Report on the Deliberation Results

December 3, 2025
Pharmaceutical Evaluation Division, Pharmaceutical Safety Bureau
Ministry of Health, Labour and Welfare

Brand Name	Opsumit 1 mg Dispersible Tablets for Pediatric Opsumit 2.5 mg Dispersible Tablets for Pediatric Opsumit Tablets 10 mg
Non-proprietary Name	Macitentan (JAN*)
Applicant	Janssen Pharmaceutical K.K.
Date of Application	March 28, 2025

Results of Deliberation

In its meeting held on December 3, 2025, the First Committee on New Drugs concluded that Opsumit 1 mg Dispersible Tablets for Pediatric, Opsumit 2.5 mg Dispersible Tablets for Pediatric, and the partial change application for Opsumit Tablets 10 mg may be approved, and that these results should be presented to the Pharmaceutical Affairs Council.

Opsumit 1 mg Dispersible Tablets for Pediatric and Opsumit 2.5 mg Dispersible Tablets for Pediatric are not classified as biological products or specified biological products. These drug products are classified as powerful drugs. The re-examination period is 10 years for Opsumit 1 mg Dispersible Tablets for Pediatric, Opsumit 2.5 mg Dispersible Tablets for Pediatric, and Opsumit Tablets 10 mg.

Approval Condition

The applicant is required to develop and appropriately implement a risk management plan.

* *Japanese Accepted Name (modified INN)*

Review Report

November 11, 2025
Pharmaceuticals and Medical Devices Agency

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

Brand Name	(a) Opsumit 1 mg Dispersible Tablets for Pediatric Opsumit 2.5 mg Dispersible Tablets for Pediatric (b) Opsumit Tablets 10 mg
Non-proprietary Name	Macitentan
Applicant	Janssen Pharmaceutical K.K.
Date of Application	March 28, 2025
Dosage Form/Strength	(a) Each tablet contains 1 or 2.5 mg of macitentan. (b) Each tablet contains 10 mg of macitentan.
Application Classification	(a) Prescription drugs (6) Drugs with a new dosage, (8-2) Drugs in an additional dosage form (outside of the re-examination period) (b) Prescription drugs (6) Drugs with a new dosage
Items Warranting Special Mention	Orphan drug (Orphan Drug Designation No. 634 of 2024 [*R6 yaku*]; PSB/PED Notification No. 1127-4 dated November 27, 2024, by the Pharmaceutical Evaluation Division, Pharmaceutical Safety Bureau, Ministry of Health, Labour and Welfare) Drug for specified use (Specific Use Drug Designation No. 3 of 2025 [*R7 tokuteiyaku*]; PSB/PED Notification No. 0331-3 dated March 31, 2025, by the Pharmaceutical Evaluation Division, Pharmaceutical Safety Bureau, Ministry of Health, Labour and Welfare)
Reviewing Office	Office of New Drug II

Results of Review

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

As a result of its review, PMDA has concluded that the products may be approved for the indication and dosage and administration shown below, with the following condition. Opsumit 1 mg Dispersible Tablets for Pediatric and Opsumit 2.5 mg Dispersible Tablets for Pediatric are not classified as biological products or specified biological products. These drug products are classified as powerful drugs.

Indication

(a) and (b)

Pulmonary arterial hypertension

(No change for [b])

Dosage and Administration

(a)

The usual dosage of macitentan for children aged ≥3 months is as follows. Each tablet is dispersed in a small amount of water for every use to be administered orally once daily.

Age ≥3 months and <6 months, dosage of 1.0 mg

Age ≥6 months and <2 years, dosage of 2.5 mg

Age ≥2 years and body weight <15 kg, dosage of 3.5 mg

Age ≥2 years and body weight ≥15 kg and <25 kg, dosage of 5.0 mg

Age ≥2 years and body weight ≥25 kg and <50 kg, dosage of 7.5 mg

Age ≥2 years and body weight ≥50 kg, dosage of 10 mg

(b)

Adults

The usual adult dosage is 10 mg of macitentan administered orally once daily.

Children

The usual dosage for children weighing ≥50 kg is 10 mg of macitentan administered orally once daily.

(Underline denotes additions.)

Approval Condition

The applicant is required to develop and appropriately implement a risk management plan.

Attachment

Review Report (1)

September 24, 2025

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 (PMDA).

Products Submitted for Approval

Brand Name	(a) Opsumit 1 mg Dispersible Tablets for Pediatric Opsumit 2.5 mg Dispersible Tablets for Pediatric (b) Opsumit Tablets 10 mg
Non-proprietary Name	Macitentan
Applicant	Janssen Pharmaceutical K.K.
Date of Application	March 28, 2025
Dosage Form/Strength	(a) Each tablet contains 1 or 2.5 mg of macitentan. (b) Each tablet contains 10 mg of macitentan.

Proposed Indication

(a) and (b)

Pulmonary arterial hypertension

(No change for [b])

Proposed Dosage and Administration

(a)

The usual dosage of macitentan for children aged ≥3 months is as follows. Each tablet is dispersed in a small amount of water for every use to be administered orally once daily.

Age ≥3 months and <6 months, dosage of 1.0 mg

Age ≥6 months and <2 years, dosage of 2.5 mg

Age ≥2 years and body weight <15 kg, dosage of 3.5 mg

Age ≥2 years and body weight ≥15 kg and <25 kg, dosage of 5.0 mg

Age ≥2 years and body weight ≥25 kg and <50 kg, dosage of 7.5 mg

Age ≥2 years and body weight ≥50 kg, dosage of 10 mg

(b)

Adults

The usual adult dosage is 10 mg of macitentan administered orally once daily.

Children

The usual dosage for children aged ≥2 years and weighing ≥50 kg is 10 mg of macitentan administered orally once daily.

(Underline denotes additions.)

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List of Abbreviations

See Appendix.

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

Macitentan is an endothelin receptor antagonist (ERA) that inhibits endothelin A (ET_A) and endothelin B (ET_B) receptors. The product was approved in Japan in March 2015 for the indication of "pulmonary arterial hypertension" with the dosage regimen for adults.

Based on the results from Japanese and foreign clinical studies, the applicant has recently submitted applications for partial change approval to add the dosage regimen for pediatric patients with pulmonary arterial hypertension (PAH) and for a marketing approval of dispersible tablets for pediatric use as an additional dosage form. Macitentan has been designated as an orphan drug (Orphan Drug Designation No. 634 of 2024 [*R6 yaku*]) and a drug for specific use (Specific Use Drug Designation No. 3 of 2025 [*R7 tokuteiyaku*]) with the intended indication of "pulmonary arterial hypertension."

As of August 2025, macitentan has been approved for the indication of "pulmonary arterial hypertension" in 81 countries or regions including the European countries and the US, and for use in children with PAH[1)] in 32 countries or regions including the European countries.

2. Quality and Outline of the Review Conducted by PMDA

While the present application pertains to the new dosages, the applications of macitentan 1 mg/ 2.5 mg dispersible tablets for children are also intended for the additional dosage form. Quality and bioequivalence (BE) data have been attached. Although this review report describes review outcomes on the new dosages only, the review on the additional dosage form at PMDA found no significant issues.

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

Although the present application pertains to the new dosages, non-clinical pharmacological data were evaluated during the review on the approval of macitentan 10 mg tablets, and thus no new data were submitted.

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

Although the present application pertains to the new dosages, non-clinical pharmacokinetic data were evaluated during the review for the approval of macitentan 10 mg tablets, and thus no new data were submitted.

5. Toxicology and Outline of the Review Conducted by PMDA

The present application pertains to the new dosages, and thus no new data were submitted.

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

6.1 Summary of biopharmaceutic studies and associated analytical methods

The proposed commercial formulations (macitentan 1 mg/2.5 mg dispersible tablets) were used in the Japanese phase III study (Study PAH3001). The foreign phase III study (Study AC-055-312) used the proposed commercial formulations and the clinical study formulations (macitentan 0.5 mg/2.5 mg/5 mg dispersible tablets). A relative bioavailability (BA) study demonstrated similarity in the pharmacokinetic

1) Children aged ≥2 years

(PK) profiles between the clinical study formulations and the proposed commercial formulations, and a BE study demonstrated bioequivalence between the proposed commercial formulations and the commercial product (macitentan 10 mg tablets) [see Sections 6.1.1 and 6.1.2]. Bioequivalence between the proposed commercial formulations, i.e., 1 mg dispersible tablets and 2.5 mg dispersible tablets, were demonstrated by dissolution tests performed in accordance with the Guideline for Bioequivalence Studies for Different Strengths of Oral Solid Dosage Forms.

Plasma concentrations of macitentan and its active metabolite, aprocitentan, were determined by liquid chromatography and tandem mass spectrometry (LC-MS/MS), with the lower limit of quantitation for both being 1.0 ng/mL.

6.1.1 Relative BA study (Study PAH1008; CTD 5.3.1.2.2 [reference data]; study period, July to October 2021)

A two-treatment, two-period crossover study was conducted to evaluate relative BA in 16 non-Japanese healthy adults who received a single oral dose of 2 5-mg dispersible tablets, the clinical study formulation, and 4 2.5-mg dispersible tablets as proposed commercial formulation in the fasted state (a ≥10-day washout period).

Geometric mean ratios [90% confidence interval (CI)] of C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$ of macitentan after the administration of 2.5 mg dispersible tablets, proposed commercial formulation, to those after the administration of 5 mg dispersible tablets as clinical study formulation, were 0.8776 [0.8358, 0.9216], 1.0124 [0.9759, 1.0502], and 1.0095 [0.9759, 1.0442], respectively.

6.1.2 BE study (Study PAH1010; CTD 5.3.1.2.1; study period, June to October 2022)

A two-treatment, two-period crossover study was conducted to evaluate BE in 28 non-Japanese healthy adults who orally received a single dose of the 10-mg tablet, the commercial product, and 4 2.5-mg dispersible tablets as proposed commercial formulation in the fasted state (a ≥10-day washout period).

Geometric mean ratios [90% CI] of C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$ of macitentan after the administration of 2.5-mg dispersible tablets as proposed commercial formulation to those after the administration of a 10-mg tablet, the commercial product, were 0.9456 [0.8794, 1.0169], 1.0354 [0.9949, 1.0777], and 1.0401 [1.0007, 1.0811], respectively.

6.2 Clinical pharmacology

6.2.1 Studies in patients

6.2.1.1 Japanese phase III study (Study PAH3001; CTD 5.3.5.2.1-2; study period, November 2022 to March 2025)

Macitentan 3.5, 5, 7.5, or 10 mg was administered orally once daily to Japanese pediatric patients with PAH aged ≥2 years according to the body weight of <15 kg, ≥15 kg and <25 kg, ≥25 kg and <50 kg, or ≥50 kg, respectively. To patients aged ≥6 months and <2 years, macitentan 2.5 mg was administered orally once daily. Tables 1 and 2 show the PK parameters of macitentan and aprocitentan.

Table 1. PK parameters of macitentan and aprocitentan in patients with PAH aged ≥2 years at steady state after multiple oral administration of macitentan

Body weight category	Dose (mg)	n	C_{max} (ng/mL)	C_{trough} (ng/mL)	AUC_{τ} (ng·h/mL)	t_{max} (h)
Macitentan						
<15 kg	3.5	2	230, 352	131[a]	3151, 5714	4.33, 7.48
≥15 kg and <25 kg	5	1	184	101	2855	3.80
≥25 kg and <50 kg	7.5	1	250	52.1	2886	4.02
≥50 kg	10	1	193	58.1	2897	3.80
Aprocitentan						
<15 kg	3.5	2	1170, 1340	1230[a]	23246, 28313	0.00, 23.33
≥15 kg and <25 kg	5	1	1000	909	14768	0.00
≥25 kg and <50 kg	7.5	1	929	949	18521	24.12
≥50 kg	10	1	764	580	15288	23.50

Individual value(s) at n = 1 or 2

a A PK sample was not collected from 1 patient, and the result at n = 1 is presented.

Table 2. Plasma concentrations of macitentan and aprocitentan in patients with PAH aged <2 years after multiple oral administration of macitentan

	Months of age	Dose (mg)	2 hours after the first dose	5 hours after the first dose	24 hours after the first dose	Week 4[a]	Week 8[a]
Macitentan							
Subject A	21 months	2.5	33.6	120	24.2	55.1	59.4
Subject B	22 months	2.5	81.4	155	61.1	143	83.5
Aprocitentan							
Subject A	21 months	2.5	7.98	65.9	162	864	982
Subject B	22 months	2.5	7.62	29.2	119	662	648

ng/mL, individual values

Subjects A and B correspond to Subjects 4 and 6 in Table 11.

a Trough concentration

6.2.1.2 Foreign phase III study (Study AC-055-312; CTD 5.3.5. 1.1; study period. ongoing since October 2017; database locked in February 2024)

Macitentan 3.5, 5, 7.5, or 10 mg was administered orally once daily to non-Japanese pediatric patients with PAH aged ≥2 years according to the body weight of ≥10 kg and <15 kg, ≥15 kg and <25 kg, ≥25 kg and <50 kg, or ≥50 kg, respectively. To patients aged ≥6 months and <2 years, macitentan 2.5 mg was administered orally once daily. Tables 3 and 4 show PK parameters of macitentan and aprocitentan.

Table 3. PK parameters of macitentan and aprocitentan in patients with PAH aged ≥2 years at Week 12 during multiple oral administration of macitentan

Body weight category	Dose (mg)	C_{max} (ng/mL)	C_{trough} (ng/mL)	AUC_{τ} (ng·h/mL)	t_{max} (h)
Macitentan					
≥10 kg and <15 kg	3.5	439 [428, 564] (n = 3)	145 [58.8, 246] (n = 6)	5796 [5622, 7234] (n = 3)	8.00 [2.02, 8.00] (n = 3)
≥15 kg and <25 kg	5	351 [191, 396] (n = 5)	103 [57.4, 402] (n = 12)	6087 [2734, 6755] (n = 5)	8.08 [3.93, 11.98] (n = 5)
≥25 kg and <50 kg	7.5	344 [241, 574] (n = 9)	173 [6.75, 581] (n = 14)	6645 [3102, 9570] (n = 9)	8.00 [3.98, 24.07] (n = 9)
≥50 kg	10	387 [131, 631] (n = 9)	226 [19.2, 334] (n = 15)	6437 [2031, 9052] (n = 9)	4.05 [1.00, 8.20] (n = 9)
Aprocitentan					
≥10 kg and <15 kg	3.5	1530 [788, 2240] (n = 3)	1100 [748, 1660] (n = 6)	30893 [15592, 36805] (n = 3)	0.00 [0.00, 24.00] (n = 3)
≥15 kg and <25 kg	5	1140 [666, 1310] (n = 5)	823 [522, 1210] (n = 12)	23842 [12921, 26622] (n = 5)	8.05 [0.00, 23.95] (n = 5)
≥25 kg and <50 kg	7.5	925 [592, 1540] (n = 9)	1024 [370, 1530] (n = 14)	20990 [12867, 30150] (n = 9)	0.00 [0.00, 12.20] (n = 9)
≥50 kg	10	1020 [663, 1770] (n = 9)	1060 [339, 1450] (n = 15)	19450 [13653, 35158] (n = 9)	7.98 [0.00, 24.00] (n = 9)

Median [minimum, maximum]

Table 4. Plasma concentrations of macitentan and aprocitentan in patients with PAH aged <2 years[a] after multiple oral administration of macitentan

Analyte	Dose (mg)	2 hours after the first dose	5 hours after the first dose	24 hours after the first dose	Week 4[b]	Week 8[b]
Macitentan	2.5	54.3 [11.2, 177] (n = 8)	126 [90.4, 440] (n = 8)	90.7 [42.0, 195] (n = 7)	87.3 [0, 186] (n = 7)	90.8 [39.8, 274] (n = 6)
Aprocitentan	2.5	7.96 [0.00, 36.6] (n = 8)	31.3 [13.8, 106] (n = 8)	230 [130, 335] (n = 7)	766 [19.5, 1020] (n = 7)	722 [131, 1460] (n = 6)

ng/mL, Median [minimum, maximum]
a Aged 1.2 to 1.9 years
b Trough concentration

6.2.1.3 PPK analysis (CTD 5.3.3.5.1)

A population pharmacokinetic (PPK) analysis (NONMEM Version 7.3) was performed on data of plasma macitentan and aprocitentan concentrations at 520 sampling points obtained from 77 subjects including pediatric patients with PAH in Studies PAH3001 and AC-055-312 as well as adult patients with PAH in Study AC-055-303_PK.[2)]

The PK profile of macitentan was described by a 1-compartment model with first-order adsorption with a lag time as well as first-order elimination and metabolism into aprocitentan. The PK profile of aprocitentan was described by a 1-compartment model with generation of aprocitentan through metabolism of macitentan and first-order elimination. Effect of body weight on CL was included for patients weighing <25 kg but was not included for those weighing ≥25 kg because of no clear trend between CL of macitentan and body weight observed in this population. In patients aged <2 years, metabolic capacity remarkably increases as metabolic enzymes mature with age (*Clin Pharmacokinet.* 2014;53:625-36, etc.), thus effect of a maturing process of the metabolic enzymes on CL of macitentan and aprocitentan was included.

2) A PK sub-study that evaluated the PK profiles of macitentan and aprocitentan after the administration of macitentan 10 mg once daily in 20 eligible subjects who participated in Study AC-055-303, an extension study of the foreign phase III study of macitentan in patients with PAH (Study AC-055-302).

The analysis set included 25 men and 52 women made up of 38 Caucasians, 2 African Americans, 11 Hispanics, 12 Asians, and 14 patients of other races. The median body weight [minimum, maximum] was 45 kg [6.1, 125] and the median age was 12 years [1.17, 72].

Age, body weight, sex, and race were examined as potential covariates on PK parameters (V and CL), but none of them were selected as new covariates in the final PPK model.

The estimation of steady-state exposure to macitentan and aprocitentan in adult and pediatric patients with PAH was performed after multiple administration of macitentan in Studies PAH3001, AC-055-312, and AC-055-303_PK using the final PPK model. Table 5 shows the results.

Table 5. Estimated exposure to macitentan and aprocitentan in adult and pediatric patients with PAH at steady state after multiple administration of macitentan by the PPK analysis

Population			n	Dose (mg)	$AUC_{0\text{-}24h\ ss}$ (ng·h/mL)	
					Macitentan	Aprocitentan
Adult	≥18 years		20	10	6398 [3202, 14318]	19757 [10765, 39923]
Pediatric	Overall		57	2.5-10	5061 [1406, 8873]	20826 [4171, 40522]
	Aged ≥6 months[a] and <2 years		9	2.5	3588 [2131, 8390]	19090 [4171, 29721]
	Aged ≥2 years and <18 years	Weighing ≥10 kg and <15 kg	5	3.5	4127 [3746, 6321]	24465 [16629, 40522]
		Weighing ≥15 kg and <25 kg	11	5	4104 [2913, 6997]	18241 [12654, 25879]
		Weighing ≥25 kg and <50 kg	18	7.5[b]	5524.5 [1406, 8873]	17690 [11386, 32348]
		Weighing ≥50 kg	14	10	6036 [3169, 8753]	25127.5 [10720, 34977]

Median [minimum, maximum]
a 1.2 years
b One patient received 5 mg.

6.R Outline of the review conducted by PMDA

6.R.1 Differences in PK profile of macitentan or aprocitentan between Japanese and non-Japanese patients

The applicant's explanation about differences in the PK profiles of macitentan and aprocitentan between Japanese and non-Japanese pediatric patients with PAH:

The PK profiles of macitentan and aprocitentan showed no significant differences between Japanese and non-Japanese healthy adults who received macitentan 10 mg once daily (see the Review Report on Opsumit Tablet 10 mg, dated February 2, 2015). The PK of macitentan and aprocitentan was assessed for differences between Japanese and non-Japanese patients based on the results from the Japanese phase III study (Study PAH3001) and foreign phase III study (Study AC-055-312) in pediatric patients with PAH. Although the limited number of Japanese patients precluded thorough evaluation, the PK profiles showed similarity between Japanese and non-Japanese patients aged <2 years receiving macitentan 2.5 mg (Tables 2 and 4). Japanese patients aged ≥2 years receiving macitentan at a dose per body weight category tended to show PK values that were lower than in non-Japanese patients but largely fell within the range of PK values in non-Japanese patients, with no marked differences in the PK profiles between Japanese and non-Japanese children (Tables 1 and 3). Therefore, it is considered that there are no substantial differences in the PK profiles of macitentan and aprocitentan between Japanese and non-Japanese children.

PMDA's view:

The limited number of Japanese patients were subjected to the PK evaluation after the administration of macitentan, which prevented a definite conclusion on differences between Japanese and non-Japanese patients in the PK profiles of macitentan and aprocitentan. However, the currently available study results indicate no marked differences between Japanese and non-Japanese patients with PAH in the PK profiles of macitentan and aprocitentan.

6.R.2 Dosage regimen of macitentan

The applicant's explanation about the rationale for the proposed dosage and administration of macitentan in pediatric patients with PAH:

(a) Rationale for the dosage regimens in Japanese and foreign phase III studies in pediatric patients

The dosage regimen of macitentan for non-Japanese pediatric patients in Study AC-055-312 was determined aiming at exposure levels similar to those in adults treated with macitentan 10 mg once daily. For patients aged ≥2 years, exposure was investigated using the PPK model constructed with plasma macitentan concentrations in non-Japanese adult patients with PAH in Study AC-055-303, assuming that the correlation between the PK and efficacy/safety of macitentan is common to adults and children. The estimated exposure in pediatric patients aged ≥2 years receiving macitentan once-daily dose of 3.5, 5, 7.5, or 10 mg by body-weight category (≥10 kg and <15 kg, ≥15 kg and <25 kg, ≥25 kg and <50 kg, or ≥50 kg, respectively) was similar to that in adult patients. For patients aged <2 years, the steady state AUC was estimated after the administration of macitentan 0.5 to 3.5 mg based on the PPK model updated with the PK data from patients aged ≥2 years who had first been included in Study AC-055-312. The predicted exposure in patients aged <2 years receiving macitentan 1 or 2.5 mg by month-age category (aged <6 months or ≥6 months and <2 years, respectively) was similar to that in adult patients (Figure 1). Based on these outcomes, the dosage regimen of macitentan in Study AC-055-312 was determined as per Table 7 [see Section 7.1.1].

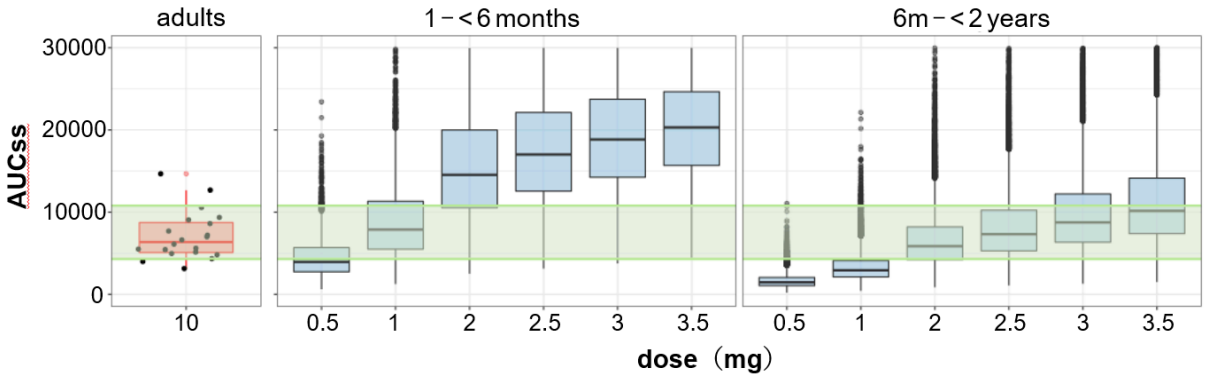

Figure 1. Estimated steady-state AUC of macitentan in pediatric patients aged <2 years receiving macitentan 0.5 to 3.5 mg

The dosage regimen of macitentan in Study PAH3001 in Japanese pediatric patients was determined in the same manner as in Study AC-055-312 based on the following findings: No significant differences were observed in the PK profiles of macitentan and aprocitentan between Japanese and non-Japanese healthy adults receiving macitentan 10 mg once daily; no marked differences were observed in efficacy and safety of macitentan between Japanese and non-Japanese adult patients with PAH (see the Review Report on Opsumit Tablet 10 mg, dated February 2, 2015).

(b) Rationale for the proposed dosage and administration of macitentan

The dosage regimen of macitentan in children was examined for validity based on $AUC_{u,combo\ ss}$ (combined unbound exposure parameter computed as the sum of macitentan and aprocitentan weighted by their unbound fraction and by their proportion of *in vitro* potency) according to different IC_{50} values of macitentan and aprocitentan against ET_A and ET_B receptors. The geometric mean ratios [90% CI] of $AUC_{u,combo\ ss}$ in pediatric patients to that in adult patients estimated by the PPK analysis were 0.94 [0.75, 1.18], 0.83 [0.7, 0.99], 0.87 [0.74, 1.03], and 1 [0.85, 1.17] in patients aged ≥2 years by body weight category (≥10 kg and <15 kg, ≥15 kg and <25 kg, ≥25 kg and <50 kg, and ≥50 kg, respectively). In contrast, the ratio was as low as 0.69 [0.57, 0.83] in patients aged ≥6 months and <2 years. The low value was attributable to the data of patients aged ≥6 months and <2 years used in the PPK analysis, of which 73% were from children aged ≥20 months. Nevertheless, $AUC_{u,combo\ ss}$ of patients with PAH aged ≥6 months and <2 years fell within a range of the exposure in patients with PAH aged ≥2 years, and thus did not differ markedly from the exposure of those aged ≥2 years. Although patients aged <6 months were not included in Study AC-055-312 or PAH3001, $AUC_{u,combo\ ss}$ was simulated by dose category using a virtual pediatric population and yielded the results shown in Figure 2. The predicted $AUC_{u,combo\ ss}$ of patients aged ≥3 months and <6 months after the administration of macitentan 1 mg did not differ markedly from those in the other age categories.

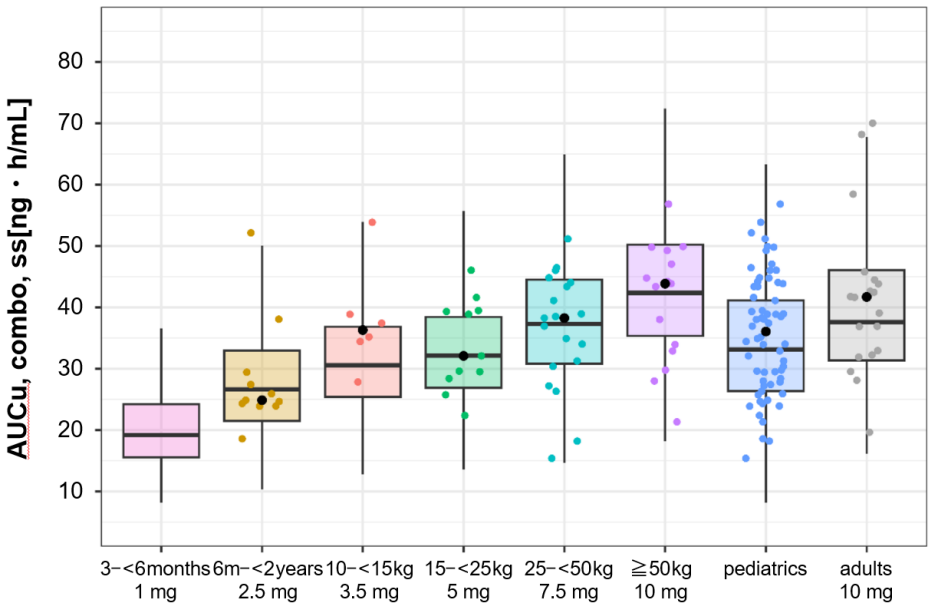

Figure 2. Simulation results of $AUC_{u,combo\ ss}$ by dose category

Based on the results in (a) and (b) above, the population to be treated with macitentan was determined as patients aged ≥3 months, and the dosage regimen in Study PAH3001 was adopted as the proposed dosage and administration of macitentan.

PMDA's view:

Despite limited data from pediatric patients treated with macitentan when Japanese and foreign phase III studies began in this population, the applicant determined the dosage regimen for each study based on available data, with doses according to age and body weight of children that were assumed to achieve exposure levels similar to that in adults. This approach is considered appropriate. The results of the

Japanese and foreign phase III studies showed similar exposure levels between patients aged ≥2 years treated with macitentan at a dose per body weight category and adult patients treated with macitentan 10 mg. The doses in patients aged ≥2 years are thus considered appropriate in terms of PK. On the other hand, the doses proposed for patients ≥3 months and <2 years are not considered appropriate from the view point of PK because the estimated exposure in patients aged ≥6 months and <2 years receiving macitentan 2.5 mg was lower than in adult patients and there are no actual exposure data from patients aged ≥3 months and <6 months or those aged ≥6 months and <1 year receiving macitentan in Studies PAH3001 or AC-055-312. Discussion will continue on the validity of the dosage regimen of macitentan for pediatric patients, taking account of the efficacy and safety results from Studies PAH3001 and AC-055-312 [see Section 7.R.6].

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

The applicant submitted the main evaluation data on efficacy and safety in the form of results from 2 studies presented in Table 6.

Table 6. Outline of main clinical studies

Data category	Region	Study code	Phase	Study population	n	Dosage regimen	Main endpoints
Evaluation	Japan	PAH3001	III	Patients with PAH aged ≥3 months and <15 years	7	Once-daily oral administration of macitentan at a dose as specified below: • Aged <6 months: 1 mg • Aged ≥6 months and <2 years: 2.5 mg • Aged ≥2 years: <15 kg, 3.5 mg ≥15 kg and <25 kg, 5 mg ≥25 kg and <50 kg, 7.5 mg ≥50 kg, 10 mg	Efficacy Safety PK
	Overseas	AC-055-312		Patients with PAH aged ≥1 month[a] and <18 years	157	Core period (before onset of disease progression event[c]) Standard of care group: 1 or 2 PAH-specific drugs (except for macitentan and PGI_2 injections) Macitentan group: Same as that in Study PAH3001	PK[b] Safety Efficacy

a "Aged ≥2 years" was revised to "aged ≥1 month" following the revision of the study protocol to version 9.0 on November 23, 2021.
b Initially planned as an event-driven study to evaluate the efficacy, safety, and PK of macitentan and changed to a study aiming to evaluate the PK, safety, and efficacy of macitentan following the revision of the study protocol to version 9.0 on November 23, 2021.
c After the onset of a disease progression event, treatment with a PAH-specific drug other than macitentan was allowed in the control group and a PAH -specific drugs other than ERA was allowed in the macitentan group.

7.1 Phase III study

7.1.1 Japanese phase III study (Study PAH3001; CTD 5.3.5.2.1; study period, November 2022 to March 2025)

An open-label, uncontrolled study was conducted at 6 study sites in Japan to evaluate the efficacy, safety, and PK of macitentan in patients with PAH aged ≥3 months and <15 years (target sample size, 6 subjects[3)]).

3) Assuming a geometric mean percent change in PVRI from baseline to Week 24, the primary endpoint, as 70% and the standard deviation of percent change in logarithmic PVRI as 0.5, the study success criterion (geometric mean percent change in PVRI ≤81.6%) would be achieved at the probability of 75.4% with the sample size of 5 determined based on feasibility investigation. In view of potential dropout, the target sample size was determined to be 6.

Eligible patients were children with PAH aged ≥3 months and <15 years meeting the following main inclusion criteria:

- Any of idiopathic pulmonary arterial hypertension (IPAH), heritable pulmonary arterial hypertension (HPAH), PAH associated with congenital heart disease (CHD),[4] drug- and toxin-induced PAH, PAH associated with human immunodeficiency virus (HIV) infection, and PAH associated with connective tissue disease, which are classified in Group 1 pulmonary hypertension (PH)
- The following criteria are met at prior right heart catheterization:
  - Mean pulmonary arterial pressure (mPAP), ≥25 mmHg
  - Pulmonary artery wedge pressure (PAWP), ≤15 mmHg
  - Pulmonary vascular resistance index (PVRI), >4 Wood Units·m^2

Patients received macitentan orally once daily for 52 weeks at a dose per age and body weight category as shown in Table 7.

Table 7. Dose by age and body weight category

Age/body weight		Dose
Aged <6 months		1 mg
Aged ≥6 months and <2 years		2.5 mg
Aged ≥2 years	<15 kg	3.5 mg
	≥15 kg and <25 kg	5 mg
	≥25 kg and <50 kg	7.5 mg
	≥50 kg	10 mg

Patients receiving a phosphodiesterase Type 5 (PDE-5) inhibitor were deemed eligible only if they were on a PDE-5 inhibitor regimen unchanged for ≥90 days prior to the screening right heart catheterization. The use of PAH-specific drugs other than PDE-5 inhibitors was allowed only for the treatment of progressing PAH.

All 7 patients enrolled received macitentan. All patients receiving macitentan were included in the safety and efficacy analysis sets. None of the patients discontinued macitentan.

The efficacy analysis set consisted of, by age category, 2 patients aged ≥6 months and <2 years and 5 patients aged ≥2 years and <15 years. Based on the clinical classification of PAH, 3 patients had IPAH and 4 patients had PAH associated with CHD. A total of 3 patients fell under the World Health Organization (WHO) Functional Class (FC) Class II[5] at baseline. A total of 6 patients used a concomitant pulmonary vasodilator (PDE-5 inhibitor) while 1 patient did not. The study drug was administered for the median of 361 days (range, 351-374).

[4] PAH associated with CHD unexplained by left-to-right shunt or that occurred after repair with no significant residual shunt (remaining or recurring ≥6 months after surgery) was eligible.

[5] Only 3 patients aged >4 years were subjected to classification.

Table 8 shows percent changes in PVRI from baseline to Week 24, the primary efficacy endpoint. The pre-determined success criterion (geometric mean percent change ≤81.6%[6)]) was achieved.

Table 8. Percent change in PVRI from baseline to Week 24 (efficacy analysis set)

	Measured value[a] (Wood Units·m^2)	Percent change from baseline[b] [2-sided 95% CI] (%)
Baseline (n = 7)	9.50 ± 5.431	59.43 [32.019, 110.303]
Week 24 (n = 7)	7.59 ± 7.086	

a Mean ± standard deviation (SD)
b Geometric mean

Table 9 shows adverse events occurring by the end of the study (Week 52).

Table 9. Adverse events (safety analysis set)

	Overall (n = 7)
All adverse events	100.0 (7)
Main adverse events[a]	
Nasopharyngitis	85.7 (6)
Pyrexia	57.1 (4)
Adenovirus infection	42.9 (3)
Streptococcal infection	42.9 (3)
Diarrhoea	42.9 (3)
Conjunctivitis	28.6 (2)
Abdominal pain	28.6 (2)
Conjunctivitis allergic	28.6 (2)
Arthropod bite	28.6 (2)

% (number of patients with the event)
a Events observed in ≥2 patients

Neither deaths nor adverse events leading to study drug discontinuation occurred. Serious adverse events occurred in 28.6% (2 of 7) of patients (metapneumovirus infection, bacteraemia, and pneumonia bacterial; and bronchitis in 1 patient each). A causal relationship to macitentan was ruled out for all these events.

7.1.2 Foreign phase III study (Study AC-055-312; CTD 5.3.5.1.1; study period; ongoing since October 2017; database locked in February 2024)

An open-label, randomized controlled study was conducted at 54 study sites outside Japan to evaluate the PK, safety, and efficacy of macitentan in comparison with the standard of care (SoC)[7)] in pediatric patients with PAH aged ≥1 month and <18 years (target sample size, approximately 200 subjects [<300 subjects][8)]).

6) A foreign phase III study of macitentan in adult patients with PAH (Study AC-055-302) demonstrated the superiority of macitentan 10 mg over placebo with respect to morbidity/mortality events and the correlation between percent changes in pulmonary vascular resistance (PVR) and morbidity/mortality events. In light of children's physiques varying greatly person to person, PVRI with body-surface-area-corrected PVR was more suitable for evaluation. In Study AC-055-302, a geometric mean percent change from baseline [2-sided 95% CI] in PVRI to Week 24 in the macitentan group was 71.4% [62.5%, 81.6%]. Furthermore, based on the results from a clinical study of sildenafil in pediatric patients with PAH (Study A1481131), a 20% decrease in PVRI was considered clinically meaningful. Based on these findings, a geometric mean percent change of ≤81.6% in PVRI at Week 24 of macitentan treatment in Study PAH3001 would be interpreted as clinically meaningful improvement, and was specified as the success criterion.

7) When the study began, the primary endpoint was the time to the first occurrence of a disease progression event. However, patient enrollment delayed due to the coronavirus disease 2019 (COVID-19) pandemic and for other reasons, and disease progression events occurred less frequently than assumed at the time of study planning. This led to the anticipation that the study period would have to be prolonged to collect the necessary number of events. After discussion with regulatory authorities of the participating countries, the primary endpoint was changed to steady-state plasma trough concentrations of macitentan and its active metabolite, following the revision of the study protocol to version 9.0 on November 23, 2021. Accordingly, the initially planned event-driven study to evaluate the efficacy, safety, and PK of macitentan was changed to a study to evaluate the PK, safety, and efficacy of macitentan.

8) It was specified in view of study feasibility. The initial target sample size was approximately 300 subjects (necessary number of events, 187).

The study consisted of a screening period, a core period for PK and safety evaluation in the macitentan and SoC groups, an extension period, and a safety follow-up period. The core period continued until the onset of a disease progression event[9] or the end date determined by the sponsor, whichever came first. This section describes results up to the end of the core period (database locked on February 28, 2024) submitted with the present application.

Patients with PAH aged ≥1 month and <18 years and weighing ≥3.5 kg[10] meeting the following main inclusion criteria were eligible:

- IPAH, HPAH, PAH associated with CHD,[4] drug/toxin-induced PAH, PAH associated with HIV infection, or PAH associated with connective tissue disease, which are included in Group 1 of the clinical classification of PH.
- WHO FC Class I, II, or III
- The following criteria were met at prior right heart catheterization.
  - mPAP, ≥25 mmHg
  - PAWP, left atrial pressure (LAP),[11] or left ventricular end diastolic pressure (LVEDP);[11] ≤15 mmHg
  - PVRI, >3 Wood Units·m^2

The study enrolled patients who were naïve to PAH treatment or receiving a monotherapy or combination therapy with up to 2 PAH-specific drugs other than macitentan and prostaglandin I_2 (PGI_2) injections. Of note, patients aged <2 years who had previously received macitentan were also deemed eligible.

Patients aged ≥2 years enrolled were randomized and assigned in a 1:1 ratio to the SoC or macitentan group. The randomization was stratified by ongoing/planned ERA treatment (yes vs no) and WHO FC (I/II vs III) at baseline.[12] All of patients aged <2 years were assigned to the macitentan group.

During the core period, the SoC[13] group received the study drug prescribed by the investigator individually before randomization, and the macitentan group received the study drug as per Table 7.

In patients aged ≥2 years, only PDE-5 inhibitors being used at the time of randomization were allowed for concomitant use. In patients aged <2 years, continuous use of concomitant oral or inhaled PGI_2 preparations was also allowed.

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9) Any of the following conditions determined by the blinded clinical event committee (CEC): (a) All-cause death, (b) atrial septostomy or Potts' anastomosis, or registration on the lung transplant list, (c) hospitalization due to worsening of PAH, or (d) clinical worsening of PAH (requiring or having started PAH-specific drugs, intravenous diuretics, or continuous oxygen use, and having at least one of the following conditions; worsening of WHO FC, new occurrence or worsening of syncope, new occurrence or worsening of at least 2 PAH symptoms, or new occurrence or worsening of signs of right heart failure not responding to oral diuretics).

10) The lower limits of age and body weight at randomization were changed from aged "≥2 years" to "≥1 month" and from "≥10 kg" to "≥3.5 kg," respectively, following the revision of the study protocol to version 9.0 on November 23, 2021.

11) The use of LAP was allowed for patients free from a pulmonary veno-occlusive disease or a serious lung disease, and the use of LVEDP was allowed if these patients were also free from mitral stenosis.

12) Assignment to the SoC group was controlled so that patients receiving ERA accounted for ≤40% of all randomized patients.

13) The SoC consisted of PAH-specific monotherapy or combination therapy with 2 drugs other than macitentan and PGI_2 injections.

When a disease progression event occurred, the use of PAH-specific drugs other than ERA was allowed in the macitentan group, and PAH-specific drugs other than macitentan were allowed for use in the SoC group. In addition, switching the PAH-specific drug from SoC to macitentan was also allowed when the investigator considered it appropriate.

In this study, 3 database lock timepoints were predetermined in view of regulatory requirements in the participating countries. The second database lock was implemented when all patients completed the core period (February 28, 2024). Based on the results up to this timepoint, the approval application was submitted in Japan. Results up to the second database lock timepoint are as follows.

(a) Patients aged ≥2 years

Of randomized 148 patients (75 in the SoC group and 73 in the macitentan group), 147 patients (75 and 72) received the study drug and were included in the safety analysis set. All the randomized patients were included in the full analysis set (FAS) 1, which also served as the primary efficacy analysis set. During the core period, 48 patients (31 and 17) discontinued the study drug primarily because of inadequate response in 15 patients (14 and 1), deaths in 8 patients (2 and 6), and adverse events in 5 patients (3 and 2).

FAS1 consisted of 35 patients (22 in the SoC group and 13 in the macitentan group) in the age category of ≥2 years and <6 years, 61 patients (32 and 29) in ≥6 years and <12 years, and 52 patients (21 and 31) in ≥12 years and <18 years. By clinical classification of PAH, 71 patients (36 and 35) had IPAH, 6 patients (5 and 1) had HPAH, and 68 patients (32 and 36) had PAH associated with CHD. By baseline WHO FC, 37 patients (18 and 19) were in Class I, 83 patients (42 and 41) in Class II, and 28 patients (15 and 13) in Class III. The SoC and macitentan groups, respectively, received the study drug for the median of 115 weeks (range, 0.1-316.4) and 168.4 weeks (range, 12.9-312.4).

The efficacy was investigated based on the number of the first disease progression event[9)] during the core period, which was 24 in the SoC group and 21 in the macitentan group. The hazard ratio[14)] in the macitentan group for time to the first disease progression event against that in the SoC group [2-sided 95% CI] was 0.828 [0.460, 1.492].

Table 10 shows adverse events occurring in ≥10% of patients in either group during the period from the randomization (Visit 2) within 30 days after the completion of study treatment or the end date of the core period, whichever came first.[15)]

[14)] A cox proportional hazards model adjusting the stratification factors at randomization (ongoing or planned ERA treatment and WHO FC).
[15)] In patients who switched from SoC to macitentan, the period was determined as until the first dose of macitentan or 30 days after the completion of SoC, whichever came first.

Table 10. Adverse events observed in ≥10% of patients in either group (safety analysis set, aged ≥2 years)

	SoC (n = 75)	Macitentan (n = 72)
All adverse events	68.0 (51)	93.1 (67)
Main events		
Upper respiratory tract infection	16.0 (12)	31.9 (23)
Nasopharyngitis	14.7 (11)	19.4 (14)
Headache	12.0 (9)	19.4 (14)
COVID-19	6.7 (5)	15.3 (11)
Gastroenteritis	1.3 (1)	11.1 (8)
Influenza	4.0 (3)	11.1 (8)
Epistaxis	10.7 (8)	6.9 (5)
Vomiting	10.7 (8)	6.9 (5)

% (number of patients with the event)

Death occurred in 8.0% (6 of 75) of patients in the SoC group (death due to disease progression in 4 patients, and COVID-19 pneumonia and sudden death in 1 patient each) and 9.7% (7 of 72) of patients in the macitentan group (death due to disease progression in 6 patients and right cardiac failure in 1 patient). None of these deaths were causally related to macitentan. Serious adverse events occurred in 21.3% (16 of 75) of patients in the SoC group and 36.1% (26 of 72) of patients in the macitentan group. Serious adverse events observed in ≥2 patients in the macitentan group were pneumonia (5 patients), anaemia, gastritis, and non-cardiac chest pain (2 patients each). A causal relationship to the study drug could not be ruled out for anaemia in 1 patient. Macitentan was discontinued, and the event resolved. Adverse events leading to the discontinuation of the study drug occurred in 2 patients in the SoC group (cardiac arrest and eye swelling/ocular hyperaemia/abdominal pain upper/ faeces discoloured/vomiting in 1 patient each) and 4 patients in the macitentan group (alanine aminotransferase [ALT] increased, anaemia, headache, and transaminases increased in 1 patient each). A causal relationship to the study drug could not be ruled out for all events in the macitentan group.

(b) Patients aged <2 years

All 9 enrolled patients received macitentan and were included in the safety analysis set and FAS2 that also served as the primary efficacy analysis set. During the core period, 1 patient discontinued the study (consent withdrawal).

All 9 patients were in the age category of ≥6 months and <2 years. By clinical classification of PAH, 4 patients had IPAH and 5 patients PAH associated with CHD. At baseline, 5 patients were with WHO FC Class I while 4 patients were with Class II. The median duration of treatment with the study drug was 37.1 weeks (range, 7.0-72.9).

Efficacy analyses revealed no disease progression events,[9)] hospitalization due to PAH, or all-cause death occurring during the study period.

According to the safety analyses, adverse events occurred in 7 patients (77.8%) during the period from Visit 2 up to either 30 days after study treatment completion or the end date of the core period, whichever came first. Adverse events observed in ≥2 patients were upper respiratory tract infection (4 patients), gastroenteritis (3 patients), and COVID-19 and pneumonia (2 patients each). Neither deaths nor adverse events leading to the discontinuation of the study drug occurred. Serious adverse events occurred in 44.4% (4 of 9) of patients (pneumonia/haematemesis, pneumonia, gastroenteritis/Salmonella

bacteraemia/constipation, and influenza in 1 patient each), and a causal relationship to macitentan was ruled out for all these events.

7.R Outline of the review conducted by PMDA

7.R.1 Development plan

The applicant's explanation about the development plan of macitentan targeting Japanese pediatric patients with PAH:

When the product development was in its planning phase in Japan, the foreign phase III study (Study AC-055-312) was underway in pediatric patients. In Japan, however, there were limited pediatric patients eligible for the clinical study due to the rareness of prevalent patients and common practice of off-label use of macitentan in pediatric patients. In Study AC-055-312, the region or country of participants was not a stratification factor. Thus Japanese pediatric patients, even if participated, would have had only a small chance to be randomized to receive macitentan and yielded only limited efficacy and safety data of macitentan.

Therefore, the applicant decided to conduct a Japanese phase III study (Study PAH3001) separately to verify the similarity of the results to the Japanese phase II/III study in Japanese adult patients with PAH (Study AC-055-307) and further evaluate the efficacy and safety of macitentan in Japanese pediatric patients with PAH utilizing the results from Study AC-055-307. This strategy is justifiable by the following reasons:

- Study PAH3001, although an open-label uncontrolled study, was designed to evaluate the efficacy of macitentan with the primary endpoint of percent change from baseline in PVRI as the objective efficacy measure, and with the success criterion that is considered clinically meaningful [see Section 7.1.1].
- Pulmonary hemodynamic parameters such as PVRI, mPAP, and cardiac index are the key factors in prognostic evaluation of pediatric patients with PAH in and outside Japan (Guidelines for Treatment of Pulmonary Hypertension [JCS 2017/JPCPHS 2017], guidelines in the EU[16)]). A clinical study in adult patients with PAH suggested a correlation between PVRI and morbidity/mortality events (*N Engl J Med.* 2013;369:809-18).
- Diagnostic criteria, clinical classification, and treatment algorithm for PAH are generally similar between pediatric and adult patients (Guidelines for Treatment of Pulmonary Hypertension [JCS 2017/JPCPHS 2017]).

PMDA accepted the applicant's explanation. When similarity is confirmed between the results from Study PAH3001 and Study AC-055-307, it is possible to evaluate the efficacy and safety of macitentan in Japanese pediatric patients with PAH by utilizing the results from Study AC-055-307.

7.R.2 Efficacy

The applicant's explanation about the efficacy of macitentan:

The percent change in PVRI from baseline to Week 24, the primary endpoint in Study PAH3001, met the pre-determined success criterion [see Section 7.1.1]. In addition, Week 24 pulmonary hemodynamic

16) Paediatric addendum to CHMP guideline on the clinical investigations of medicinal products for the treatment of pulmonary arterial hypertension. EMA/CHMP/213972/2010

parameters in individual patients tended to improve, and all 3 patients with evaluable WHO FC maintained their baseline FC (Table 11). These results suggest the efficacy of macitentan in Japanese pediatric patients with PAH.

Table 11. Results in individual patients in Study PAH3001 (efficacy analysis set)

		Case 1	Case 2	Case 3	Case 4	Case 5	Case 6	Case 7
Patient characteristics	Sex	Male	Female	Female	Male	Male	Male	Female
	Clinical classification of PAH	IPAH	PAH associated with CHD	PAH associated with CHD	PAH associated with CHD	IPAH	PAH associated with CHD	IPAH
	Age	11 years	30 months	3 years	21 months	13 years	22 months	9 years
	Body weight	Category 3*	Category 1*	Category 1*	Category 1*	Category 4*	Category 1*	Category 2*
Concomitant pulmonary vasodilator		Tadalafil	Tadalafil	Tadalafil	Tadalafil	Tadalafil	No	Tadalafil
PVRI (Wood Units·m^2)								
Baseline		17.7	4.9	4.5	5.3	15	6.7	12.3
Week 24		20.6	1.5	4.9	2.7[a]	10	1.3	12.1
mPAP (mmHg)								
Baseline		68	25	36	30	50	42	67
Week 24		83	17	36	22[a]	37	21	46
Cardiac index (L/min/m^2)								
Baseline		3.5	3.9	5.1	4.3	2.8	4.6	4.7
Week 24		3.6	5.2	3.7	4.8[a]	2.9	5.2	3.3
WHO FC[b]								
Baseline		II	-	-	-	II	-	II
Week 24		II	-	-	-	II	-	II

a Right heart catheterization at Week 24 was postponed to Week 40 due to pyrexia associated with a complication (upper respiratory tract inflammation).
b Assessed only in patients aged >4 years

There were no clear differences in patient characteristics between pediatric patients in Study PAH3001 and adult patients in Study AC-055-307 that could potentially affect efficacy evaluation (Table 12). The percent change from baseline in PVRI at Week 24 in Study PAH3001 (the geometric mean [2-sided 95% CI], 59.43% [32.019%, 110.303%]) was comparable to the results (the geometric mean [2-sided 95% CI], 60.6% [52.5%, 70.1%]) of 28 patients treated with macitentan in Study AC-055-307, indicating similar levels of efficacy of macitentan expected in Japanese pediatric patients with PAH to that in Japanese adult patients with PAH:

* For the provision of new drug approval information, body weights have been replaced with the following weight categories: Category 1, <15 kg; Category 2, ≥15 kg and <25 kg; Category 3, ≥25 kg and <50 kg; and Category 4, ≥50 kg.

Table 12. Distribution of patient characteristics in Studies PAH3001 and AC-055-307 (efficacy analysis set)

		Pediatric	Adult
		Study PAH3001 (n = 7[a])	Study AC-055-307 (n = 28[a])
Sex	Male	57.1 (4)	14.3 (4)
	Female	42.9 (3)	85.7 (24)
Baseline PVRI (Wood Units·m^2)		9.50 ± 5.431[b] 6.74 [4.5, 17.7][c]	12.80 ± 5.763[b] 11.98 [5.9, 26.6][c]
Baseline mPAP (mmHg)		45.4 ± 17.09[b] 42.0 [25, 68][c]	38 ± 10[b] 36 [25, 56][c]
Clinical classification of PAH	IPAH	42.9 (3)	39.3 (11)
	HPAH	0 (0)	3.6 (1)
	PAH associated with CHD	57.1 (4)	7.1 (2)
	PAH associated with connective tissue disease	0 (0)	50.0 (14)
WHO FC[d]	I	0 (0)	3.6 (1)
	II	100 (3)	57.1 (16)
	III	0 (0)	39.3 (11)
	IV	0 (0)	0 (0)
Status of concomitant use of PAH-specific drug	Yes	85.7 (6)	64.3 (18)
	No	24.3 (1)	35.7 (10)

% (number of patients with the event)
a Served as the efficacy analysis set in Study PAH3001 and the per protocol set (PPS) in Study AC-055-307.
b Mean ± SD
c Median [minimum, maximum]
d Assessed only in 3 patients aged >4 years in Study PAH3001.

PMDA's view:

According to the results of hemodynamic parameters (PVRI and mPAP) of individual patients in Study PAH3001, 4 of 7 patients showed adequate decreases in PVRI and mPAP while 2 patients had unchanged PVRI (1 patient with decreased mPAP and the other with unchanged mPAP) and 1 patient had increased PVRI and mPAP. Based on these outcomes of hemodynamics after the treatment with macitentan, it is considered that 4 patients responded to macitentan while 1 patient did not, and 2 patients showed no change. Overall, the data including the primary endpoint results are suggestive of the efficacy of macitentan in Japanese pediatric patients with PAH. The degree of declines in PVRI observed in Study PAH3001 was considered comparable to that in Study AC-055-307 in Japanese adult patients with PAH. Therefore, macitentan is expected to have efficacy in pediatric patients with PAH as it is in adult patients with PAH.

7.R.3 Safety

The applicant's explanation about differences in the safety profile of macitentan between adult and pediatric patients with PAH:

Table 13 shows adverse events that occurred in Studies PAH3001 and AC-055-312. All were known events in adults. Although infections tended to occur at high incidences in children compared to adults, this tendency is not considered a critical safety concern in pediatric patients because a causal relationship to macitentan was ruled out for all relevant events and, generally, infections are reported to be more prevalent in children (*Epidemiol Infect*. 2014;142:1355-61).

Table 13. Adverse events in Japanese and foreign clinical studies in pediatric and adult patients with PAH (safety analysis set)

	Pediatric			Adult	
	Foreign		Japan	Foreign	Japan
	Study AC-055-312[b] (aged ≥2 years) (n = 72)	Study AC-055-312[b] (aged <2 years) (n = 9)	Study PAH3001[c] (n = 7)	Study AC-055-302[b] (n = 242[d])	Study AC-055-307[c] (n = 30)
All adverse events	93.1 (67)	77.8 (7)	100 (7)	94.6 (229)	96.7 (29)
Adverse events leading to death	0 (0)	0 (0)	0 (0)	6.6 (16)	3.3 (1)
Serious adverse events	36.1 (26)	44.4 (4)	28.6 (2)	45.0 (109)	23.3 (7)
Adverse events leading to treatment discontinuation	5.6 (4)	0 (0)	0 (0)	10.7 (26)	3.3 (1)
Main adverse events[a]					
Upper respiratory tract infection	31.9 (20)	44.4 (4)	14.3 (1)	15.3 (37)	3.3 (1)
Nasopharyngitis	19.4 (14)	0 (0)	85.7 (6)	14.0 (34)	43.3 (13)
Headache	19.4 (14)	0 (0)	0 (0)	13.6 (33)	43.3 (13)
COVID-19	15.3 (11)	22.2 (2)	0 (0)	0 (0)	0 (0)
Gastroenteritis	11.1 (8)	33.3 (3)	0 (0)	3.3 (8)	3.3 (1)
Diarrhoea	9.7 (7)	0 (0)	42.9 (3)	9.1 (22)	26.7 (8)
Pyrexia	9.7 (7)	11.1 (1)	57.1 (4)	3.7 (9)	6.7 (2)
Abdominal pain	6.9 (5)	0 (0)	28.6 (2)	2.9 (7)	0 (0)
Pneumonia	6.9 (5)	22.2 (2)	14.3 (1)	4.1 (10)	0 (0)
Arthropod bite	4.2 (3)	0 (0)	28.6 (2)	0.4 (1)	0 (0)
Conjunctivitis	2.8 (2)	11.1 (1)	28.6 (2)	2.5 (6)	0 (0)
Conjunctivitis allergic	1.4 (1)	0 (0)	28.6 (2)	0.4 (1)	0 (0)
Adenovirus infection	0 (0)	0 (0)	42.9 (3)	0 (0)	0 (0)
Streptococcal infection	0 (0)	0 (0)	42.9 (3)	0 (0)	0 (0)

% (number of patients with the event)

a Events observed in ≥15% of patients in either study in pediatric patients with PAH

b Median duration of macitentan treatment (range) was 168.4 weeks (12.9-312.4) in Study AC-055-312 and 118.4 weeks (0.3-188.0) in Study AC-055-302.

c At Week 52

d Macitentan 10 mg group

The occurrence of adverse events characteristic of macitentan, i.e., "events related to anemia/decreased hemoglobin,"[17] "events related to decreased blood pressure,"[18] and "events related to hepatic dysfunction"[19] did not tend to differ markedly between pediatric and adult patients.

Furthermore, the safety database owned by the applicant (from October 18, 2013 to October 17, 2022) shows that 417 pediatric patients aged ≥2 years and <12 years and 172 pediatric patients aged <2 years received macitentan in Japan or other countries, and no new safety concerns have been raised among these patients.

Based on the above, the applicant considers that safety of macitentan does not clearly differ between pediatric and adult patients.

17) Events falling under the Standardised MedDRA queries (SMQ) in the medical dictionary for regulatory activities (MedDRA) of "Haematopoietic erythropenia" or "Haematopoietic cytopenias affecting more than one type of blood cell" or the MedDRA preferred term (PT) of "Anaemia" (except for events falling under a MedDRA PT of "Blood disorder")

18) Events falling under the MedDRA PTs of "Blood pressure ambulatory decreased," "Blood pressure decreased," "Blood pressure diastolic decreased," "Blood pressure immeasurable," "Blood pressure orthostatic decreased," "Blood pressure systolic decreased," "Blood pressure systolic inspiratory decreased," "CT hypotension complex," "Diastolic hypotension," "Dialysis hypotension," "Hypotension," "Hypotensive crisis," "Mean arterial pressure decreased," "Neonatal hypotension," "Orthostatic hypotension," "Post procedural hypotension," or "Procedural hypotension"

19) Events falling under the MedDRA SMQ of "Hepatic disorders" (except for events falling under the MedDRA SMQ of "Liver-related coagulation and bleeding disturbances" or the MedDRA PTs of "Ascites," "Bacterascites," "Biliary ascites," or "Haemorrhagic ascites")

PMDA's view:
In view of the occurrence of adverse events in Japanese and foreign clinical studies of macitentan and post-marketing safety information in pediatric use of macitentan in and outside Japan, currently there is no tendency toward increasing safety concerns in pediatric patients with PAH compared to adult patients. However, macitentan should be prescribed for pediatric patients by physicians with adequate knowledge and experience in treatment of PAH, in light of the extremely limited number of patients evaluated in the clinical studies, longer durations of treatment with macitentan expected in pediatric patients with PAH than in adults, and a decision warranting careful consideration on the concomitant use of macitentan with the other PAH-specific drugs for pediatric patients with PAH. The "Precautions Concerning Indication" section should provide a cautionary note that the use of macitentan should be considered only for patients deemed eligible, under the direction of a physician with adequate knowledge and experience in treatment of pulmonary arterial hypertension in children.

7.R.4 Clinical positioning

The applicant's explanation about the clinical positioning of macitentan:
Treatment strategies for pediatric PAH were determined with reference to the treatment algorithm for adults. The initial combination therapy uses multiple pulmonary vasodilators each acting through different mechanisms (including ERA). According to the Japanese clinical practice guideline, all recommended ERAs as PAH-specific drugs for pediatric use are Class IIa[20)] with the Level of evidence C[21)] as is the case for adults (Guideline on the Management of Pulmonary Thromboembolism, Deep Venous Thrombosis, and Pulmonary Hypertension [JCS/JPCPHS 2025]). Ambrisentan was approved only for patients aged ≥8 years. Bosentan, approved for patients aged ≥1 year, has been reported to have potential risk of hepatotoxicity and interact with concomitant drugs that are essential in treatment of PAH (e.g., sildenafil, warfarin) (*Heart.* 2016;102:ii67-85). In contrast, macitentan reduced the risk of morbidity/mortality events and is suggested to have less impact on liver functions than bosentan in the clinical studies in adult patients with PAH. According to the Medical Data Vision database (as of November 2022), macitentan accounted for approximately 70% of ERAs administered to patients aged <15 years.

The efficacy and safety of macitentan have been further confirmed in Study PAH3001. Thus, macitentan will be an option in ERAs for the initial combination therapy in the treatment of pediatric PAH as it is in adult PAH.

PMDA's view:
The applicant explains that macitentan will be an option in ERAs for the initial combination therapy in the treatment of pediatric PAH as it is in adult PAH, which is acceptable. Also, macitentan is useful in view of its dosage form suitable for pediatric use.

20) Highly likely to be effective or useful based on evidence and opinions.
21) Consensus reached among experts and/or in small-scale clinical research (including retrospective and registry-based studies).

7.R.5 Intended population

The applicant's explanation:

The applicant proposed pediatric patients with PAH as the intended population to be treated with macitentan at the new dosages, irrespective of WHO FC or clinical classification of PAH, including those who were not enrolled in Study PAH3001.

The results from Study PAH3001, etc. indicates that macitentan is expected to be efficacious and safe in pediatric patients with PAH as it is in adult patients [see Sections 7.R.2 and 7.R.3]. In addition, the Guideline on the Management of Pulmonary Thromboembolism, Deep Venous Thrombosis, and Pulmonary Hypertension (JCS/JPCPHS 2025) recommends initial combination therapies with an ERA and a PDE-5 inhibitor for low risk patients including those with WHO FC I and the use of macitentan for adult and pediatric patients with PAH, irrespective of the clinical classification of PAH. Given this, it is appropriate to provide macitentan to pediatric patients with PAH as a treatment option, irrespective of WHO FC and clinical classification of PAH, as practiced for adult patients. The current package insert offers a cautionary note that the efficacy and safety in adult patients with WHO FC I have not been established because only 2 patients in this category were included in the Japanese or foreign clinical studies in adults with PAH. In view of the descriptions in the above-mentioned Japanese clinical practice guideline, etc., however, another cautionary note for pediatric use is considered unnecessary.

PMDA's view:

It is difficult to evaluate the efficacy and safety of macitentan at the new dosages based on WHO FC or clinical classification of PAH due to the limited number of patients participated to the clinical studies submitted. However, PAH is a refractory and progressive disease for which an early start of an aggressive combination therapy with drugs acting through different mechanisms is recommended as for adult patients. WHO FC can vary by treatment or pathological condition, and the Japanese clinical practice guideline does not advise treatment for children based on clinical classification of PAH. Therefore, it is possible to define the target population of the new dosages of macitentan as pediatric patients with PAH, irrespective of WHO FC or clinical classification of PAH, with a note that its efficacy and safety have not been established in patients with WHO FC I as well as in adult patients:

Based on the above, the package insert should provide the following notes in the "Precautions Concerning Indication" section. The information about WHO FC and clinical classification of PAH for pediatric patients participated in the clinical studies should also be given through the package insert, etc.

Precautions Concerning Indication (excerpt of the precautions relating to this application)

- The efficacy and safety have not been established in patients with WHO FC I.
- The use of macitentan should be considered only for patients deemed eligible under the direction of a physician with adequate knowledge and experience in treatment of pulmonary arterial hypertension in children.
- Before using macitentan, the necessity of the treatment should be determined with reference to the latest treatment guidelines, etc. and based on a full understanding of the information provided in the "17. Clinical Studies" section and of the characteristics of patients included in the clinical studies (e.g., clinical classification of PAH, WHO FC, and age).

7.R.6 Dosage and administration

The applicant's explanation about the proposed dosage and administration of macitentan in pediatric patients with PAH:

Study PAH3001, for which the dosage regimen was determined to achieve an exposure level similar to that in adult patients, demonstrated promising efficacy and safety in pediatric patients as well as in adults. Therefore, the proposed dosage and administration in pediatric patients aged ≥3 months should be defined as per Study PAH3001.

In light of the extremely limited number of pediatric patients aged ≥1 year and <2 years as well as the absence of patients aged <1 year in Studies PAH3001 and AC-055-312, PMDA asked the applicant to justify the dosage regimen for pediatric patients aged ≥3 months and <2 years proposed as per Study PAH3001.

The applicant's explanation:

Studies PAH3001 and AC-055-312 aimed to enroll pediatric patients with PAH aged ≥3 months and those aged ≥1 month, respectively, as eligible population. However, no pediatric patients aged <1 year were enrolled, and there were few patients aged ≥1 year and <2 years enrolled. This resulted from the facts that many cases of PAH in low age patients are associated with CHD, and in these studies, the inclusion of patients with PAH associated with repaired CHD was limited to those who had had the surgery at least 6 months ago [see the note 4] from a viewpoint of efficacy and safety evaluation of macitentan.

However, among patients with PAH associated with CHD, those with moderate pulmonary hypertension who were conventionally on the borderline for surgical indication or assessed as ineligible for surgery can be eligible after a preoperative combination therapy with pulmonary vasodilators started early (*J Heart Lung Transplant.* 2019;38:879-901, etc.). Furthermore, because PAH may persist postoperatively, the administration of pulmonary vasodilators begins immediately after the surgery (JCS 2022 Guideline on Management and Re-Interventional Therapy in Patients with Congenital Heart Disease Long-Term after Initial Repair). Thus, there is a need for pulmonary vasodilators in pediatric patients aged ≥3 months in clinical practice. According to a specified use-results survey implemented after the approval of macitentan, the safety analysis set of 4100 patients included 204 children (aged ≥7 years and <15 years), 230 infants (aged ≥1 year and <7 years), and 171 neonates and suckling infants (aged <1 year). Therefore, many pediatric cardiologists are presumed be keen on using macitentan to treat pediatric patients with PAH including those aged <1 year.

Accordingly, dosage and administration were further reviewed as detailed (a) to (c) below, utilizing the results from the specified use-results survey.

(a) Aged ≥1 year and <2 years

Study PAH3001 included 2 Japanese pediatric patients aged ≥1 year and <2 years (Cases 4 and 6 in Table 11, treated with macitentan for 52 weeks). During the study, they received macitentan and concomitant drugs without any dosage regimen change that could potentially affect efficacy and safety evaluation of macitentan. These 2 patients showed improved pulmonary hemodynamic parameters

including PVRI at Week 24 or 40, while the severity of PAH remained unchanged in both patients throughout the study period. A serious adverse event (bronchitis) occurred in 1 of the 2 patients, but its causal relationship to macitentan was ruled out and the event resolved during macitentan treatment.

Study AC-055-312 included 9 non-Japanese patients aged ≥1 year and <2 years (range, 14-23 months of age; median duration of macitentan treatment [range], 37.14 weeks [7.0-72.9]). They received macitentan and concomitant drugs without any dosage regimen changes that could potentially affect efficacy and safety evaluation of macitentan. During the study period, clinical event committee (CEC)-confirmed disease progression events, hospitalization due to PAH, or all-cause deaths (including death due to PAH) were not reported from these 9 patients. No worsening of WHO FC was observed during the study period. Of 4 patients with baseline WHO FC II, 1 patient achieved improvement to WHO FC I at Week 24 and maintained the improved condition until the final evaluation. In 4 of the 9 patients, serious adverse events (pneumonia in 2 patients, and gastroenteritis, influenza, Salmonella bacteraemia, constipation, and haematemesis in 1 patient each) occurred. A causal relationship to macitentan was ruled out for all events, which resolved during macitentan treatment.

The specified use-results survey involved 64 pediatric patients aged ≥1 year and <2 years. Of these, 8 patients who did not receive other pulmonary vasodilators during macitentan treatment were selected for the efficacy and safety evaluation of macitentan. All 8 patients had PAH associated with CHD. A total of 2 patients received macitentan at doses (2-3 mg) around the proposed dose (2.5 mg) and 6 patients at doses <2 mg. In a total of 7 patients eligible for efficacy evaluation (receiving macitentan at doses <2 mg or around the proposed dose), mPAP or WHO FC improved in 3 patients and showed no change in 4 patients. The safety analysis revealed no adverse events occurring in the 8 patients selected.

(b) Aged ≥6 months and <1 year

Although Studies PAH3001 and AC-055-312 included no pediatric patients with PAH aged ≥6 months and <1 year, the specified use-results survey involved 59 patients in this age category. Of these, 3 patients who did not receive other pulmonary vasodilators during macitentan treatment and were eligible for efficacy evaluation (all receiving macitentan at doses <2 mg) were selected for the WHO FC-based assessment, which showed improvement in all 3 patients. The safety evaluation involving 5 patients including these 3 patients and 2 patients receiving macitentan at doses (2-3 mg) around the proposed dose (2.5 mg) revealed a death of 1 patient due to serious adverse events (pulmonary congestion and pulmonary hypertension), but a causal relationship to macitentan was ruled out for pulmonary congestion and pulmonary hypertension. No adverse events occurred in the other 4 patients.

(c) Aged ≥3 months and <6 months

Although Studies PAH3001 and AC-055-312 included no patients with PAH aged ≥3 months and <6 months, the specified use-results survey involved 48 patients in this age category. Of these, 6 patients did not receive other pulmonary vasodilators during macitentan treatment and were eligible for efficacy evaluation (receiving macitentan at doses [0.8-1.2 mg] around the proposed dose [1.0 mg] or <0.8 mg). A total of 4 patients showed improvement in mPAP and/or WHO FC, while 1 patient each showed no change and no improvement. The safety evaluation involved 10 patients including these 6 patients and 4 patients receiving macitentan at a dose higher than the proposed dose (1.2 mg) and revealed adverse

events occurring in 2 patients. Both events were reported as serious (portal shunt procedure and normochromic normocytic anaemia in 1 patient each). A causal relationship to macitentan could not be ruled out for normochromic normocytic anaemia, but both events were reported as resolved.

In addition to the results from Studies PAH3001 and AC-055-312 as well as the specified use-results survey that yielded the following observations, post-marketing information in Japan and from abroad (from October 2013 to October 2022) about 10 patients aged ≥6 months and <2 years and 5 patients aged <6 months treated with macitentan 10 mg, a dose higher than proposed, indicated no additional safety concerns. Therefore, also taking account of no new development plan for macitentan targeting patients with PAH aged <2 years in and outside Japan, it is appropriate to adopt the dosage regimen used in Study PAH3001 for patients aged ≥3 months and <2 years.

- Macitentan demonstrated improved pulmonary hemodynamics in patients aged ≥1 year and <2 years similar to that in those aged ≥2 years, with no clear difference in safety.
- According to the specified use-results survey, pulmonary hemodynamics and/or WHO FC improved in some patients aged ≥3 months and <2 years receiving macitentan alone at a dose similar to or lower than proposed, and no new safety concerns have been raised in this age group including patients receiving macitentan at a dose higher than proposed.

PMDA's view:

Because Study PAH3001 yielded the efficacy/safety results and the PK of patients aged ≥2 years similar to the results in adult patients, it is justifiable to adopt the dosage regimen used in Study PAH3001 for patients aged ≥1 year and <2 years in view of the following.

- Study PAH3001 enrolled 2 patients in this age category, both showing improved PVRI. In Study AC-055-312 involving 9 patients in this age category, WHO FC improved in 1 patient and was maintained in 7 patients.
- The safety profile of this age group did not tend to differ from that of patients aged ≥2 years.

Studies PAH3001 and AC-055-312 did not enroll patients aged ≥3 months and <1 year. The exclusion of patients with PAH aged <1 year is considered inevitable in view of the rareness of the disease and the limited number of low-age patients meeting the inclusion criteria of Studies PAH3001 and AC-055-312. It would be more appropriate if clinical study data on PK and efficacy/safety were collected from this population before the approval application to justify the PPK analysis-based assumption and explain the efficacy and safety of macitentan administered according to the proposed dosage and administration. However, from the following viewpoints, it is possible to determine the dosage regimen for patients aged ≥3 months and <1 year as per Study PAH3001 only if appropriate measures including patient monitoring and adverse event management are fulfilled by physicians with adequate knowledge and experience in treatment of pediatric PAH.

- In Japan, off-label use of macitentan has been a common practice for pediatric patients with PAH including those aged <1 year, based on the recommendation in the Japanese clinical practice guideline.
- A simulation using PK data of macitentan from patients with PAH suggested that exposure levels may be slightly lower in patients aged <1 year treated with macitentan according to the proposed dosage and administration than in adult patients receiving macitentan according to the approved

dosage and administration (10 mg) [see Section 6.R.2]. However, based on the results of Study AC-055-302 in adults,[22] significant attenuation of efficacy is unlikely to occur even at an exposure level lower than that in adults receiving macitentan 10 mg, if within the range predicted by the simulation.

- The specified use-results survey suggests that the safety of macitentan is manageable in pediatric patients treated at doses around the proposed dose, albeit in the limited number of cases investigated.

The Dosage and Administration of macitentan and the Precautions Concerning Dosage and Administration should be presented as follows.

Dosage and Administration

Opsumit 1 mg/2.5 mg Dispersible Tablets for Pediatric

The usual dosage of macitentan for children aged ≥3 months is as follows. Each tablet is dispersed in a small amount of water for every use to be administered orally once daily.

Age ≥3 months and <6 months, dosage of 1.0 mg

Age ≥6 months and <2 years, dosage of 2.5 mg

Age ≥2 years and body weight <15 kg, dosage of 3.5 mg

Age ≥2 years and body weight ≥15 kg and <25 kg, dosage of 5.0 mg

Age ≥2 years and body weight ≥25 kg and <50 kg, dosage of 7.5 mg

Age ≥2 years and body weight ≥50 kg, dosage of 10 mg

Opsumit Tablets 10 mg

Adults

The usual adult dosage is 10 mg of macitentan administered orally once daily.

Children

The usual dosage for children weighing ≥50 kg is 10 mg of macitentan administered orally once daily.

Precautions Concerning Dosage and Administration

Opsumit 1 mg Dispersible Tablets for Pediatric and Opsumit 2.5 mg Dispersible Tablets for Pediatric

The efficacy and safety of macitentan have not been confirmed when administered according to the approved dosage and administration in pediatric patients aged <1 year. The dosage and administration have been determined based on the results of the pharmacokinetic data-based simulation in patients with PAH aged ≥1 year in clinical studies.

7.R.7 Post-marketing investigations

For the present application, the applicant has no plan of additional pharmacovigilance activities. From the following viewpoints, PMDA accepted the applicant's policy on post-marketing investigations of macitentan that they will continue the regular pharmacovigilance activities without conducting post-marketing surveillance as an additional pharmacovigilance activity.

- Exposure to macitentan in pediatric patients is unlikely to exceed the exposure range in adult patients.

[22] In Study AC-055-302, the efficacy of macitentan 3 and 10 mg was evaluated in patients with PAH. For the first morbidity/mortality event, the primary endpoint, the hazard ratio [2-sided 97.5% CI] in comparison with the placebo group was 0.704 [0.516, 0.960] in the macitentan 3 mg group and 0.547 [0.392, 0.762] in the macitentan 10 mg group. A geometric mean percent change in PVR from baseline to Week 24 [2-sided 95% CI] was 76.9% [69.8%, 84.6%] in the macitentan 3 mg group and 71.3% [62.4%, 81.4%] in the macitentan 10 mg group.

- Adverse events observed during the clinical studies in pediatric patients are all known in adults, indicating no clear differences in the safety profiles between adults and children.
- The specified use-results survey after the approval of macitentan has also collected information on its pediatric use. The re-examination covering these data has not raised particular problems.

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 inspection and a data integrity assessment in accordance with the provisions of the Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices. 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 5.3.5.2.1-2) were subjected to an on-site GCP inspection, in accordance with the provisions of the Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices. On the basis of the inspection, 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 data submitted, PMDA has concluded that macitentan has efficacy in the treatment of pediatric PAH with acceptable safety in view of its benefits. Macitentan is clinically meaningful because it offers a new treatment option for pediatric patients with PAH. PMDA considers that the dosage regimen and the eligible ages, etc. for macitentan are subject to further discussion.

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

Review Report (2)

November 10, 2025

Product Submitted for Approval

Brand Name	(a) Opsumit 1 mg Dispersible Tablets for Pediatric Opsumit 2.5 mg Dispersible Tablets for Pediatric (b) Opsumit Tablets 10 mg
Non-proprietary Name	Macitentan
Applicant	Janssen Pharmaceutical K.K.
Date of Application	March 28, 2025

List of Abbreviations

See Appendix.

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 below. 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).

At the Expert Discussion, the expert advisors supported PMDA's conclusion on efficacy, safety, clinical positioning, intended population, dosage and administration, and post-marketing investigations presented in the Review Report (1).

1.1 Risk management plan (draft)

In view of the discussions presented in Section "7.R.7" in the Review Report (1), PMDA has concluded that the risk management plan (draft) for macitentan should include the safety specification presented in Table 14, and that the applicant should conduct additional pharmacovigilance activities and additional risk minimization activities presented in Table 15.

Table 14. Safety and efficacy specifications in the risk management plan (draft)

Safety specification		
Important identified risks	Important potential risks	Important missing information
• Hepatic dysfunction • Teratogenicity • Anemia, hemoglobin decreased • Decreased blood pressure • Patients with pulmonary veno-occlusive disease (PVOD)	• Menstrual disorder (including hemorrhage) • Ovarian cyst • Testicular disorder and male infertility	• Patients aged <1 year
Efficacy specification		
None		

Table 15. Summary of additional pharmacovigilance activities and additional risk minimization activities included under the risk management plan (draft)

Additional pharmacovigilance activities	Additional risk minimization activities
None	• Organize and disseminate materials for patients

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, with the following condition. As the product is an orphan drug, the re-examination period should be 10 years.

Indication

Pulmonary arterial hypertension

Dosage and Administration

Opsumit 1 mg/ 2.5 mg Dispersible Tablets for Pediatric

The usual dosage macitentan for children aged ≥3 months is as follows. Each tablet is dispersed in a small amount of water for every use to be administered orally once daily.

Age ≥3 months and <6 months, dosage of 1.0 mg

Age ≥6 months and <2 years, dosage of 2.5 mg

Age ≥2 years and body weight <15 kg, dosage of 3.5 mg

Age ≥2 years and body weight ≥15 kg and <25 kg, dosage of 5.0 mg

Age ≥2 years and body weight ≥25 kg and <50 kg, dosage of 7.5 mg

Age ≥2 years and body weight ≥50 kg, dosage of 10 mg

Opsumit Tablets 10 mg

Adults

The usual adult dosage is 10 mg of macitentan administered orally once daily.

Children

The usual dosage for children weighing ≥50 kg is 10 mg of macitentan administered orally once daily.

Approval Condition

The applicant is required to develop and appropriately implement a risk management plan.

List of Abbreviations

ALT	Alanine aminotransferase
AUC_{0-t}	Area under the plasma concentration-time curve from time 0 to the time of the last quantifiable concentration
$AUC_{0-24\ h\ ss}$	Steady-state area under the plasma concentration-time curve from time 0 to 24 hours after drug administration
$AUC_{0-\infty}$	Area under the plasma concentration-time curve from time 0 to infinity
BA	Bioavailability
BE	Bioequivalence
CEC	Clinical event committee
CHD	Congenital heart disease
CI	Confidence interval
C_{max}	Maximum plasma concentration
COVID-19	Coronavirus Disease 2019
C_{trough}	Trough plasma concentration
ERA	Endothelin receptor antagonist
ET_A	Endothelin A
ET_B	Endothelin B
FAS	Full analysis set
HIV	Human immunodeficiency virus
HPAH	Heritable pulmonary arterial hypertension
IPAH	Idiopathic pulmonary arterial hypertension
LAP	Left atrial pressure
LC-MS/MS	Liquid chromatography and tandem mass spectrometry
LVEDP	Left ventricular end diastolic pressure
Macitentan	Macitentan
MedDRA	Medical dictionary for regulatory activities
mPAP	Mean pulmonary arterial pressure
PAH	Pulmonary arterial hypertension
PAWP	Pulmonary artery wedge pressure
PDE	Phosphodiesterase
PGI_2	Prostaglandin I_2
PH	Pulmonary hypertension
PK	Pharmacokinetics
PMDA	Pharmaceuticals and Medical Devices Agency
PPK	Population pharmacokinetics
PPS	Per protocol set
PT	Preferred term
PVR	Pulmonary vascular resistance
PVRI	Pulmonary vascular resistance index
SMQ	Standardised MedDRA queries
t_{max}	Time to maximum plasma concentration
WHO	World Health Organization