHO-FC | | |
|---|---|---|---|---|---|---|
| | Baseline | Week 12 | Change | Baseline | Week 12 | Change |
| Subject 1 | 43 | 45 | 2 | II | II | Unchanged |
| Subject 2 | 88 | 80 | −8 | III | II | Improved |
| Subject 3 | 36 | 38 | 2 | II | II | Unchanged |

Safety analysis was performed using data from the study. Adverse events occurred in 3 of 3 subjects (100%). Adverse events noted in more than 1 subject were nasopharyngitis, pruritus, contact dermatitis, and headache (in 2 subjects each).

Adverse events whose causal relationships to the study drug were not ruled out were noted in 2 of 3 subjects (66.7%; flushing, nausea, malaise, headache, diarrhoea, and myalgia; headache, pain in jaw, platelet count decreased, eczema nummular, and blood alkaline phosphatase decreased).

No deaths occurred. A serious adverse event (gastroenteritis) was noted in 1 subject but its causal relationship to the study drug was ruled out.

No adverse events leading to treatment discontinuation were noted.

(b) Study AC-066A309

All the 3 subjects having completed Study AC-066A308 participated in Study AC-066A309. All of the 3 subjects were included in the safety analysis set and FAS. The FAS was used as the efficacy analysis population. No subjects were withdrawn from the study.

Table 3 shows the total duration of treatment with epoprostenol and the infusion rates at Weeks 24 and 48 in subjects participating in both Studies AC-066A308 and AC-066A309.

As the efficacy data, the changes in WHO-FC from baseline at Week 24 and 48 are also shown in Table 3.

Table 3. Total duration of treatment with epoprostenol as well as the infusion rate and change in WHO-FC at Weeks 25 and 48 in subjects participating in both Studies AC-066A308 and AC-066A309 (FAS)

| | Duration of treatment (days) | Infusion rate[a] (ng/kg/min) | | WHO-FC | | | |
|---|---|---|---|---|---|---|---|
| | | Week 24 | Week 48 | Baseline | Week 24 | Week 48 | Change |
| Subject 1 | 366 | 34.45 | 41.20 | II | II | II | Unchanged |
| Subject 2 | 358 | 23.20 | 24.01 | III | II | II | Improved |
| Subject 3 | 366 | 16.01 | 24.02 | II | II | II | Unchanged |

a Calculated from the latest body weight that was measured prior to the date of dosage change (flow rate for the infusion pump, concentration of the reconstituted solution, or infusion rate)

Safety analysis was performed using data from the studies. Adverse events occurred in 3 of 3 subjects (100%) until Week 52. Adverse events noted in ≥2 subjects were nasopharyngitis, platelet count decreased, pruritus, diarrhoea, contact dermatitis, and headache (in 2 subjects each).

Adverse events whose causal relationships to the study drug were not ruled out were noted in 3 of 3 subjects (100%; diarrhoea, headache, malaise, flushing, nausea, myalgia, and platelet count decreased; diarrhoea and hot flush; platelet count decreased, headache, pain in jaw, eczema nummular, and blood alkaline phosphatase decreased).

No deaths occurred. Serious adverse events (gastroenteritis and pneumonia) were noted in 1 subject but the causal relationship between each event and the study drug was ruled out.

No adverse events leading to treatment discontinuation were noted.

### 7.2 Japanese and foreign clinical reports

Literature searches were performed in the PubMed database (keywords, “pulmonary hypertension” and “child or pediatric” and “epoprostenol or prostanoid or $PGI_2$”) and the database provided on the Japan Medical Abstracts Society website (keywords, “pulmonary hypertension” and “children/adolescents (≤18 years of age)” and “epoprostenol or prostanoid or $PGI_2$” and “human”) (accessed on [redacted], 2016). The searches retrieved the following 5 reports containing the outcomes of treatment with epoprostenol in pediatric patients with PAH <15 years of age (n = at least 25) (Table 4).

Table 4. Japanese and foreign clinical reports containing the outcomes of epoprostenol-treated pediatric patients with PAH

| Original article (CTD No.) | Patients (receiving epoprostenol) | Dose (ng/kg/min) | Outcomes |
|---|---|---|---|
| *Circulation.* 1999;99: 1197-1208[a] (5.4.6) | 31 patients with PPH <16 years of age (WHO-FC unknown) | Outcomes<br>At the start of treatment[e]: 4 ± 2 (range, 2-10)<br>3 years later[e]: 122 ± 36 | Efficacy<br>4-year survival rate[g]: 94%<br>* Outcomes at endpoint (at 21 ± 11[e] months [range, 3-46 months]) are shown below.<br>Change in PVRI[f]: –15.6 [–20.2, –11.1] Wood units·m$^2$<br>Change in mPAP[f]: –25.3 [–33.3, –17.3] mmHg<br>NYHA-FC[e]: 3.30 ± 0.54 before treatment with epoprostenol<br>1.96 ± 0.71 at endpoint<br>Safety<br>Death occurred in 1 patient.<br>The following complications were frequently noted: pain in jaw, diarrhoea, flushing, headache, pain of lower extremities, queasy/vomiting, and tolerance. |
| *Circulation.* 2004;110: 660-665[a,c] (5.4.39) | 35 patients with IPAH <16 years of age (WHO-FC II-IV) | Not mentioned | Efficacy<br>10-year survival rate[g]: 61%<br>* Outcomes at endpoint (at 53 ± 28[e] months [range, 9-102 months]) are shown below.<br>Change in PVRI[f]: –14 [–19, –9] Wood units·m$^2$<br>Change in mPAP[f]: –19 [–27, –11] mmHg |
| *Heart.* 2007;93: 739-743[a] (5.4.22) | 39 patients with PH 4 months to 17 years of age (34 patients with PAH) (WHO-FC III/IV) | Prescription<br>Infusion was initiated at 2 and the infusion rate was increased according to the patient's symptoms<br>Outcomes<br>Mean[e]: 29.6 ± 15.2 (range, 6-63) | Efficacy<br>3-year survival rate[g]: 84%<br>WHO-FC[d]: baseline, 3.6<br>1 year later, 2.6 (improved in 30 patients, unchanged in 4 patients, and worsened in 3 patients) |
| *J Heart Lung Transplant.* 2013;32: 546-552[a] (5.4.32) | 57 patients with PAH 7.8 ± 4.7 years of age[i] or 5.5 ± 4.4 years of age[j] (WHO-FC unknown) | Prescription<br>Infusion rate was increased to 4 on admission<br>Target dose: 30-50<br>Outcomes<br>4 years later[h]: 34 (range, 23-77) | Efficacy<br>PVRI[e]: at the start of treatment, 20 ± 13.4 Wood units·m$^2$<br>4 years later, 14.8 ± 3.8 Wood units·m$^2$<br>mPAP[e]: at the start of treatment, 68.1 ± 21.4 mmHg<br>4 years later, 74.2 ± 15.8 mmHg |
| *Pediatr Cardiol.* 2013;34: 1628-1636[a] (5.4.24) | 175 patients with PH 0-18 years of age (WHO-FC unknown) | Not mentioned | Safety<br>Main adverse events were as follows: pulmonary haemorrhage in 23 patients, cardiac failure in 17 patients, haemoptysis and right ventricular failure in 14 patients each, cardiac arrest in 13 patients, dyspnoea in 11 patients, and cyanosis, hypoxia, oxygen saturation decreased, and pneumonia in 9 patients each. |
| *Circ J.* 2007;71: 1785-1790[b] (5.4.28) | 31 patients with IPAH ≤18 years of age (WHO-FC II-IV) | Prescription<br>Infusion was initiated at 0.5-2 and the infusion rate was increased by increments of 0.5-1.0 every 2-4 weeks.<br>Outcomes<br>3 years later[e]: 24.7 ± 6.7 | Efficacy<br>3-year survival without lung transplantation[g]: 79.4%<br>mPAP[e]: baseline, 84.1 ± 19.1 mmHg<br>3 years later, 53.1 ± 10.0 mmHg<br>WHO-FC: Improved to Class II in 18 patients and remained at Class III in 4 patients. A total of 22 patients were analyzed (8 patients who died and 1 patient who underwent lung transplantation were excluded).<br>Safety<br>Death occurred in 8 patients. |

a: Foreign report
b: Japanese report
c: Report of the follow-up of the cases reported in CTD 5.4.6
d: Mean
e: Mean ± standard deviation (SD)
f: Mean (95% CI)
g: Kaplan-Meier estimate
h: Median
I: Patients who received epoprostenol alone
j: Patients who switched from epoprostenol to treprostinil

### 7.3 Reports based on Japanese post-marketing surveillance

CTD 5.3.6.6: An interim report on the specified drug use-results survey on long-term treatment with Epoprostenol ACT
CTD 5.4.42: *Heart*. 2008;40:34-43[2]

## 7.R Outline of the review conducted by PMDA

### 7.R.1 Clinical positioning of Epoprostenol ACT

PMDA asked the applicant to explain the clinical positioning of Epoprostenol ACT in the treatment of PAH in pediatric patients in Japan, for example, by referring to comparison with drugs in the same class, proper drug selection, and co-administration.

The applicant's response:
A consensus on the treatment algorithm for pediatric patients with IPAH or HPAH was reached in the Fifth WHO Pulmonary Hypertension (PH) World Symposium held in 2013 (*J Am Coll Cardiol.* 2013;62:D117-126). The treatment algorithm recommends that patients should be categorized into those at lower risk of death and those at higher risk of death before determination of treatment. The treatment algorithm for the diagnosis and treatment of pediatric PH provided by the Pediatric Pulmonary Hypertension Guidelines from the American Heart Association and American Thoracic Society (AHA/ATS Guidelines) (*Circulation*. 2015;132:2037-2099) is roughly the same as the contents agreed upon in the Fifth WHO PH World Symposium, although the criteria for the evaluation of patients' risk and the strength of recommendations in the treatment algorithm slightly differ between the two treatment algorithms. These guidelines recommend intravenous injection of epoprostenol or intravenous or subcutaneous injection of treprostinil for higher-risk pediatric patients with PAH. The strength of recommendations of epoprostenol in these guidelines is Class I (Level of Evidence B). They also recommend that treatment with $PGI_2$ preparations (intravenous or subcutaneous injection) should be initiated at a timely manner and that the early concomitant use of endotheline receptor antagonist (ERA) or PDE-5 inhibitors with $PGI_2$ preparations should be considered. In lower-risk pediatric patients, the oral administration of ERA or PDE-5 inhibitors or the inhalation of iloprost or treprostinil is recommended and combination therapy is useful to achieve the treatment goals.

In Japan, the Japanese Circulation Society (JCS) published the "Guidelines for Drug Therapy in Pediatric Patients with Cardiovascular Diseases" (Guidelines for the Diagnosis and Treatment of Cardiovascular Diseases, Fiscal Year 2010-2011 JCS Joint Working Group Report), which present the

[2] Report on the use-results survey of Flolan for injection

treatment algorithm for pediatric patients with PAH. In the guidelines, epoprostenol is recommended as a drug for the patients with WHO-FC III or IV PAH. For WHO-FC III PAH patients, oral PAH drugs (bosentan hydrate, sildenafil) and inhaled iloprost are recommended at the same level as epoprostenol. Furthermore, for WHO-FC IV PAH patients, epoprostenol is recommended at a higher level than oral PAH drugs and other $PGI_2$ preparations. In addition, the guidelines also recommend the combination therapy with oral PAH drugs and epoprostenol for WHO-FC III or IV PAH patients, although the oral PAH drugs are limited to those approved at the time of the compilation.

While several PAH drugs have been approved for adults on the basis of clinical study data, only bosentan hydrate has been approved as a PAH drug for children in Japan. Bosentan hydrate is currently used worldwide without sufficient clinical study data. With these backgrounds, some amendments were made to the treatment algorithm for PAH in adults (Guidelines for Treatment of Pulmonary Hypertension [JCS2012], [Guidelines for the Diagnosis and Treatment of Cardiovascular Diseases, Fiscal Year 2011 JCS Joint Working Group Report] and the guidelines for the diagnosis and treatment of pulmonary hypertension from the European Society of Cardiology and the European Respiratory Society (ESC/ERS Guidelines) [*Eur Heart J*. 2016; 37:67-119]) at the time of the compilation of the algorithm for PAH in children. However, the treatment algorithm for PAH in children still shares the important part with that for PAH in adults, and their treatment policies are basically the same. In addition, epoprostenol has been recommended for both adult and pediatric patients with severe PAH symptoms (WHO-FC III or IV) by Japanese and foreign guidelines, and its clinical positioning does not differ between adults and children.

Besides epoprostenol, treprostinil (a $PGI_2$ preparation) has been recommended by Japanese and foreign guidelines on pediatric PAH for patients classified as WHO-FC III or IV. However, experience with the long-term use of epoprostenol in pediatric patients has been accumulated and therefore both guidelines recommend epoprostenol at the same level as or at a higher level than treprostinil.

On the basis of the above information on the strength of recommendations in Japanese and foreign guidelines on pediatric PAH and of the characteristics of subjects participating in clinical studies, epoprostenol is considered as the first-line drug to be used alone or in combination with ERA or PDE-5 inhibitors in pediatric patients with severe PAH classified as WHO-FC III or IV and higher-risk pediatric patients with PAH.

PMDA's view:

Pediatric PAH was also discussed in the Fifth WHO PH World Symposium held in 2013. The discussion addressed differences between pediatric PAH and adult PAH, and it was pointed out that the proportion of pediatric patients with IPAH or HPAH and CHD-PAH is large while PAH associated with connective tissue disease is rare in children. The treatment of pediatric PAH has been performed by referring to the results of large-scale clinical studies conducted in adult patients with PAH or on the basis of the clinical experience of pediatric PAH specialists. The treatment algorithm for pediatric patients with IPAH or HPAH agreed upon in the Fifth WHO PH World Symposium and the AHA/ATS Guidelines on the diagnosis and treatment of pediatric PH recommend that patients with negative response to acute vasoreactivity testing should be classified into lower-risk and higher-risk patients on the basis of clinical

symptoms, pulmonary hemodynamics, echocardiographic findings, and other findings, and that the treatment policy should be determined according to the risk level. The guidelines also recommend that continuous intravenous administration or subcutaneous administration of $PGI_2$ preparations should be initiated in higher-risk patients without delay.

In Japan, the "Guidelines for Drug Therapy in Pediatric Patients with Cardiovascular Diseases" recommend the use of epoprostenol in pediatric patients with PAH classified as WHO-FC III or IV. The "Clinical Guidelines for Medical Treatment of Pediatric Heart Failure ( Japanese Society of Pediatric Cardiology and Cardiac Surgery [JSPCCS] 2015, *Pediatric Cardiology and Cardiac Surgery*. 31[Supple 2]) advises that the basics of the treatment of pediatric PAH be the general supportive therapy plus treatment with 3 classes of pulmonary vasodilators, $PGI_2$ preparations, PDE-5 inhibitors, and ERA, as is recommended by the treatment guidelines for PAH in adults (Guidelines for Treatment of Pulmonary Hypertension [JCS 2012]). The guidelines recommend that the patients should be treated according to the severity of symptoms. Specifically, the following procedures are recommended: (i) WHO-FC II patients should start treatment with a PDE-5 inhibitor or ERA alone, and WHO-FC III patients should start treatment with a PDE-5 inhibitor or ERA alone or a PDE-5 inhibitor and ERA in combination. (ii) Response to the initial treatment should be assessed approximately 3 months after the start of treatment, and additional treatment should be given to patients with inadequate short-term response. (iii) Continuous intravenous administration of epoprostenol should be considered for refractory patients who remain in WHO-FC III. In light of the fact that the Japanese guidelines have generally been developed in accordance with the latest European and American guidelines, the positioning of Epoprostenol ACT in the treatment of pediatric PAH in Japan is likely to be similar to that in the foreign guidelines. Therefore, Epoprostenol ACT can be an option for the treatment of severe pediatric PAH if the product is made available in clinical settings in Japan.

### 7.R.2 Use of data from non-Japanese patients

The applicant used data from non-Japanese patients, including the results of foreign clinical studies and published literature, in addition to the results of the Japanese clinical studies conducted in pediatric patients with PAH [see Sections "7.R.3 Efficacy," "7.R.4 Safety," and "7.R.6 Dosage and administration"] to explain the efficacy, the safety, and the justification for the dosage and administration of Epoprostenol ACT. PMDA's view on this issue is presented below:

As for intrinsic ethnic factors, there are no ethnic differences in the pathology of PAH between children and adults. The distribution of etiologies of PAH in Japan is similar to that in foreign countries. No major differences have been shown in the epidemiology of PAH in adults (Health and Labour Sciences Research Grant-supported Research Program on Measures against Intractable Diseases etc. [Research on Measures against Intractable Diseases], Investigative research on respiratory failure, Fiscal Year 2013 General/Partial Research Report. 2014:49-53; *Circulation*. 2010;122:164-172) between Japanese and non-Japanese patients. There should be no difference in intringic ethnic factors that would affect the efficacy and safety of epoprostenol in pediatric patients with PAH, taking also account of the clinical trials of the generic version of epoprostenol in adult patients with PAH (foreign clinical studies that evaluated the safety etc. of the generic version of epoprostenol versus Flolan [the product marketed

overseas, which is Flolan for injection in Japan]; Japanese and foreign clinical studies that evaluated the safety etc. of the medication switch from Flolan or Flolan for injection to the generic version of epoprostenol), clinical studies of the generic version of epoprostenol in pediatric patients with PAH, and literature reports on the generic version of epoprostenol [see Section "7. Clinical Efficacy and Safety and Outline of the Review Conducted by PMDA"]. Furthermore, there should be no differences in extrinsic ethnic factors that would affect the efficacy and safety of epoprostenol in pediatric patients with PAH, for the following reasons: (i) The same criteria for the diagnosis and the same disease and severity classifications of PAH in adults are adopted in and outside Japan, (ii) the Japanese treatment guidelines for PAH have generally been developed in accordance with the latest European and American guidelines, and (iii) the treatment of pediatric PAH both in and outside Japan is determined based on the guidelines recommended for adult PAH patients. On the basis of the above, it is acceptable to evaluate the efficacy and safety of epoprostenol in Japanese pediatric patients with PAH using data from non-Japanese patients, including the results of foreign clinical studies and published literature, in addition to the results of Japanese clinical trials conducted in pediatric patients with PAH.

### 7.R.3 Efficacy

PMDA's view on the efficacy of Epoprostenol ACT:

The positioning of $PGI_2$ preparations as PAH drugs has been clearly indicated by the treatment algorithm for pediatric PAH which was revised on the basis of the discussion in the Fifth WHO PH World Symposium. The Japanese and foreign guidelines for pediatric PAH recommend the use of epoprostenol in higher-risk PAH patients classified as WHO-FC III or IV [see Section "7.R.1 Clinical positioning of Epoprostenol ACT"].

The Japanese and foreign published literature present the outcomes suggesting the efficacy of epoprostenol (improvement in pulmonary hemodynamics, WHO-FC, etc.) [see Section "7.2 Japanese and foreign clinical reports"]. Experience with the use of epoprostenol in pediatric patients with PAH in routine clinical settings in Japan [see Sections "7.2 Japanese and foreign clinical reports" and "7.3 Reports based on Japanese post-marketing surveillance"] has also been reported. In addition, the efficacy and safety of epoprostenol in Japanese adult patients with PAH have been demonstrated, and there should be no difference in the pathology or treatment of PAH between adults and children. Therefore, the efficacy of epoprostenol can be expected in pediatric patients with PAH as well as in adult patients with PAH. Furthermore, PVRI tended to improve and WHO-FC was maintained in all of the 3 subjects participating in Study AC-066A308, though the number of subjects evaluated was very small [see Section "7.1 Japanese phase III study and Japanese phase III long-term extension study"]. This supports the efficacy of Epoprostenol ACT in pediatric patients with PAH.

The final decision on the appropriateness of the PMDA's view on the efficacy of Epoprostenol ACT in pediatric patients with PAH will be made on the basis of the comments from the expert advisors at the Expert Discussion.

### 7.R.4 Safety

PMDA asked the applicant to explain the safety of Epoprostenol ACT in children, particularly the appropriateness of the precautions in the package insert, by clarifying whether there are any concerns about the use of the product in children in comparison with adults.

The applicant's response:

The incidence of adverse events was analyzed with the data from Studies AC-066A308 and AC-066A309 in Japanese pediatric patients with PAH as well as Japanese and foreign clinical trials conducted in adult patients with PAH (Studies AC-066A301/A302[3] and AC-066A305[4]). Table 5 shows the summary of adverse events occurring in patients receiving 52-week therapy with epoprostenol in the above studies. According to the analysis of 52-week data, neither death nor adverse events leading to treatment discontinuation were noted in the pediatric patients with PAH. The adverse events noted commonly in adults and children were headache, diarrhoea, nasopharyngitis, flushing, pain in jaw, and nausea. The incidences of these adverse events did not largely differ between adults and children. The events were less severe in children than in adults and the outcomes of most cases were "resolving" in children. The adverse events occurring in more than one pediatric subject were pruritus and platelet count decreased. The case of pruritus was mild and considered unrelated to the study drug. Platelet count decreased has already been listed as an adverse reaction to epoprostenol in the package insert.

Table 5. Summary of adverse events noted in clinical studies conducted in children and adults

| | Children | Adults | |
|---|---|---|---|
| | Japanese | Japanese | Non-Japanese |
| | Study AC-066A308/A309[a,b] (N = 3) | Study AC-066A305[c] (N = 8) | Studies AC-066A301/A302[c] (N = 41) |
| Adverse events | 100 (3) | 100 (8) | 97.6 (40) |
| Death | 0 (0) | 0 (0) | 4.9 (2) |
| Serious adverse events | 33.3 (1) | 50.0 (4) | 51.2 (21) |
| Adverse events possibly related to the study drug | 100 (3) | 62.5 (5) | 51.2 (21) |
| Adverse events leading to treatment discontinuation | 0 (0) | 0 (0) | 2.4 (1) |
| Adverse events noted in more than one pediatric subject | | | |
| Headache | 66.7 (2) | 25.0 (2) | 34.1 (14) |
| Nasopharyngitis | 66.7 (2) | 37.5 (3) | 26.8 (11) |
| Diarrhoea | 66.7 (2) | 12.5 (1) | 17.1 (7) |
| Contact dermatitis | 66.7 (2) | 0 (0) | 2.4 (1) |
| Pruritus | 66.7 (2) | 0 (0) | 0 (0) |
| Platelet count decreased | 66.7 (2) | 0 (0) | 0 (0) |

% (n)

Results at Week 52 of treatment

a: Combined data from Studies AC-066A308 and AC-066A309

b: Safety analysis set

c: All treated set

[3] A foreign clinical study that evaluated the influence of the medication switch from Flolan to epoprostenol (open-label, 12-week treatment) and its extension trial

[4] A Japanese clinical study that evaluated the influence of the medication switch from Flolan for injection to epoprostenol (open-label)

Table 6 shows the summary of adverse events in adults and children enrolled in the specified use-results survey of epoprostenol,[5] indicating no differences in the incidence of adverse events between adults and children. While the incidences of device occlusion and diarrhoea were high in adults, these events were not reported in children. The adverse events whose incidence were higher by ≥10% in children than in adults were infection, device related infection, and pulmonary haemorrhage. All cases of infection were considered unrelated to epoprostenol. Device-related infection and pulmonary haemorrhage have already been listed as adverse reactions to epoprostenol in the package insert. The incidence of adverse reactions was lower in children than in adults. Adverse events leading to death ocurred in 2 children <1 year of age and 2 children ≥1 year of age. The details were as follows: 1 child <1 year of age experienced pulmonary hypertension and pulmonary haemorrhage, and another experienced lung disorder; 1 child ≥1 year of age experienced multiple organ dysfunction syndrome and another experienced pulmonary haemorrhage. All the events except for the pulmonary haemorrhage occurring in the child <1 year of age were considered unrelated to epoprostenol. There were no death, serious adverse events, or adverse events leading to treatment discontinuation whose incidences were clearly higher in children than in adults.

Table 6. Summary of adverse events noted in adults and children in the specified use-results survey of epoprostenol[5]

| | Children (N = 17) | Adults (N = 120) |
|---|---|---|
| Adverse events | 70.6 (12) | 59.2 (71) |
| Death | 23.5 (4) | 10.0 (12) |
| Serious adverse events | 47.1 (8) | 38.3 (46) |
| Adverse events possibly related to the study drug | 23.5 (4) | 30.8 (37) |
| Adverse events leading to treatment discontinuation | 23.5 (4) | 19.2 (23) |
| Adverse events noted in more than one pediatric patient | | |
| Device-related infection | 23.5 (4) | 13.3 (16) |
| Infection | 17.6 (3) | 0 (0) |
| Anaemia | 11.8 (2) | 4.2 (5) |
| Pulmonary haemorrhage | 11.8 (2) | 0 (0) |

% (n)

According to the use-results survey of Flolan for injection[6] (*Prog Med*. 2015;35:1333-1341), the incidence of adverse drug reactions in patients <15 years of age was 19.5% (43 of 221 patients, 105 events), which was lower than the incidence of adverse drug reactions in adults ≥15 years and <65 years of age (45.9% [192 of 418 patients, 532 events]). Of the adverse drug reactions whose incidences were high in the overall population, those whose incidences were high in the patients <15 years of age were flushing (10 events in 6 patients), headache (4 events in 4 patients), and blood pressure decreased (3 events in 3 patients). The incidences of subjective symptoms, such as headache, diarrhoea, pain in jaw, and arthralgia, classified as adverse drug reactions tended to be lower in children than in adults.

[5] Data from 137 patients (including those with PH other than PAH) whose case report form (CRF) data were locked by 31 March, 2016.

[6] Including patients with PH other than PAH

As described above, no major differences in the safety profile of epoprostenol were observed between children and adults, nor were there any concerns about adverse events or adverse drug reactions specific to children. For these reasons, the safety of epoprostenol in pediatric patients with PAH is considered to be similar to that in adult patients with PAH. Therefore, the precautionary statement for pediatric use can be the same as that for use in adults.

PMDA's view:
The safety of epoprostenol was evaluated based on the incidence of adverse events in Japanese and foreign clinical studies and the adverse events reported in the use-results survey and published literature. Although the interpretation of the results was limited because of a small number of patients evaluated, there is currently no evidence suggesting increased safety concern in pediatric patients with PAH as compared with adult patients with PAH. Furthermore, according to the use-results survey of Flolan for injection[6] (see the re-examination reports of "Flolan for injection"), 221 patients <15 years of age were included in the safety analysis set. The incidence of adverse drug reactions was 19.5% (43 of 221 patients, 105 events), which was lower than the incidence of adverse drug reactions in adults ≥15 years and <65 years of age (45.9% [192 of 418 patients]). The seriousness and outcomes of adverse drug reactions reported did not tend to differ markedly between children and adults. The incidences of subjective symptoms, such as headache, pain in jaw, and arthralgia, classified as adverse drug reactions were lower in children than in adults. The 221 pediatric patients included those aged ≤12 months who were hardly able to complain of subjective symptoms, and this age group (35 neonates and 57 infants) accounted for 41.6% of the overall children. The incidence of adverse drug reactions in the age group was as low as 12.0% (11 of 92 patients). This may have contributed to the low incidences of adverse drug reactions in children. However, given the safety profile identified, any safety problems specific to children are currently unlikely to be raised. Therefore, it is appropriate for the applicant to adopt the same precautionary statement for pediatric use as that for use in adults. However, epoprostenol should be prescribed by physicians with sufficient knowledge of and experience with the treatment of pediatric PAH, in light of the fact that the assessment of subjective symptoms such as headache, pain in jaw, and arthralgia is difficult in infants and young children, that the number of subjects evaluated in clinical studies was extremely small, and that information on the long-term safety of epoprostenol is still limited while children will receive it for a longer time than adults. The final decision on the precautions to be included in the package insert should be made on the basis of the comments from the expert advisors at the Expert Discussion.

### 7.R.5 Indication

#### 7.R.5.1 WHO-FC

PMDA asked the applicant to explain the justification for specifying "pulmonary arterial hypertension" as the indication of epoprostenol regardless of WHO-FC, by referring to the efficacy and safety of epoprostenol for each WHO-FC reported in the data from Japanese clinical studies conducted in pediatric patients with PAH, post-marketing surveillance, and published literature.

The applicant's response:

In Study AC-066A308, the changes in PVRI from baseline to Week 12 by WHO-FC were −2.43 and −2.59 Wood units·$m^2$ in 2 subjects classified as WHO-FC II and −3.24 Wood units·$m^2$ in 1 subject classified as WHO-FC III. According to the report from Yung et al. (*Circulation.* 2004;110:660-665), patients with IPAH <16 years of age classified as WHO-FC II to IV received long-term treatments with epoprostenol (53 ± 28 months [mean ± SD]) and the change in PVRI from baseline (mean [95% confidence interval]) in 31 patients whose pulmonary hemodynamics were evaluable was −14 [−19, −9] Wood units·$m^2$. Data from Study AC-066A308 and literature reports showed that mPAP also tended to improve after treatment with epoprostenol [see Section "7.2 Japanese and foreign clinical reports"]. On the basis of the above, improvement in pulmonary hemodynamics is seen in pediatric patients with PAH receiving epoprostenol, regardless of WHO-FC.

The data from Study AC-066A308/A309 (the pooled data of Study AC-066A308 and Study AC-066A309) were analyzed to identify changes in WHO-FC from baseline to Week 48 by WHO-FC. The outcomes were unchanged in 2 subjects in WHO-FC II at baseline but 1 subject in WHO-FC III at baseline had improvement to WHO-FC II. The data from the specified use-results survey of epoprostenol[5] were analyzed to identify the changes in WHO-FC from baseline to the treatment completion/endpoint in the 12 pediatric patients whose WHO-FC status was evaluated before and after treatment (1 WHO-FC I, 2 WHO-FC II, 6 WHO-FC III, and 3 WHO-FC IV patients at baseline). The outcomes were "worsening" in 3 patients (who had all been classified as WHO-FC III at baseline) and "improved" in 4 patients (of whom 2 had been classified as WHO-FC III and 2 as WHO-FC IV at baseline). Furthermore, analysis was performed with the data from the use-results survey of Flolan for injection in patients with PAH[6] (*Heart*. 2008;40:34-43). The baseline New York Heart Association functional class (NYHA-FC) was evaluated in pediatric patients in the survey. The percentage of patients whose NYHA-FC was improved after 1 year of treatment was 30.0% (3 of 10 patients), 31.0% (9 of 29 patients), and 16.7% (3 of 18 patients) for baseline NYHA-FC II, III, and IV, respectively. The percentage of patients with unchanged NYHA-FC was 10.0% (1 of 10 patients), 20.7% (6 of 29 patients), and 5.6% (1of 18 patients) for baseline NYHA-FC II, III, and IV, respectively. The worsening of NYHA-FC was experienced only by 20.0% of the patients (2 of 10 patients) classified as NYHA-FC II at baseline.

According to the data from Study AC-066A308/A309, all the subjects were alive at Week 52. In the specified use-results survey of epoprostenol,[5] the survival status of the 14 pediatric patients whose WHO-FC was evaluated (1 WHO-FC I patient, 2 WHO-FC II patients, 6 WHO-FC III patients, and 5 WHO-FC IV patients) were as follows: survival over the follow-up period (median, 347 days; range, 3 days to 24 months) was confirmed in 11 patients and death occurred in 2 WHO-FC III patients and 1 WHO-FC IV patient. In the use-results survey of Flolan for injection[6] (*Heart*. 2008;40:34-43), the 2-year survival rate was 100% for pediatric patients classified as NYHA-FC I or II who received epoprostenol. Moreover, the 4-year survival rate was also 100% among the NYHA-FC I patients. On the other hand, the 1-year survival rates after epoprostenol administration among the pediatric patients classified as NYHA-FC III and IV were 87.8% and 47.9%, respectively. Meanwhile, according to the report from Lammers et al. (*Heart*. 2007;93:739-743) on the patients with PH aged 4 months to 17 years

classified as WHO-FC III or IV, the rates of 1-, 2-, and 3-year survival after the start of epoprostenol administration were 94%, 90%, and 84%, respectively. According to the report from Nakayama et al. (*Circ J*. 2007;71:1785-1790) on the patients with IPAH ≤18 years of age classified as WHO-FC II-IV, the rates of 1-, 2-, and 3-year survival without lung transplantation after the start of epoprostenol administration were 100%, 96.3%, and 79.4%, respectively.

On the basis of the above, although the number of reports of the evaluation of the efficacy of epoprostenol in pediatric patients with PAH by WHO-FC is limited, all of them suggested improvement in the morbidity of PAH, and thus the efficacy of epoprostenol can be expected in pediatric patients with PAH, regardless of WHO-FC.

Analysis of safety data from Study AC-066A308/A309 showed no clear influence of WHO-FC on the type or incidence of adverse events. No patients classified as WHO-FC II or III experienced adverse events leading to treatment discontinuation or death. Table 7 shows the summary of adverse events by WHO-FC in pediatric patients (excluding 3 patients whose baseline WHO-FC was unknown) enrolled in the specified use-results survey of epoprostenol.[5] The adverse event whose number of cases was larger by ≥ 2 among the WHO-FC IV pediatric patients than among the patients in other functional classes was infection. However, all of the cases of infection were non-serious and considered unrelated to epoprostenol. Of 14 pediatric patients whose WHO-FC was evaluated, 3 patients (21.4%, 2 WHO-FC III and 1 WHO-FC IV patients) died. Serious adverse events were not reported in the WHO-FC I or II pediatric patients and were noted only in the WHO-FC III or IV pediatric patients. However, the incidence of adverse events did not tend to differ markedly between the patients classified as WHO-FC III and those classified as WHO-FC IV.

Table 7. Summary of adverse events by WHO-FC in pediatric patients in the specified use-results survey of epoprostenol[5]

| | WHO-FC I (N = 1) | WHO-FC II (N = 2) | WHO-FC III (N = 6) | WHO-FC IV (N = 5) |
|---|---|---|---|---|
| Adverse events | 0 (0) | 50.0 (1) | 83.3 (5) | 80.0 (4) |
| Death | 0 (0) | 0 (0) | 33.3 (2) | 20.0 (1) |
| Serious adverse events | 0 (0) | 0 (0) | 50.0 (3) | 40.0 (2) |
| Adverse events possibly related to the study drug | 0 (0) | 50.0 (1) | 16.7 (1) | 20.0 (1) |
| Adverse events leading to treatment discontinuation | 0 (0) | 50.0 (1) | 33.3 (2) | 20.0 (1) |
| Adverse events noted in more than one patient | | | | |
| Device-related infection | 0 (0) | 0 (0) | 16.7 (1) | 40.0 (2) |
| Infection | 0 (0) | 0 (0) | 0 (0) | 40.0 (2) |
| Anaemia | 0 (0) | 0 (0) | 16.7 (1) | 20.0 (1) |
| Pulmonary haemorrhage | 0 (0) | 0 (0) | 16.7 (1) | 20.0 (1) |

% (n)

On the basis of the above, there should be no major difference in the safety of epoprostenol depending on WHO-FC.

The latest Japanese and foreign guidelines for the treatment of pediatric PAH strongly recommend the use of epoprostenol as a therapeutic drug for patients with PAH classified as WHO-FC III or IV, and therefore epoprostenol is expected to be administered to patients with severe PAH [see Section “7.R.1

Clinical positioning of Epoprostenol ACT"]. According to the data from the specified use-results survey of Flolan for injection[6] (*Prog Med*. 2015; 35: 1333-1341) in which 221 pediatric patients <15 years of age were enrolled, 6 patients were classified as NYHA-FC I and 19 as NYHA-FC II; approximately 10% (25 of 221) of the enrolled patients had mild PAH. This suggests that epoprostenol is possibly administered to pediatric patients with PAH in any WHO-FC. Although the above evaluation of efficacy and safety data included only limited information on the pediatric patients with PAH classified as WHO-FC I, the efficacy and safety of epoprostenol are unlikely to differ markedly among patients in different WHO-FCs. Furthermore, the indication of epoprostenol for adult patients is "pulmonary arterial hypertension" regardless of WHO-FC, and the pathophysiology and treatment response of pediatric patients with PAH have been reported to be similar to those of adult patients, although the distribution of underlying etiologies of PAH in adults differs from that in children (*Eur Respir J*. 2011;37:665-677, *Eur Respir J*. 2003;21:155-176). On the above grounds, the indication of epoprostenol for pediatric patients with PAH should be "pulmonary arterial hypertension" regardless of WHO-FC as is the indication of epoprostenol for adult patients with PAH.

PMDA's view:

Study AC-066A308 included 2 WHO-FC II patients and 1 WHO-FC III patient, and PVRI decreased in all of the patients after treatment with epoprostenol. However, no patients classified as WHO-FC I or IV were enrolled in the clinical study. The specified use-results survey of epoprostenol[5] included 17 pediatric patients, of whom 12 were evaluated for pre- and post-treatment WHO-FC (1 WHO-FC I, 2 WHO-FC II, 6 WHO-FC III, and 3 WHO-FC IV patients). The changes in WHO-FC from baseline to the treatment completion/endpoint were analyzed using the data obtained. The outcomes were "unchanged" in all of the patients in WHO-FC I or II at baseline, "improved" in 2 and "unchanged" in 1 of the patients in WHO-FC III at baseline, and "improved" in 2 and "unchanged" in 1 of the patients in WHO-FC IV at baseline. In the use-results survey of Flolan for injection[6] (*Heart*. 2008;40:34-43), the changes in NYHA-FC after 1 year of epoprostenol administration in the pediatric patients whose baseline NYHA-FC were evaluated. The outcomes were "improved" in 3 and "unchanged" in 1 of the 10 NYHA-FC II patients, "improved" in 9 and "unchanged" in 6 of the 29 NYHA-FC III patients, and "improved" in 3 and "unchanged" in 1 of the 18 NYHA-FC IV patients. Safety analysis of the data from Study AC-066A308/A309 and the specified use-results survey of epoprostenol[5] showed no major differences in the safety profile of epoprostenol in pediatric patients depending on WHO-FC. In light of the above results, the efficacy of epoprostenol has been demonstrated and the safety is acceptable for the pediatric patients in WHO-FC II and III.

The applicant had difficulty enrolling pediatric patients with PAH classified as WHO-FC I to evaluate the hemodynamics, for some reasons, including the following: (i) Many of such pediatric patients have no subjective symptoms that would lead to medical consultation, (ii) making a definitive diagnosis of PAH is difficult for physicians other than specialists, and (iii) highly invasive epoprostenol therapy is rarely used at the initial stage of treatment even when the diagnosis is confirmed. Such a situation is understandable. The specified use-results survey of epoprostenol[5] included 1 WHO-FC I pediatric patient, who remained in WHO-FC I. However, the assessment of the efficacy is difficult because only

1 such patient was evaluated in the survey. Furthermore, unlike oral PAH drugs, Epoprostenol ACT is a powder for solution for injection requiring continuous infusion, which entails catheter insertion and carrying an infusion pump regularly, resulting in a significant impairment in the quality of life (QOL) of patients. Taking account of this fact, the risk-benefit balance in WHO-FC I patients, who have relatively mild conditions and no subjective symptoms, is inferred to be different from that in WHO-FC II to IV patients, who have subjective symptoms. Thus, careful consideration is necessary before the use of Epoprostenol ACT in WHO-FC I patients.

The efficacy and safety of epoprostenol in WHO-FC IV patients cannot be evaluated on the basis of the results of clinical studies because no such patients were not enrolled in Study AC-066A308 conducted in pediatric patients with PAH in Japan. However, the specified use-results survey of epoprostenol[5] and the use-results survey of Flolan for injection[6] (*Heart*. 2008;40:34-43) presented data showing that WHO-FC improved in some WHO-FC IV pediatric patients although the number of patients evaluated was extremely small. This suggests that the efficacy of epoprostenol is promising. Furthermore, the specified use-results survey of epoprostenol[5] showed no major differences in the incidence of adverse events between the pediatric patients in WHO-FC III and those in WHO-FC IV. Taking account of these findings, epoprostenol can be administered safely also to pediatric patients in WHO-FC IV. PAH is a progressive, fatal disease. Therefore, an early start of active treatment is recommended for adult patients with PAH and the combination therapy using multiple drugs with different mechanisms of action selected from among $PGI_2$ preparations, ERA, and PDE-5 inhibitors or sGC stimulants has been advised for patients with severe symptoms or patients with inadequate response to single-drug therapy. This treatment policy is likely to be applicable to pediatric PAH. Considering that the patients' WHO-FC varies depending on the changes in treatment or conditions and that the Japanese and foreign treatment guidelines recommend the use of epoprostenol for pediatric patients with PAH classified as WHO-FC III or IV, it is highly meaningful to include severe pediatric PAH classified as WHO-FC IV in the indication of Epoprostenol ACT.

On the basis of the above, it is acceptable that Epoprostenol ACT is indicated for "pulmonary arterial hypertension" regardless of WHO-FC, provided that physicians are advised to decide whether to use Epoprostenol ACT by referring to the latest guidelines for the treatment of PAH. The final decisions on the indication of Epoprostenol ACT and the information to be included in the package insert should be made on the basis of the comments from expert advisors in the Expert Discussion.

#### 7.R.5.2 Underlying etiology

PMDA asked the applicant to explain the justification for specifying "pulmonary arterial hypertension" as the indication of epoprostenol regardless of underlying etiology, by referring to differences in underlying etiology between adult and pediatric patients with PAH as well as the efficacy and safety of epoprostenol for each underlying etiology (e.g., IPAH, HPAH, CHD-PAH) on the basis of the results of Japanese clinical studies, the post-marketing surveillance data, published literature, and other data.

The applicant's response:

In Study AC-066A308, all the 3 subjects evaluated had IPAH. All of them experienced a decrease in PVRI from baseline to Week 12. Yung et al. also reported that epoprostenol decreased PVRI in the study involving patients with IPAH <16 years of age (*Circulation*. 2004; 110:660-665). A trend toward improved mPAP after treatment with epoprostenol was also reported in Study AC-066A308 involving patients with IPAH and the published literature [see Section "7.2 Japanese and foreign clinical reports"].

In addition, the changes in WHO-FC from baseline to Week 48 were analyzed with data from Study AC-066A308/A309. The outcomes were "improved" in 1 (from WHO-FC III to II) and "unchanged" in 2 of the 3 subjects (in WHO-FC II). The specified use-results survey of epoprostenol[5] included 17 pediatric patients, of whom 12 (5 with IPAH, 4 with CHD-PAH, and 3 with other conditions[7] [2 with portopulmonary hypertension and 1 with other PH]) were evaluated for pre- and post-treatment WHO-FC. The changes in WHO-FC from baseline to the treatment completion/endpoint by underlying etiology were analyzed with data from the 12 patients. The outcomes were "improved" in 2, "unchanged" in 3, and "worsened" in 0 of the 5 patients with IPAH; "improved" in 1, "unchanged" in 2, and "worsened" in 1 of the 4 patients with CHD-PAH; and "improved" in 1, "unchanged" in 0, and "worsened" in 2 of the 3 patients with other conditions.

In Study AC-066A308/A309, all of the subjects were alive at Week 52. In the specified use-results survey of epoprostenol,[5] the survival status of the 17 pediatric patients (7 with IPAH, 4 with CHD-PAH, and 6 with other conditions[7] [2 with portopulmonary hypertension and 4 with other PH]) were as follows: survival over the follow-up period (median, 329 days; range, 3 days to 24 months) was confirmed in 13 patients, and death occurred in 1 patient with IPAH, 1 patient with CHD-PAH, and 2 patients with other conditions (1 with chronic lung disease and 1 with portopulmonary hypertension). Meanwhile, according to Nakayama et al.'s report (*Circ J*. 2007;71:1785-1790) on the study involving patients with IPAH ≤18 years of age, the rates of 1-, 2-, and 3-year survival without lung transplantation after the start of epoprostenol administration were 100%, 96.3%, and 79.4%, respectively. According to Yung et al.'s report (*Circulation*. 2004;110:660-665) on the study involving patients with IPAH <16 years of age, the rates of 1-, 5-, and 10-year survival of patients receiving epoprostenol were 94%, 81%, and 61%, respectively.

On the basis of the above, the evaluation of pulmonary hemodynamics, WHO-FC, etc. in patients with IPAH receiving epoprostenol showed favorable outcomes for all of the parameters. The changes in WHO-FC were analyzed with data from the pediatric patients with CHD-PAH enrolled in the specified use-results survey of epoprostenol.[5] The outcomes were "improved" or "unchanged" in 3 patients and "worsened" in 1 patient. No major differences in the rate of survival over the follow-up period were observed between the patients with CHD-PAH and those with IPAH. Because there were a certain number of patients with CHD-PAH who were able to undergo long-term continuous treatment with epoprostenol, those data suggest the efficacy in patients with CHD-PAH. In addition, although no data from patients with HPAH were available, the efficacy of epoprostenol in the treatment of HPAH can be

[7] Patients with PH other than IPAH or CHD-PAH

similar to that in the treatment of IPAH because the same medical treatments and treatment policies are recommended for IPAH and HPAH by the latest Japanese guidelines for the treatment of adult PAH.

According to the analysis of safety data from Study AC-066A308/A309 in which all the subjects had IPAH, nasopharyngitis, diarrhoea, platelet count decreased, contact dermatitis, pruritus, and headache were noted in more than 1 patient each. However, no subjects experienced treatment discontinuation due to adverse events or death. Table 8 shows the summary of adverse events by underlying etiology in pediatric patients enrolled in the specified use-results survey of epoprostenol.[5] The only adverse event whose number of cases differed by ≥ 2 among pediatric patients with IPAH, those with CHD-PAH, and those with other conditions[7] was anaemia. All the cases of anaemia were non-serious and considered unrelated to epoprostenol in 1 of 2 patients. Although device-related infection and infection were noted in 4 and 3 patients, respectively, their incidences did not differ largely depending on the underlying etiology. The incidences of serious adverse events tended to be slightly higher in patients with other conditions[7] than in those with IPAH or CHD-PAH. However, of the 16 cases of serious adverse events, only 1 case of pulmonary haemorrhage noted in a patient with IPAH and 1 case of ascites noted in a patient with other conditions[7] were considered related to medication. Thus, the data from the specified use-results survey of epoprostenol[5] identified no adverse events whose incidences differ markedly depending on the underlying etiology, and adverse events reported were similar. Although no patients with HPAH were enrolled in the survey, the safety profile of epoprostenol in patients with HPAH is considered to be basically the same as that in patients with IPAH because, as mentioned above, the basic pathology of HPAH is similar to that of IPAH.

Table 8. Summary of adverse events by underlying etiology in pediatric patients in the specified use-results survey of epoprostenol[5]

| | IPAH (N = 7) | HPAH (N = 0) | CHD-PAH (N = 4) | Other conditions[a] (N = 6) |
|---|---|---|---|---|
| Adverse events | 57.1 (4) | — | 75.0 (3) | 83.3 (5) |
| Death | 14.3 (1) | — | 25.0 (1) | 33.3 (2) |
| Serious adverse events | 28.6 (2) | — | 50.0 (2) | 66.7 (4) |
| Adverse events possibly related to the study drug | 42.9 (3) | — | 0 (0) | 16.7 (1) |
| Adverse events leading to treatment discontinuation | 28.6 (2) | — | 25.0 (1) | 33.3 (2) |
| Adverse events noted in more than one patient | | | | |
| Device-related infection | 14.3 (1) | — | 50.0 (2) | 16.7 (1) |
| Infection | 14.3 (1) | — | 25.0 (1) | 16.7 (1) |
| Anaemia | 28.6 (2) | — | 0 (0) | 0 (0) |
| Pulmonary haemorrhage | 14.3 (1) | — | 25.0 (1) | 0 (0) |

% (n)

a: Patients with PH other than IPAH or CHD-PAH

On the basis of the above, the efficacy of epoprostenol can be expected in the treatment of IPAH, HPAH, and CHD-PH, and epoprostenol can be administered safely. In light of the fact that the indication of epoprostenol for adult patients with PAH is "pulmonary arterial hypertension" regardless of underlying etiology and that the pathophysiology and treatment response of pediatric patients with PAH have been reported to be similar to those of adult patients (*Eur Respir J.* 2011;37:665-677, *Eur Respir J.*

2003;21:155-176), the indication of epoprostenol for pediatric patients with PAH should be "pulmonary arterial hypertension" regardless of underlying etiology as is the indication of epoprostenol for adult patients with PAH.

However, the efficacy and safety of epoprostenol in the treatment of PAH associated with connective tissue disorder has not been established. This is based on the following reasons: (i) IPAH and CHD-PAH account for a large proportion of PHA in children <15 years of age, which suggests that PAH associated with connective tissue disorder is extremely rare, and (ii) many of the pediatric patients with PAH enrolled in the use-results survey of epoprostenol or Flolan for injection[6] (*Prog Med*. 2015; 35: 1333-1341) had IPAH or CHD-PAH. Therefore, the applicant considers it necessary to specify that the statement that "the safety and efficacy of epoprostenol in the treatment of PAH other than primary pulmonary hypertension (PPH) and PH associated with connective tissue disorder have not been established" in the "Precautions for Indication" section in the current package insert is applicable only to adults. The applicant also intends to add the statement that the efficacy and safety of epoprostenol have not been established in the treatment of PAH other than IPAH/HPAH and CHD-PAH in children.

PMDA's view:
In the Fifth WHO PH World Symposium, the etiologies of pediatric PAH were discussed on the basis of the Nice classification as in the discussion of PAH in adults (*J Am Coll Cardiol*. 2013;62:D117-126). Although the proportion of each underlying etiology differed between children and adults, treatment policies adopted for children were the same as those for adults. PAH is a rare disease and the number of pediatric patients is even smaller. Therefore, it is understandable that the applicant had difficulty in conducting clinical trials involving pediatric patients with PAH other than IPAH/HPAH and CHD-PAH such as PAH associated with connective tissue disorder. The results of Japanese clinical studies, post-marketing surveillance data, and published literature suggest that the efficacy and safety of epoprostenol in pediatric patients with IPAH/HPAH and CHD-PAH, which mainly constitute Group 1 PAH, should be basically similar regardless of underlying etiology. In addition, the Japanese and foreign guidelines including the latest treatment algorithm for PAH in adults recommend the same therapies for the overall Group 1 PAH. This would be based on the idea that the therapeutic effects of the recommended therapies can be expected regardless of underlying etiology. Therapies for pediatric patients with PAH have been selected with reference to the results of the large-scale clinical studies conducted in adult patients with PAH, and moreover, the treatment algorithm for pediatric PAH does not differentiate the therapies depending on the underlying etiology. On the basis of the above, the indication of epoprostenol should include PAH due to the underlying etiologies other than those investigated in clinical studies and it should be specified as "pulmonary arterial hypertension" regardless of underlying etiology. In addition, it is appropriate to specify in the "Precautions for Indications" section that the efficacy and safety of epoprostenol have not been established in the treatment of PAH other than IPAH/HPAH and CHD-PAH in children. The final decisions on the indication of epoprostenol and the information to be included in the package insert should be made on the basis of the comments from the expert advisors at the Expert Discussion.

### 7.R.6 Dosage and administration

#### 7.R.6.1 Justification for the dosage and administration

The applicant's explanation on the justification for the dosage and administration of epoprostenol:
To determine the dosage regimen for the Japanese clinical studies, the applicant investigated the methods of administration actually adopted for the treatment of pediatric patients in the planned study sites, those recommended by the Japanese and foreign guidelines for the treatment of adult PAH, and those presented in Japanese and foreign literature.

The investigation revealed that the infusion of epoprostenol was started at 0.5 ng/kg/min in many of the planned study sites (medical institutions). The Japanese and foreign guidelines recommend that the starting doses of epoprostenol in adult patients with PAH should be 2 to 4 ng/kg/min (the ESC/ERS Guidelines), 2 ng/kg/min (the ACCF/AHA Guidelines), and 1 to 2 ng/kg/min (the Guidelines for Treatment of Pulmonary Hypertension [JCS 2012]). In the Japanese and foreign literature on pediatric PAH [see Sections "7.2 Japanese and foreign clinical reports" and "7.3 Reports based on Japanese post-marketing surveillance"], the infusion was initiated at 2 ng/kg/min in most pediatric patients with PAH (including those with PH other than PAH).

An investigation of the method of dose escalation adopted in the planned study sites for the determination of the optimum infusion rate showed that the interval between dose increases and the increment of dose varied depending on institution. For example, the dose was escalated by increments of 0.5 to 2.0 ng/kg/min every 0.5 to 1 day in some institutions and escalated by increments of 0.5 to 1.0 ng/kg/min every 2 to 4 weeks in other institutions. Meanwhile, the Japanese and foreign guidelines for the treatment of adult patients with PAH only recommend that the dose should be increased while monitoring the onset of adverse drug reactions. The interval between increases is not specified in the guidelines. According to Nakayama et al.'s report (*Circ J*. 2007;71:1785-1790) on the study involving patients with IPAH ≤18 years of age, the dose was escalated by increments of 0.5 to 1.0 ng/kg/min every 2 to 4 weeks. According to Lammers et al.'s report (*Heart.* 2007;93:739-743) on the study involving patients with PH 4 months to 17 years of age, the dose was escalated while evaluating the severity of disease, clinical response to treatment, and the onset of adverse drug reactions. No investigations revealed the method of dose escalation after the determination of the optimum infusion rate.

The optimum infusion rate and the maximum dose were 20 to 40 ng/kg/min in most of the medical institutions designated as study sites. According to the Japanese and foreign guidelines, the optimum infusion rate and the maximum dose are 20 to 40 ng/kg/min (the ESC/ERS Guidelines), 25 to 40 ng/kg/min (the ACCF/AHA Guidelines), and 20 to 40 ng/kg/min (the Guidelines for Treatment of Pulmonary Hypertension [JCS 2012]). The Japanese and foreign literature on pediatric PAH [see Sections "7.2 Japanese and foreign clinical reports" and "7.3 Reports based on Japanese post-marketing surveillance"] revealed that the optimum infusion rate markedly differed between patients depending on the duration of treatment and other factors.

As for the method of tapering the dose, the Japanese and foreign guidelines for the treatment of adult patients with PAH (the ESC/ERS Guidelines and the Guidelines for Treatment of Pulmonary Hypertension [JCS 2012]) advise that abrupt discontinuation or sudden large reduction in infusion rate

should be avoid due to the risk of fatal rebound effect.

The additional investigation after the preparation of the protocols of the Japanese clinical studies revealed that the starting dose recommended by the latest guidelines for the treatment of pediatric PAH (the AHA/ATS Guidelines) was 1 to 2 ng/kg/min. The guidelines advise that the dose should be escalated while monitoring the onset of adverse drug reactions and that the optimum infusion rate should be 50 to 80 ng/kg/min. In the specified use-results survey of epoprostenol,[5] the starting dose in the pediatric patients in whom epoprostenol therapy was newly introduced (8 patients) was 0.3 to 4.1 ng/kg/min, and the infusion rate at endpoint (at 9 days to 13 months after the start of treatment) was 1.7 to 35 ng/kg/min. The infusion rate at endpoint (at 3 days to 2 years after the start of treatment) in all the pediatric patients including those switching from Flolan for injection (17 patients) was 1.7 to 120 ng/kg/min. The results of the follow-up investigation did not differ markedly from the results of the investigation made for the development of the protocols.

On the basis of the above and in light of the safety in pediatric patients with PAH, the applicant developed the protocols of the Japanese clinical studies requiring the following: the infusion should be started at 0.5 to 2.0 ng/kg/min and, in principle, the dose should be escalated by increments of 0.5 to 2.0 ng/kg/min every 1 to 4 weeks while monitoring the patient's condition (e.g., symptoms, blood pressure, heart rate, hemodynamics). The protocols also stipulated that the optimum infusion rate should range from 20 to 40 ng/kg/min and that the dose should be decreased in patients with any clinical signs suggestive of excessive dose or a steep increase in cardiac output (e.g., dyspnoea, fatigue, weight decreased, tachycardia, vomiting). The dose had to be tapered by decrements of 0.5 to 2.0 ng/kg/min in principle. Table 9 summarizes the infusion rates and the methods of dose adjustment actually employed in the Japanese clinical studies conducted according to the above dosage regimen. Because the efficacy and safety of epoprostenol administered at the above dosage regimen to pediatric patients with PAH were confirmed in the studies, selecting the above dosage regimen is justifiable for Japanese children.

Table 9. Actual infusion rates and methods of dose adjustment in the Japanese clinical studies

| | Infusion rate[a] (ng/kg/min) | | Increment of dose (ng/kg/min) [minimum, maximum] | | Interval between dose increases (day) [minimum, maximum] | |
|---|---|---|---|---|---|---|
| | At the start | Week 52 | From the start to Week 12 | From Week 12 to Week 52 | From the start to Week 12 | From Week 12 to Week 52 |
| Subject 1 | 0.51 | 41.20 | [0.31, 1.01] | [0.04, 1.15] | [0.1, 17.4] | [1.1, 28.0] |
| Subject 2 | 0.97 | 24.01 | [0.75, 1.26] | [0.28, 1.78] | [1.8, 15.0] | [2.0, 106.0] |
| Subject 3 | 0.56 | 26.08 | [0.56, 1.41] | [0.28, 1.72] | [3.0, 14.0] | [9.0, 28.0] |

a: Calculated using the latest body weight measured before the date of dosage change (flow rate of the infusion pump, concentration of the reconstituted solution, or infusion rate)
* The dose was tapered in no subjects.

PMDA's view:

Before designing Study AC-066A308, the applicant explored the Japanese and foreign guidelines on adult and pediatric PAH, Japanese and foreign literature, and the actual usage of epoprostenol in pediatric patients with PAH in the medical institutions designated as study sites to determine the dosage regimen that would enable finer dose adjustments with consideration of the safety in pediatric patients

with PAH. The results of the clinical studies conducted with the above dosage regimen suggested the efficacy of epoprostenol in Japanese pediatric patients with PAH although the number of patients evaluated was very small [see Section "7.R.3. Efficacy"]. No particularly serious problem was noted in safety either [see Section "7.R.4 Safety"]. Therefore, the proposed dosage and administration should be acceptable.

The final decision on the appropriateness of the PMDA's view on the dosage and administration should be made on the basis of the comments from the expert advisors at the Expert Discussion.

#### 7.R.6.2 Age of patients eligible for treatment with epoprostenol

PMDA asked the applicant to explain the reasons why the applicant selected the same dosage and administration for younger children (neonates in particular) and older children with PAH, despite the fact that all of the 3 patients enrolled in the Japanese clinical studies were ≥8 years of age and that the efficacy and safety in younger children were not evaluated in the studies.

The applicant's response:

First, the differences in the pharmacokinetics of epoprostenol depending on age are unlikely to affect the efficacy and safety of epoprostenol, as described in Section "6.R.1 Influence of age on the pharmacokinetics of epoprostenol."

In addition, all of the 3 subjects enrolled in Study AC-066A308 were ≥1 year of age (8, 10, and 14 years of age), and the subjects showed improvement in terms of PVRI, mPAP, and WHO-FC. In Study AC-066A308/A309, all the subjects were alive at Week 52. The data from the specified use-results survey of epoprostenol[5] were analyzed to identify the changes in WHO-FC from baseline to the treatment completion/endpoint in the 12 patients whose WHO-FC was assessed before and after treatment, and the outcomes were "improved" in 1, "unchanged" in 1, and "worsened" in 1 of the 3 patients <1 year of age; and "improved" in 3, "unchanged" in 4, and "worsened" in 2 of the 9 patients ≥1 year and <15 years of age. The survival over the follow-up period (median, 13 months; range, 111 days to 24 months) was confirmed in 8 of the 10 patients ≥1 year and <15 years of age. The follow-up period was short (median, 74 days; range, 3 days to 13 months) in many of the patients <1 year of age, but the survival over the follow-up period was confirmed in 5 of the 7 patients. The follow-up period in 6 of the 7 patients <1 year of age was <6 months. Follow-up was discontinued in 2 patients who died, and the reasons for the discontinuation of follow-up in other 4 patients were persistent pulmonary hypertension of the newborn (PPHN) (improved or resulting in referral to another hospital), hypoxaemia associated with meconium aspiration syndrome (improved), and congenital isolated pulmonary vein stenosis (resulting in medication switch). The follow-up period was >6 months in 1 patient who was a 2-month-old child with CHD-PAH and the patient had continuously been receiving epoprostenol for 13 months (as of March 31, 2016). In the use-results survey of Flolan for injection conducted in patients with PAH[6] (*Heart*. 2008;40:34-43), the 3-year survival rates in epoprostenol-treated patients <1 year of age, those ≥1 year and <10 years of age, and those ≥10 years and <15 years of age were 44.4%, 68.7%, and 76.4%, respectively. The survival rate tended to be lower in patients <1 year of age than in those ≥1 year of age. This may be partly because some of the patients were withdrawn while the number of the patients <1

year of age was as small as 7. The 6-month and 3-year survival rates in the patients <1 year of age were 44.4% and 44.4%, respectively, indicating that survival was successfully maintained from 6 months to 3 years after the start of treatment.

The above findings have demonstrated that the overall efficacy of epoprostenol in children <1 year of age is similar to that in children ≥1 year of age, although the number of the reports on the evaluation of the efficacy of epoprostenol in pediatric patients with PAH by age was limited.

Safety data were analyzed. All the subjects enrolled in Study AC-066A308/A309 were ≥1 year of age. Nasopharyngitis, diarrhoea, platelet count decreased, contact dermatitis, pruritus, and headache occurred in more than 1 subject each. However, no subject experienced treatment discontinuation due to adverse events or death. Table 10 shows the summary of adverse events by age in pediatric patients enrolled in the specified use-results survey of epoprostenol.[5] The only adverse event whose number of cases differed by ≥2 between the patients <1 year of age and the patients ≥1 year of age was infection. All of the cases were considered non-serious and unrelated to epoprostenol. The tabulation of the adverse drug reactions and serious adverse events reported in pediatric patients did not identify any event whose incidence differed largely by age. The incidence of adverse events did not differ markedly between the patients <1 year of age and the patients ≥1 year and <15 years of age. Death occurred in 2 patients <1 year of age (pulmonary hypertension and pulmonary haemorrhage; and lung disorder) and 2 patients ≥1 year and <15 years of age (multiple organ dysfunction syndrome or pulmonary haemorrhage). All the cases were considered unrelated to epoprostenol, except for the case of pulmonary haemorrhage occurring in a patient <1 year of age.

Table 10. Summary of adverse events by age in pediatric patients in the specified use-results survey of epoprostenol[5]

| | <1 year of age (N = 7) | ≥1 year of age (N = 10) |
|---|---|---|
| Adverse events | 85.7 (6) | 60.0 (6) |
| Death | 28.6 (2) | 20.0 (2) |
| Serious adverse events | 57.1 (4) | 40.0 (4) |
| Adverse events possibly related to the study drug | 28.6 (2) | 20.0 (2) |
| Adverse events leading to treatment discontinuation | 28.6 (2) | 30.0 (3) |
| Adverse events noted in more than one patient | | |
| Device-related infection | 28.6 (2) | 20.0 (2) |
| Infection | 42.9 (3) | 0 (0) |
| Anaemia | 14.3 (1) | 10.0 (1) |
| Pulmonary haemorrhage | 14.3 (1) | 10.0 (1) |

% (n)

Thus, the results of Study AC-066A308/A309, the use-results survey of epoprostenol, and the use-results survey of Flolan for injection[6] have demonstrated that the overall efficacy and safety of epoprostenol in patients <1 year of age are similar to those in patients ≥1 year of age. Furthermore, because neonates and younger infants are supposed to receive epoprostenol in hospital, the safety of treatment in this patient population can sufficiently be secured. Therefore, the efficacy and safety of

epoprostenol in younger children including neonates are expected to be similar to those in older children or adults, and the lower limit for the age of children to be treated with epoprostenol is unnecessary.

PMDA's view:
The pediatric patients evaluated in Study AC-066A308 were ≥8 years of age and no younger children were enrolled in the study. However, the use-results survey of epoprostenol, the use-results survey of Flolan for injection, published literature, and other data [see Sections "7.2 Japanese and foreign clinical reports" and "7.3 Reports based on Japanese post-marketing surveillance"] have demonstrated the overall efficacy of epoprostenol in pediatric patients with PAH ≥1 year of age in terms of the improvement in PVRI, unchanged WHO-FC, the improvement in 6-minute walking distance, and other indices. On the basis of the above, the safety profile of epoprostenol is unlikely to raise any significant concerns.

Because no patients <1 year of age were enrolled in Study AC-066A308 conducted in Japan, the efficacy of epoprostenol could not be evaluated in patients of this age group. In the specified use-results survey of epoprostenol,[5] WHO-FC was evaluated in only 3 patients <1 year of age, and the outcomes were "improved," "unchanged," and "worsened" in 1 patient each. The follow-up period was <6 months in as many as 6 of the 7 patients <1 year of age. However, follow-up was discontinued in 2 patients who died, and the reasons for the discontinuation of follow-up in other 4 patients were PPHN (improved or resulting in referral to another hospital) in 2 patients, hypoxaemia associated with meconium aspiration syndrome (improved) in 1 patient, and congenital isolated pulmonary vein stenosis (resulting in medication switch) in 1 patient. These were the patients with conditions where epoprostenol was administered for a relatively short period immediately after birth or patients for whom epoprostenol was unlikely to be indicated. Meanwhile, the 1 patient with CHD-PAH <1 year (aged 2 months) who was followed for >6 months had continuously been receiving epoprostenol for 13 months. Therefore, although the number of evaluated patients was very small, there is some evidence suggesting that the efficacy of epoprostenol can be expected also in patients with PAH <1 year of age. According to the safety data from the specified use-results survey of epoprostenol,[5] the incidence of overall adverse events among the patients <1 year of age (85.7%, 6 of 7 patients) tended to be higher than that among the patients ≥1 year and <15 years of age (60.0%, 6 of 10 patients). Nine serious adverse events were noted in 4 patients <1 year of age, but all the cases were considered unrelated to epoprostenol, except for 1 case of pulmonary haemorrhage and 1 case of ascites. The incidence of each adverse event did not differ markedly between children <1 year of age and children ≥1 year of age.

In pediatric patients, IPAH or HPAH and CHD-PAH account for a large proportion of the underlying etiologies. In particular, CHD-PAH is considered to develop early in life. An early and appropriate treatment would enable surgical treatment in some patients, while treatment of perioperative PAH or postoperative residual PAH would further improve prognosis in other patients. Based on these findings and taking account of the data from the above-mentioned specified use-results surveys, it is meaningful to offer epoprostenol as a therapeutic option for patients <1 year of age if the package insert specifies that the efficacy and safety of epoprostenol have not been established in patients <1 year of age. Although experience with the use of epoprostenol in neonates is particularly limited, epoprostenol

should be made available in clinical settings as a drug for pediatric patients including low birth-weight newborns and neonates, for the following reasons: (i) PAH in neonates often requires urgent treatment and thus some patients with more severe conditions will need an immediate treatment with epoprostenol, and (ii) treatment with epoprostenol is supposed to be started carefully during hospitalization by specialists in the treatment of PAH.

The final decision on PMDA's view on the use of epoprostenol in patients <1 year of age and the details of the statements to be included in the package insert should be made on the basis of the comments from the expert advisors at the Expert Discussion.

### 7.R.7 Post-marketing investigations

PMDA's view on post-marketing investigations:

The use of epoprostenol in pediatric patients with PAH has been recommended by Japanese and foreign guidelines on pediatric PAH. The specified use-results survey has collected data from a certain number of pediatric patients with PAH treated with epoprostenol. In addition, the data from Japanese clinical trials and published literature show no evidence suggesting a trend toward an increased risk of any specific adverse event in children. In light of such circumstances, it is not meaningful to conduct new post-marketing surveillance after the addition of the dosage and administration of epoprostenol for children. The applicant should conduct routine pharmacovigilance activities including the collection of spontaneous reports and literature review and should evaluate the necessity of another post-marketing surveillance on the basis of the information from these activities. However, additional pharmacovigilance or risk minimization activities are unnecessary at present.

## 8. Results of Compliance Assessment Concerning the New Drug Application Data and Conclusion Reached by PMDA

### 8.1 PMDA's conclusion concerning the results of document-based GLP/GCP inspections and data integrity assessment

The new drug application data were subjected to a document-based compliance inspection and a data integrity assessment in accordance with the provisions of the Act on Securing Quality, Efficacy and Safety of Pharmaceuticals, Medical Devices, Regenerative and Cellular Therapy Products, Gene Therapy Products, and Cosmetics. On the basis of the inspection and assessment, PMDA concluded that there were no obstacles to conducting its review based on the application documents submitted.

### 8.2 PMDA's conclusion concerning the results of the on-site GCP inspection

The new drug application data (CTD 5.3.5.2.1, CDT 5.3.5.2.2, and CTD 5.3.5.2.6) were subjected to an on-site GCP inspection, in accordance with the provisions of the Act on Securing Quality, Efficacy and Safety of Pharmaceuticals, Medical Devices, Regenerative and Cellular Therapy Products, Gene Therapy Products, and Cosmetics. PMDA concluded that there were no obstacles to conducting its review based on the application documents submitted.

## 9. Overall Evaluation during Preparation of the Review Report (1)

On the basis of the submitted data, PMDA has concluded that Epoprostenol ACT has efficacy in the treatment of PAH in children, and that Epoprostenol ACT has acceptable safety in view of its benefits. The product has clinical significance because it offers a new treatment option for pediatric patients with PAH. PMDA considers that the indication(s), dosage and administration, age of pediatric patients for which Epoprostenol ACT is indicated, and the details of precautions in the package insert should be further evaluated.

PMDA has concluded that Epoprostenol ACT may be approved if the product is not considered to have any particular problems based on comments from the Expert Discussion.

**Review Report (2)**

January 18, 2017

**Product Submitted for Approval**

| | |
|---|---|
| **Brand Name** | Epoprostenol ACT 0.5 mg<br>Epoprostenol ACT 1.5 mg |
| **Non-proprietary Name** | Epoprostenol Sodium |
| **Applicant** | Actelion Pharmaceuticals Japan Ltd. |
| **Date of Application** | March 04, 2016 |

## 1. Content of the Review

Comments made during the Expert Discussion and the subsequent review conducted by the Pharmaceuticals and Medical Devices Agency (PMDA) are summarized in the following. The expert advisors present during the Expert Discussion were nominated based on their declarations etc. concerning the product submitted for marketing approval, in accordance with the provisions of the Rules for Convening Expert Discussions etc. by Pharmaceuticals and Medical Devices Agency (PMDA Administrative Rule No. 8/2008 dated December 25, 2008).

### 1.1 Efficacy and safety

At the Expert Discussion, the expert advisors supported PMDA's conclusion on the issues presented in Sections "7.R.3 Efficacy" and "7.R.4 Safety" of Review Report (1).

### 1.2 Indication

At the Expert Discussion, the expert advisors supported PMDA's conclusion on the issues presented in Section "7.R.5 Indication" of Review Report (1). Therefore, PMDA has concluded that the Indication and the Precautions for Indications should be stated as follows:

[Indication]
Pulmonary arterial hypertension

[Precautions for Indications]
(1) to (5) (Omitted)
(6) The safety and efficacy of epoprostenol in the treatment of pulmonary arterial hypertension other than idiopathic or heritable pulmonary arterial hypertension and pulmonary arterial hypertension associated with congenital heart disease have not been established in children.

(Underline denotes additions)

### 1.3 Dosage and administration

At the Expert Discussion, the expert advisors supported PMDA's conclusion on the issues presented in Section "7.R.6 Dosage and administration" of Review Report (1). Therefore, PMDA has concluded that

the dosage and administration should be stated as follows, and that the "Important Precautions" and "Pediatric Use" sections should include the following precautionary statements:

[Dosage and Administration]
[Children]
Dosage (at the start of treatment)
After reconstitution with the solvent provided (saline), the reconstituted solution (epoprostenol) is administered by continuous intravenous infusion via an electronic infusion device for continuous infusion (a syringe pump or an infusion pump). Usually, infusion of epoprostenol should be initiated in children at an infusion rate of 0.5 to 2 ng/kg/min. In principle, the dosage should be increased by increments of 0.5 to 2 ng/kg/min every 1 to 4 weeks, with careful monitoring of the patient's condition (e.g., symptoms, blood pressure, heart rate, and hemodynamics). The optimum infusion rate should be determined within a range from 20 to 40 ng/kg/min. Flushing (excluding slight one), headache, or queasy may occurr after an increase in the infusion rate. If such symptoms (even mild ones) occur, further increases in the dosage should be avoided. If the symptom persists, the dosage should be gradually decreased by decrements of 0.5 to 2 ng/kg/min.

Continuous infusion
The infusion should be continued at the optimum infusion rate thereafter. The patient should be monitored regularly for dosage ajustment. The dosage should be adjusted by increments or decrements of 0.5 to 2 ng/kg/min according to the patient's condition (e.g., symptoms, blood pressure, heart rate, and hemodymanics).

[Important Precautions]
(1) (Omitted)
(2) Appropriate response to changes in the patient's symptoms is important <u>for</u> the use of the product. <u>Therefore</u>, the product should be administered only to patients suitable for treatment with the product in medical institutions capable of providing sufficient treatment in case of emergency <u>and</u> by physicians <u>with</u> sufficient knowledge of and experience with the treatment of pulmonary hypertension and cardiac failure <u>(physicians with sufficient knowledge of and experience with the treatment of pediatric pulmonary arterial hypertension in pediatric patients in particular)</u>.
(3) (Omitted)

(Underline denotes changes)

[Pediatric Use]
The safety of epoprostenol in low birth-weight infants, neonates <u>or infants</u> has not been established.

(Underline denotes changes)

## 2. Overall Evaluation

As a result of the above review, PMDA has concluded that the product may be approved for the indication and dosage and administration shown below.

**Indication**

Pulmonary arterial hypertension

(Unchanged)

**Dosage and Administration**

Adults

Dosage (at the start of treatment)

After reconstitution with the solvent provided (saline), the reconstituted solution (epoprostenol) is administered by continuous intravenous infusion via an electronic infusion device for continuous infusion (a syringe pump or an infusion pump). Usually, infusion of epoprostenol should be initiated in adults at the infusion rate of 2 ng/kg/min. The dosage should be increased by increments of 1 to 2 ng/kg/min every ≥15 minutes, with careful monitoring of the patient's condition (e.g., symptoms, blood pressure, heart rate, and hemodynamics). The optimum infusion rate should be determined within a range not exceeding 10 ng/kg/min.

The onset of adverse reactions, such as flushing (excluding slight one), headache, and queasy, after an increase in infusion rate is an important factor for determining the optimum infusion rate. If such symptoms (even mild ones) occur, further increases in the dosage should be avoided. If the symptom persists, the dosage should be gradually decreased by decrements of 2 ng/kg/min every ≥15 minutes.

Continuous infusion

The infusion should be continued at the optimum infusion rate thereafter. The patient should be monitored regularly for dosage ajustment. The dosage should be adjusted by increments or decrements of 1 to 2 ng/kg/min every ≥15 minutes according to the patient's condition (e.g., symptoms, blood pressure, heart rate, and hemodymanics).

Children

Dosage (at the start of treatment)

After reconstitution with the solvent provided (saline), the reconstituted solution (epoprostenol) is administered by continuous intravenous infusion via an electronic infusion device for continuous infusion (a syringe pump or an infusion pump). Usually, infusion of epoprostenol should be initiated in children at an infusion rate of 0.5 to 2 ng/kg/min. In principle, the dosage should be increased by increments of 0.5 to 2 ng/kg/min every 1 to 4 weeks, with careful monitoring of the patient's condition (e.g., symptoms, blood pressure, heart rate, and hemodynamics). The optimum infusion rate should be determined within a range from 20 to 40 ng/kg/min. Flushing (excluding slight one), headache, or queasy may occurr after an increase in infusion rate. If such symptoms (even mild ones) occur, further increases in the dosage should be avoided. If the symptom persists, the dosage should be gradually decreased by decrements of 0.5 to 2 ng/kg/min.

Continuous infusion

The infusion should be continued at the optimum infusion rate thereafter. The patient should be monitored regularly for dosage ajustment. The dosage should be adjusted by increments or decrements of 0.5 to 2 ng/kg/min according to the patient's condition (e.g., symptoms, blood pressure, heart rate, and hemodymanics).

(Underline denotes addition)