▼This medicinal product is subject to additional monitoring in Australia due to approval of an extension of indications. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse events at www.tga.gov.au/reporting-problems.

AUSTRALIAN PRODUCT INFORMATION

OPSUMIT (macitentan)

film-coated tablet and dispersible tablet

OPSUMIT® may cause birth defects and is contraindicated in pregnancy.
See section 4.3 CONTRAINDICATIONS and Section 4.6 FERTILITY, PREGNANCY and LACTATION.

1 NAME OF THE MEDICINE

macitentan

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

OPSUMIT is available as a film-coated tablet containing 10 mg of macitentan or as a dispersible tablet containing 2.5 mg of macitentan.

Excipients with known effects:

10 mg film-coated tablet: Lactose and Soya bean products.

For the full list of excipients, see Section 6.1 LIST OF EXCIPIENTS.

3 PHARMACEUTICAL FORM

Film-coated tablet

10 mg – white to off-white, round, biconvex film-coated tablet, debossed with “10” on both sides.

Dispersible tablet

2.5 mg – white to almost white, round, immediate-release dispersible tablet, debossed with a “2.5” on one side and with “Mn” on the other side.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

Film-coated tablets

OPSUMIT, as monotherapy or in combination with approved PAH treatments (phosphodiesterase-5 inhibitors or inhaled prostanoids), is indicated for the treatment of:

- idiopathic pulmonary arterial hypertension
- heritable pulmonary arterial hypertension
- pulmonary arterial hypertension associated with connective tissue disease
- pulmonary arterial hypertension associated with congenital heart disease with repaired shunts

in patients with WHO Functional class II, III or IV symptoms.

Dispersible tablets

Paediatric (2 years to less than 18 years of age)

OPSUMIT, as monotherapy or in combination, is indicated for the treatment of:

- idiopathic pulmonary arterial hypertension
- heritable pulmonary arterial hypertension
- pulmonary arterial hypertension associated with connective tissue disease
- pulmonary arterial hypertension associated with congenital heart disease with repaired shunts
- pulmonary arterial hypertension with co-incidental congenital heart disease

in paediatric patients with WHO Functional class I, II, III or IV symptoms.

4.2 DOSE AND METHOD OF ADMINISTRATION

Treatment with OPSUMIT should only be initiated and monitored by a physician experienced in the treatment of PAH.

Dosage

Adults

The recommended dose of OPSUMIT in adults is one 10 mg film-coated tablet taken orally once daily. Doses higher than 10 mg daily have not been studied and are not recommended.

OPSUMIT is also available as 2.5 mg dispersible tablets. OPSUMIT administered in the form of 4 x 2.5 mg dispersible tablets is bioequivalent to 1 x 10 mg film-coated tablet. Therefore, 4 x 2.5 mg dispersible tablets may be used as direct replacements for patients who are unable to swallow a 10 mg film-coated tablet (see Section 5.2 PHARMACOKINETIC PROPERTIES – Paediatrics).

Paediatrics (2 years to less than 18 years of age)

The recommended dose of OPSUMIT in paediatric patients aged 2 years to less than 18 years is based on body weight (Table 1). OPSUMIT should be taken once daily.

Table 1: Dosing regimen based on body weight		
Body Weight (kg)	**Daily Dose**	**Recommended Number of Tablets to Be Dispersed**
≥ 10 and < 20	5 mg	2 x 2.5 mg
≥ 20 and < 40	7.5 mg	3 x 2.5 mg
≥ 40	10 mg	4 x 2.5 mg

Film-coated tablets

OPSUMIT is also available as a 10 mg film-coated tablet. OPSUMIT administered in the form of 1 x 10 mg film coated tablet is bioequivalent to 4 x 2.5 mg dispersible tablets. Therefore, 1 x 10 mg film-coated tablet may be used as a direct replacement for paediatrics patients less than 18 years who weigh at least 40 kg (see Section 5.2 PHARMACOKINETIC PROPERTIES – Paediatrics).

Special populations

Dosage adjustment in elderly patients

No dose adjustment is required in patients over the age of 65 years.

Dosage adjustment in patients with hepatic impairment

Based on pharmacokinetic data, no dose adjustment is required in patients with mild or moderate hepatic impairment. There is no clinical experience with the use of OPSUMIT in PAH patients with moderate or severe hepatic impairment.

OPSUMIT is contraindicated in patients with severe hepatic impairment, or clinically significant elevated hepatic aminotransferases (greater than 3 times the Upper Limit of Normal (> 3 × ULN); see Section 4.3 CONTRAINDICATIONS.

Dosage adjustment in patients with renal impairment

Based on pharmacokinetic data, no dose adjustment is required in patients with renal impairment. There is no clinical experience with the use of OPSUMIT in PAH patients with severe renal impairment. The use of OPSUMIT is not recommended in patients undergoing dialysis.

Paediatric population (below 2 years)

The safety and efficacy of OPSUMIT in children below 2 years of age have not been established. Currently available data are described in Section 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS), Section 5.1 PHARMACODYNAMICS PROPERTIES and Section 5.2 PHARMACOKINETIC PROPERTIES but no recommendation on a posology can be made.

Administration

Film-coated tablets
OPSUMIT should be taken orally once a day with or without food. The film-coated tablets are not breakable and are to be swallowed whole, with water.

Dispersible tablets
OPSUMIT should be taken orally once a day at about the same time, with or without food. OPSUMIT dispersible tablet(s) must be dispersed in room temperature liquids and are to be taken as an oral suspension only. The oral suspension must be prepared and administered using either a stainless-steel spoon or a small glass. Care should be taken to ensure the entire dose of medicine has been taken. If not administered right away the medicine should be discarded and a new dose of medicine should be prepared. Hands must be thoroughly washed and dried before and after preparation of the medicine.

Administration by a stainless-steel spoon
The prescribed daily dose of dispersible tablet(s) should be added to room temperature drinking water in a stainless-steel spoon to form a white cloudy liquid. The liquid can be gently stirred for 1 to 3 minutes using a knife tip to speed up dissolution. Either administer the medicine to the patient right away or mix it further with a small portion of apple sauce or yoghurt to aid with administration. A little more water, apple sauce or yoghurt should be added to the spoon and administered to the patient to make sure the entire dose of medicine has been taken.

Alternatively, instead of drinking water, the oral suspension can be prepared in orange juice, apple juice or skimmed milk.

Administration by a glass
The prescribed daily dose of dispersible tablet(s) should be placed in a small glass containing a small volume (from 10 mL up to maximum 100 mL) of room temperature drinking water to form a white cloudy liquid. The liquid can be gently stirred with a spoon for 1 to 2 minutes. Administer the medicine to the patient right away. A little more water (minimum 5 mL) should be added to the glass and stirred with the same spoon to re-suspend any remaining medicine. The entire contents of the glass should be administered to the patient to make sure all the medicine has been taken.

4.3 CONTRAINDICATIONS

OPSUMIT is contraindicated in:

- Women who are or may become pregnant (See Boxed Warning and Section 4.6 FERTILITY, PREGNANCY AND LACTATION).
- Women of child-bearing potential who are not using reliable contraception (See Section 4.6 FERTILITY, PREGNANCY AND LACTATION). Women must not become pregnant for at least 3 months after stopping treatment with OPSUMIT.
- Hypersensitivity to the active substance or to any of the excipients listed in Section 6.1 LIST OF EXCIPIENTS.
- Patients with severe hepatic impairment (with or without cirrhosis) (See Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE – Liver function).

- Patients with baseline values of hepatic aminotransferases (aspartate aminotransferase [AST] and/or alanine aminotransferase [ALT]) greater than 3 times the Upper Limit of Normal (ULN) (See Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE – Liver function).

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Macitentan has only been studied in a limited number of patients with WHO functional class IV symptoms.

Macitentan has only been studied in a limited number of patients with PAH due to HIV, drugs or toxins.

The efficacy and safety of macitentan when co-administered with epoprostenol has not been specifically studied in controlled clinical trials.

Liver function
Hepatic enzyme elevations, and in some cases serious hepatic events, potentially related to therapy have been observed with endothelin receptor antagonists (ERAs).

The incidence of aminotransferase elevations (ALT/AST) > 3 × ULN was 3.4% on macitentan 10 mg and 4.5% on placebo in a double-blind study in patients with PAH. The incidence of elevations in ALT > 3 × ULN were 3.4% on macitentan 10 mg and 1.6% on placebo (see Section 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)). The incidence of ALT > 8 × ULN were 2.1% on macitentan 10 mg and 0.4% on placebo.

Opsumit is not to be initiated in patients with severe hepatic impairment or elevated aminotransferases (> 3 × ULN) (see Section 4.3 CONTRAINDICATIONS) and is not recommended in patients with moderate hepatic impairment. Liver enzyme tests should be obtained prior to initiation of macitentan and monthly monitoring of aminotransferases during treatment with macitentan is recommended. Patients should be monitored for signs of hepatic injury.

If clinically relevant aminotransferase elevations occur, or if elevations are accompanied by an increase in bilirubin > 2 × ULN, or by clinical symptoms of hepatic injury (e.g. jaundice), macitentan treatment should be discontinued. Re-initiation of macitentan may be considered following the return of hepatic enzyme levels to within the normal range in patients who have not experienced clinical symptoms of hepatic injury and following the advice of a liver specialist.

Caution should be exercised when OPSUMIT is used concomitantly with medicinal products known to be associated with hepatic injury as the additive effects of OPSUMIT with these agents are not known.

Haematological Changes
Decreases in haemoglobin concentration and haematocrit have occurred following administration of other ERAs and were observed in clinical studies with OPSUMIT (see Section 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)).

In placebo-controlled studies, macitentan-related decreases in haemoglobin concentration were not progressive, stabilised after the first 4-12 weeks of treatment and remained stable during chronic treatment. Cases of anaemia requiring blood cell transfusion have been reported with OPSUMIT and other ERAs. Initiation of OPSUMIT is not recommended in patients with clinically significant anaemia. It is recommended that haemoglobin concentrations be measured prior to initiation of treatment and tests repeated during treatment as clinically indicated.

Fluid retention
Oedema or fluid retention has been observed with ERAs and may also be a clinical consequence of PAH. OPSUMIT 10 mg was not associated with increased incidences of treatment-emergent oedema or fluid retention in a long-term placebo-controlled trial (see Section 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)).

If clinically significant fluid retention develops during therapy with OPSUMIT, with or without associated weight gain, further evaluation should be undertaken to determine the cause, such as underlying heart failure, and the possible need for specific treatment should be considered.

Pulmonary veno-occlusive disease
Cases of pulmonary oedema have been reported with vasodilators (mainly prostacyclins) when used in patients with pulmonary veno-occlusive disease. Consequently, if signs of pulmonary oedema occur when OPSUMIT is administered in patients with PAH, the possibility of pulmonary veno-occlusive disease should be considered. Discontinuation of OPSUMIT should be considered in patients with treatment-related pulmonary veno-occlusive disease.

Use in renal impairment
Patients with renal impairment may run a higher risk of experiencing hypotension and anaemia during treatment with macitentan. Therefore, monitoring of blood pressure and haemoglobin should be considered. There is no clinical experience with the use of OPSUMIT in patients with severe renal impairment. Caution is recommended in this population. There is no experience with the use of OPSUMIT in patients undergoing dialysis, therefore OPSUMIT is not recommended in this population.

Use in Patients with pre-existing hypotension
Hypotension has been associated with the use of ERAs. Caution should be exercised when initiating macitentan in patients with pre-existing hypotension and blood pressure in such patients should be monitored closely.

Use in the Elderly
Of the total number of subjects in the clinical study of OPSUMIT for PAH, 14% were 65 and over. No overall differences in safety or effectiveness were observed between these subjects and younger subjects. Limited data are available in those > 75 years of age, therefore caution is recommended.

Paediatric Use
The safety and efficacy of OPSUMIT in children below 2 years of age have not been established. Currently available data are described in Section 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS), Section 5.1 PHARMACODYNAMICS PROPERTIES and Section 5.2 PHARMACOKINETIC PROPERTIES but no recommendation on a posology can be made.

Effects on laboratory tests
See Section 4.8 ADVERSE EFFECT (UNDESIRABLE EFFECTS) - Laboratory Abnormalities.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

***In vitro* studies**
The metabolism of macitentan to its active metabolite aprocitentan is catalysed by CYP3A with minor contributions from CYP2C8, CYP2C9 and CYP2C19.

Macitentan and its active metabolite do not have clinically relevant inhibitory or inducing effects on CYP enzymes.

Macitentan and its active metabolite are not substrates of the multi-drug resistance protein (P-gp, MDR-1) or organic anion transporting polypeptides (OATP1B1 and OATP1B3).

Macitentan and its active metabolite are unlikely to inhibit hepatic or renal drug transporters at clinically relevant concentrations, including the multi-drug resistance protein (P-gp, MDR-1), the multidrug and toxin extrusion transporters (MATE1 and MATE2-K), the organic anion transporters (OAT1 and OAT2), the organic cation transporters (OCT1 and OCT2), the bile salt export pump (BSEP), the sodium-dependent co-transporting polypeptide (NTCP), and the organic anion transporting polypeptides (OATP1B1 and OATP1B3).

***In vivo* studies**

Warfarin*:* Macitentan given as multiple doses of 10 mg once daily had no effect on exposure to S-warfarin (CYP2C9 substrate) or R-warfarin (CYP3A4 substrate) after a single dose of 25 mg warfarin. The pharmacodynamic effect of warfarin on International Normalised Ratio (INR) was not affected by macitentan. The pharmacokinetics of macitentan and its active metabolite were not affected by warfarin.

Sildenafil*:* At steady-state, the exposure to sildenafil 20 mg t.i.d. was increased by 15% during concomitant administration of macitentan 10 mg once daily. Sildenafil, a CYP3A4 substrate, did not affect the pharmacokinetics of macitentan, while there was a 15% reduction in the exposure to the active metabolite of macitentan. These changes are not considered clinically relevant. In a placebo-controlled trial in patients with PAH, the efficacy and safety of macitentan in combination with sildenafil were demonstrated.

Strong CYP3A4 inhibitors*:* In the presence of ketoconazole 400 mg once daily, a strong CYP3A4 inhibitor, exposure to macitentan increased approximately 2-fold. The predicted increase was approximately 3-fold in the presence of ketoconazole 200 mg twice daily using physiologically based pharmacokinetic (PBPK) modelling. Exposure to the active metabolite of macitentan was reduced by 26%. Caution should be exercised when macitentan is administered concomitantly with strong CYP3A4 inhibitors (e.g., itraconazole, ketoconazole, voriconazole, clarithromycin, ritonavir, and saquinavir).

Fluconazole: In the presence of fluconazole 400 mg daily, a moderate dual inhibitor of CYP3A4 and CYP2C9, exposure to macitentan may increase approximately 3.8-fold based on physiologically based pharmacokinetic (PBPK) modelling. Caution should be exercised when macitentan is administered concomitantly with moderate dual inhibitors of CYP3A4 and CYP2C9 (e.g., fluconazole and amiodarone).

Caution should also be exercised when macitentan is administered concomitantly with both a moderate CYP3A4 inhibitor (e.g., ciprofloxacin, ciclosporin, diltiazem, erythromycin, verapamil) and moderate CYP2C9 inhibitor (e.g., miconazole, piperine).

***HIV drugs*:** Effects of other strong CYP3A4 inhibitors such as ritonavir on macitentan were not studied, but are likely to result in an increase in macitentan exposure at steady state similar to that seen with ketoconazole.

Ciclosporin A*:* Concomitant treatment with ciclosporin A 100 mg b.i.d., combined CYP3A4 and OATP inhibitor, did not alter the steady-state exposure to macitentan and its active metabolite to a clinically relevant extent.

Strong CYP3A4 inducers*:* Concomitant treatment with rifampicin 600 mg daily, a potent inducer of CYP3A4, reduced the steady-state exposure to macitentan by 79% but did not affect the exposure to the active metabolite. Reduced efficacy of macitentan in the presence of a potent inducer of CYP3A4 such as rifampicin should be considered. The combination of macitentan with strong CYP3A4 inducers (e.g., rifampicin, St. John's Wort, carbamazepine, and phenytoin) should be avoided.

Hormonal contraceptives*:* Macitentan does not affect the exposure to CYP3A4 substrates. In healthy subjects, macitentan 10 mg once daily did not affect the pharmacokinetics of a single dose of an oral contraceptive (norethisterone 1 mg and ethinyl estradiol 35 µg).

Breast cancer resistance protein (BCRP) substrate drugs: Macitentan 10 mg once daily did not affect the pharmacokinetics of oral riociguat or rosuvastatin (riociguat 1 mg, rosuvastatin 10 mg).

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

Male fertility

Reversible testicular tubular dilatation was observed in chronic toxicity studies at exposures greater than 7- fold and 23 - fold the human exposure in rats and dogs, respectively. After 2 years of treatment, tubular atrophy was seen in rats at 4-fold the human exposure. Macitentan did not affect male or female fertility in rats at exposures ranging from approximately 18- to 44-fold the human exposure, respectively. In a 26-week study in male rats treated with macitentan, there was no effect on sperm count or motility but there was a dose-dependent increase in the incidence of morphologically abnormal sperm at or above 7-fold the human exposure. No testicular findings were noted in mice after treatment up to 2 years.

Decreases in sperm count have been observed in patients taking ERAs. OPSUMIT, like other ERAs, may have an adverse effect on spermatogenesis.

Use in pregnancy
Category X

Due to a high mortality risk to both mother and foetus, pregnancy is considered contraindicated in PAH.

Teratogenicity is a class effect of endothelin receptor antagonists.

There are no data on the use of macitentan in pregnant women. OPSUMIT is contraindicated during pregnancy and in women of childbearing potential who are not using reliable contraception. If OPSUMIT is used during pregnancy, or if the patient becomes pregnant while taking OPSUMIT, advise the patient of the potential harm to the foetus.

Macitentan was teratogenic in rabbits and rats at all doses tested. In both rabbits and rats, there were cardiovascular and mandibular arch fusion abnormalities. A no effect level for teratogenicity has not been established. Administration of macitentan to female rats from late pregnancy through lactation

caused reduced pup survival and impairment of the male fertility of the offspring at all dose levels tested.

Use in women of child-bearing potential

In females of child-bearing potential, pregnancy should be excluded before the start of treatment with macitentan and prevented thereafter by the use of two reliable methods of contraception. If necessary, patients should discuss with their doctor or gynaecologist which methods would be most suitable for them. Given the teratogenic nature of the drug, women should not become pregnant for 3 months after discontinuation of OPSUMIT. Monthly pregnancy tests during treatment with OPSUMIT are recommended to allow the early detection of pregnancy.

It is not known whether macitentan is present in semen. It is therefore not known whether there is the potential for foetal harm (teratogenicity) resulting from transfer of macitentan via semen.

Use in lactation

It is not known whether OPSUMIT is excreted into human breast milk. In rats, OPSUMIT and its metabolites were excreted into milk during lactation. Breast-feeding is not recommended during treatment with OPSUMIT. A risk to newborns/infants cannot be excluded.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

The effects of this medicine on a person's ability to drive and use machines were not assessed as part of its registration. See Section 4.8 ADVERSE EFFECT (UNDESIRABLE EFFECTS).

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Experience from clinical studies

The safety of macitentan has been evaluated in a long-term placebo-controlled trial of 742 adult and adolescent patients with symptomatic PAH (SERAPHIN study). The mean treatment duration was 103.9 weeks in the macitentan 10 mg group, and 85.3 weeks in the placebo group. The majority of adverse events (AEs) were mild to moderate in intensity. The most commonly reported AEs were nasopharyngitis (14.0% vs 10.4%), headache (13.6% vs 8.8%) and anaemia (13.2% vs 3.2%) (Table 2).

Table 3 presents adverse reactions occurring in macitentan-treated subjects at an incidence < 3 % and with a placebo-corrected difference ≥ 1 % (during treatment and up to 28 days after treatment discontinuation). Adverse reactions are listed by system organ class and frequency category, using the convention: common (≥ 1/100 and < 1/10). Within each frequency group, adverse reactions are presented in order of decreasing seriousness.

Frequency determination does not account for other factors including varying study duration, pre-existing conditions, and baseline patient characteristics.

Table 2 **Adverse events occurring in ≥ 3 % of macitentan-treated subjects and at a greater incidence than placebo (during treatment and up to 28 days after treatment discontinuation)**

System Organ Class / Preferred Term	Placebo N=249		Macitentan 10 mg N=242	
	No.	%	No.	%
Blood and lymphatic system disorders				
Anaemia	8	3.2%	32	13.2%
Thrombocytopenia	7	2.8%	12	5.0%
Gastrointestinal disorders				
Diarrhoea	17	6.8%	22	9.1%
Abdominal pain upper	11	4.4%	11	4.5%
General disorders and administration site conditions				
Oedema peripheral	45	18.1%	44	18.2%
Pyrexia	9	3.6%	9	3.7%
Infections and infestations				
Upper respiratory tract infection	33	13.3%	37	15.3%
Nasopharyngitis	26	10.4%	34	14.0%
Bronchitis	14	5.6%	28	11.6%
Urinary tract infection	14	5.6%	21	8.7%
Respiratory tract infection viral	9	3.6%	15	6.2%
Pharyngitis	7	2.8%	15	6.2%
Influenza	4	1.6%	14	5.8%
Sinusitis	6	2.4%	11	4.5%
Gastroenteritis	3	1.2%	8	3.3%
Rhinitis	2	0.8%	8	3.3%
Metabolism and nutrition disorders				
Hypokalaemia	14	5.6%	14	5.8%
Musculoskeletal and connective tissue disorders				
Arthralgia	10	4.0%	11	4.5%
Myalgia	4	1.6%	8	3.3%
Nervous system disorders				
Headache	22	8.8%	33	13.6%

System Organ Class / Preferred Term	Placebo N=249		Macitentan 10 mg N=242	
	No.	%	No.	%
Psychiatric disorders				
Insomnia	10	4.0%	17	7.0%
Depression	8	3.2%	8	3.3%
Skin and subcutaneous tissue disorders				
Skin ulcer	3	1.2%	8	3.3%
Vascular disorders				
Hypotension	11	4.4%	15	7.0%

Table 3 Adverse reactions occurring in macitentan-treated subjects at an incidence < 3 % and with a placebo-corrected difference ≥ 1 % (during treatment and up to 28 days after treatment discontinuation)

System Organ Class	Common ≥ 1/100 and < 1/10)
Eye disorders	Conjunctivitis
Gastrointestinal disorders	Abdominal pain, Irritable bowel syndrome, Haemorrhoids
Hepatobiliary disorders	Cholelithiasis
Infections and infestations	Lower respiratory tract infection, Gastroenteritis viral, Tracheitis, Tonsillitis
Investigations	Haemoglobin decreased, Haematocrit decreased, Blood urea increased
Metabolism and nutrition disorders	Hyperkalaemia
Musculoskeletal and connective tissue disorders	Systemic sclerosis, Costochondritis
Nervous system disorders	Migraine
Reproductive system and breast disorders	Metrorrhagia, Menorrhagia, Ovarian cyst, Gynaecomastia
Respiratory, thoracic and mediastinal disorders	Rhinorrhoea, Productive cough, Bronchial hyperreactivity
Skin and subcutaneous tissue disorders	Pruritus, Eczema, Urticaria
Vascular disorders	Flushing

Experience from paediatric clinical study (PAH)

Paediatric population (aged ≥ 2 years to less than 18 years)

The safety of macitentan was evaluated in TOMORROW, a Phase 3 study of paediatric patients with PAH. A total of 72 patients, aged ≥ 2 years to less than 18 years were randomised and received OPSUMIT. The mean age at enrolment was 10.5 years (range 2.1 years – 17.9 years). The median duration of treatment in the randomised study was 168.4 weeks (range 12.9 weeks – 312.4 weeks) in the OPSUMIT arm.

Overall, the safety profile in this paediatric population was consistent with that observed in the adult population. The following adverse drug reactions have been reported with higher frequency in paediatric patients: upper respiratory tract infection (31.9%), rhinitis (8.3%), and gastroenteritis (11.1%). The majority of adverse reactions were mild to moderate in intensity.

Paediatric population (aged ≥ 1 month to < 2 years)

An additional 11 patients, aged ≥ 1 month to less than 2 years old were enrolled to receive OPSUMIT without randomisation, 9 patients from the open-label arm of the TOMORROW study and 2 Japanese patients from the PAH3001 study. At enrolment, the age range of the patients from the TOMORROW study was 1.2 years to 1.9 years and the median duration of treatment was 37.1 weeks (range 7.0 – 72.9 weeks). At enrolment, the ages of the 2 patients from PAH3001 were 21 months and 22 months. Overall, the safety profile in this paediatric population was consistent with that observed in the adult population and paediatric population aged ≥ 2 years to less than 18 years.

Description of selected adverse reactions

Oedema/fluid retention has been associated with the use of ERAs and is also a clinical manifestation of right heart failure and underlying PAH disease. In SERAPHIN, a long-term double-blind study in patients with PAH, the incidence of oedema AEs in the macitentan 10 mg and placebo treatment groups was 21.9% and 20.5% respectively. This corresponded to 11.0 events / 100 patient-years on macitentan 10 mg compared to 12.5 events / 100 patient-years on placebo.

Laboratory abnormalities

Liver aminotransferases

The incidence of elevated aminotransferases in the study of OPSUMIT in PAH is shown in Tables 4 and 5.

Table 4 Incidence of Elevated Aminotransferases (ALT/AST) in the SERAPHIN Study

	OPSUMIT 10 mg (N=242)	Placebo (N=249)
>3 x ULN	3.4%	4.5%
>5 x ULN	2.5%	2%
>8 x ULN	2.1%	0.4%

Table 5 Incidence of Elevated ALT in the SERAPHIN Study

	OPSUMIT 10 mg (N=242)	Placebo (N=249)
>3 x ULN	3.4%	1.6%
>5 x ULN	2.5%	1.2%
>8 x ULN	2.1%	0.4%

In SERAPHIN, a double-blind study in patients with PAH, discontinuations for hepatic AEs were 3.3% in the OPSUMIT 10 mg group vs. 1.6% for placebo.

Haemoglobin

In SERAPHIN, a double-blind study in patients with PAH, macitentan 10 mg was associated with a mean decrease in haemoglobin versus placebo of 10 g/L. A decrease from baseline in haemoglobin concentration to below 100 g/L was reported in 8.7% of patients treated with macitentan 10 mg and 3.4% of placebo-treated patients.

White blood cells

In SERAPHIN, a double-blind study in patients with PAH, macitentan 10 mg was associated with a decrease in mean leucocyte count from baseline of 0.7×10^9/L versus no change in placebo-treated patients.

Platelets

In SERAPHIN, a double-blind study in patients with PAH, macitentan 10 mg was associated with a decrease in mean platelet count of 17×10^9/L, versus a mean decrease of 11×10^9/L in placebo-treated patients.

Long-term safety

550 patients entered a long-term open-label extension study (182 patients who continued on OPSUMIT 10 mg and 368 patients crossed over to OPSUMIT 10 mg from either placebo or macitentan 3 mg) and were followed for a median exposure of 3.3 years and a maximum exposure of 10.9 years. 242 patients received OPSUMIT 10 mg in the double-blind study with 182 continuing in the open label study, giving a median exposure of 4.6 years and a maximum exposure of 11.8 years. The safety profile was consistent with that described above.

Post-marketing experience

Table 6 Post Marketing Adverse Events: common (> 1/100, < 1/10); uncommon (> 1/1,000, < 1/100)

System organ class	Frequency	Adverse reaction
Immune system disorders	Uncommon*	Hypersensitivity reactions (angioedema, and rash)
	Common*	pruritus
Respiratory, thoracic & mediastinal disorders	Common†	Nasal congestion

General disorders & Administration site conditions	Very common§	Oedema/fluid retention
Vascular disorders	Common	Flushing

**Frequency Classification "common" and "uncommon" based on pooled double-blind studies.*
†Frequency Classification "common" based on pooled double-blind studies.

§ Frequency Classification "very common" based on double-blind studies

Reporting suspected adverse effects
Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at https://www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

Macitentan has been administered as a single dose of up to and including 600 mg to healthy adult subjects. AEs of headache, nausea, and vomiting were observed. In the event of an overdose, standard supportive measures must be taken, as required. Due to the high degree of protein binding of macitentan, dialysis is unlikely to be effective.

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of action
Endothelin (ET)-1 and its receptors (ETA and ETB) mediate a variety of effects such as vasoconstriction, fibrosis, proliferation, hypertrophy, and inflammation. In disease conditions such as pulmonary arterial hypertension (PAH), the local ET system is upregulated and is involved in vascular hypertrophy and in organ damage.

Macitentan is an orally active, dual ETA and ETB receptor antagonist that prevents the binding of ET-1 to its receptors. Macitentan displays high affinity for and sustained occupancy of the ET receptors in human pulmonary arterial smooth muscle cells and has physicochemical properties favouring penetration into lung tissue, particularly in disease conditions.

In animal models of pulmonary hypertension, macitentan selectively decreased mean pulmonary arterial pressure without affecting systemic blood pressure, prevented pulmonary arterial hypertrophy and right ventricular remodeling, and significantly increased survival.

Cardiac Electrophysiology: In a randomised, placebo-controlled four-way crossover study with a positive control in healthy adult subjects, repeated doses of macitentan 10 and 30 mg (3 times the recommended dosage) had no significant effect on the QTc interval.

Clinical trials

Efficacy in Patients with Pulmonary Arterial Hypertension

A multi-centre, double-blind, placebo-controlled, parallel-group, event-driven, Phase 3 outcome study (AC-055-302/SERAPHIN) was conducted in 742 patients with symptomatic PAH, who were randomised to three treatment groups (placebo [N=250], 3 mg [N=250] or 10 mg [N=242] of macitentan once daily), to assess the long-term effect on morbidity or mortality. At baseline, the majority of enroled patients (64%) were treated with a stable dose of specific therapy for PAH, either oral phosphodiesterase inhibitors (61%) and/or inhaled/oral prostanoids (6%). The primary study endpoint was the time to first occurrence of a morbidity or mortality event, up to end of treatment (EOT), defined as death, or atrial septostomy, or lung transplantation, or initiation of intravenous (i.v.) or subcutaneous (s.c.) prostanoids, or other worsening of PAH. Other worsening of PAH was defined as the presence of all of the three following components: a sustained decrease in 6-minute walk distance (6MWD) of at least 15% from baseline; worsening of PAH symptoms (worsening of WHO Functional Class [FC] or right heart failure); and need for new treatment for PAH. All events were confirmed by an independent adjudication committee, blinded to treatment allocation.

The median treatment duration was 101, 116, and 118 weeks in the placebo, macitentan 3 mg, and 10 mg group, respectively, up to a maximum of 188 weeks on macitentan.

Efficacy was evaluated up to the end of double-blind treatment (EOT). The EOT either coincided with end of study (EOS) for patients who completed the study as scheduled or occurred earlier in case of premature discontinuation of study drug. For those patients who stopped treatment prior to EOS, PAH therapy, including macitentan, may have been initiated. All patients were followed up to EOS for vital status. The ascertainment rate for vital status at the EOS was greater than 95%.

The mean age of all patients was 46 years (range 12–85 years of age) with the majority of subjects being Caucasian (55%) and female (77%). Approximately 52%, 46%, and 2% of patients were in WHO FC II, III, and IV, respectively. Patients with WHO Functional Class I were excluded from the study.

Idiopathic or heritable PAH was the most common aetiology in the study population (57%), followed by PAH due to connective tissue disorders (31%), PAH associated with congenital heart disease with shunts (8%), and PAH associated with other aetiologies (drugs and toxins [3%] and HIV [1%]).

Outcome endpoints

Treatment with OPSUMIT 10 mg resulted in a 45% reduction (HR 0.55, 97.5% CI 0.39-0.76; logrank $p<0.0001$) in the occurrence of the primary endpoint up to end of double-blind treatment compared to placebo (Figure 1 and Table 7). The beneficial effect of OPSUMIT 10 mg was primarily attributable to a reduction in clinical worsening events (deterioration in 6MWD and worsening of PAH symptoms and need for additional PAH treatment). The treatment effect was established early and sustained for a median duration of 2 years.

Figure 1 Kaplan-Meier estimates of the risk of first morbidity/mortality event in SERAPHIN

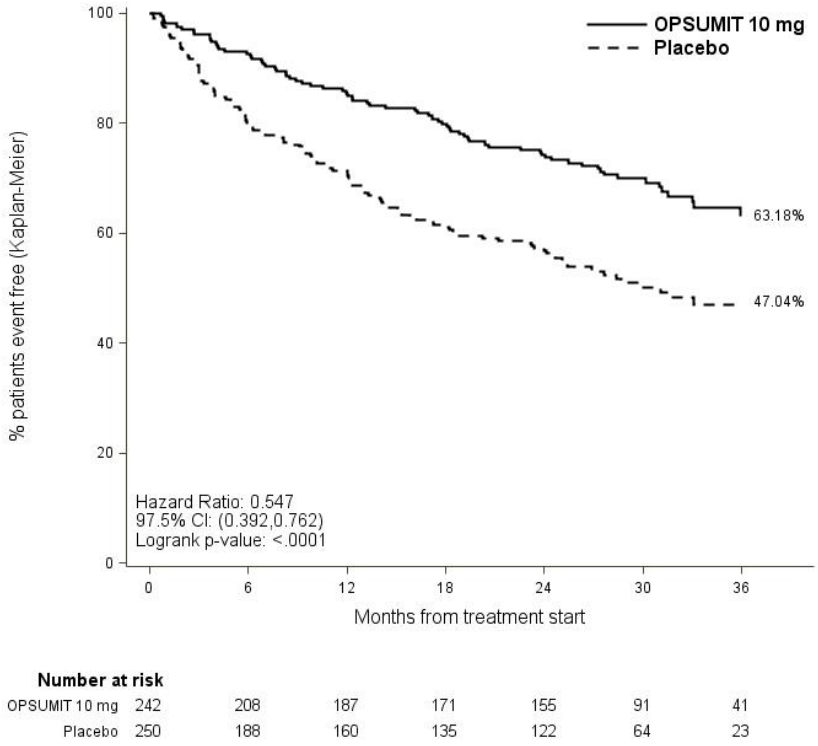


Table 7 Summary of Primary Endpoint Events

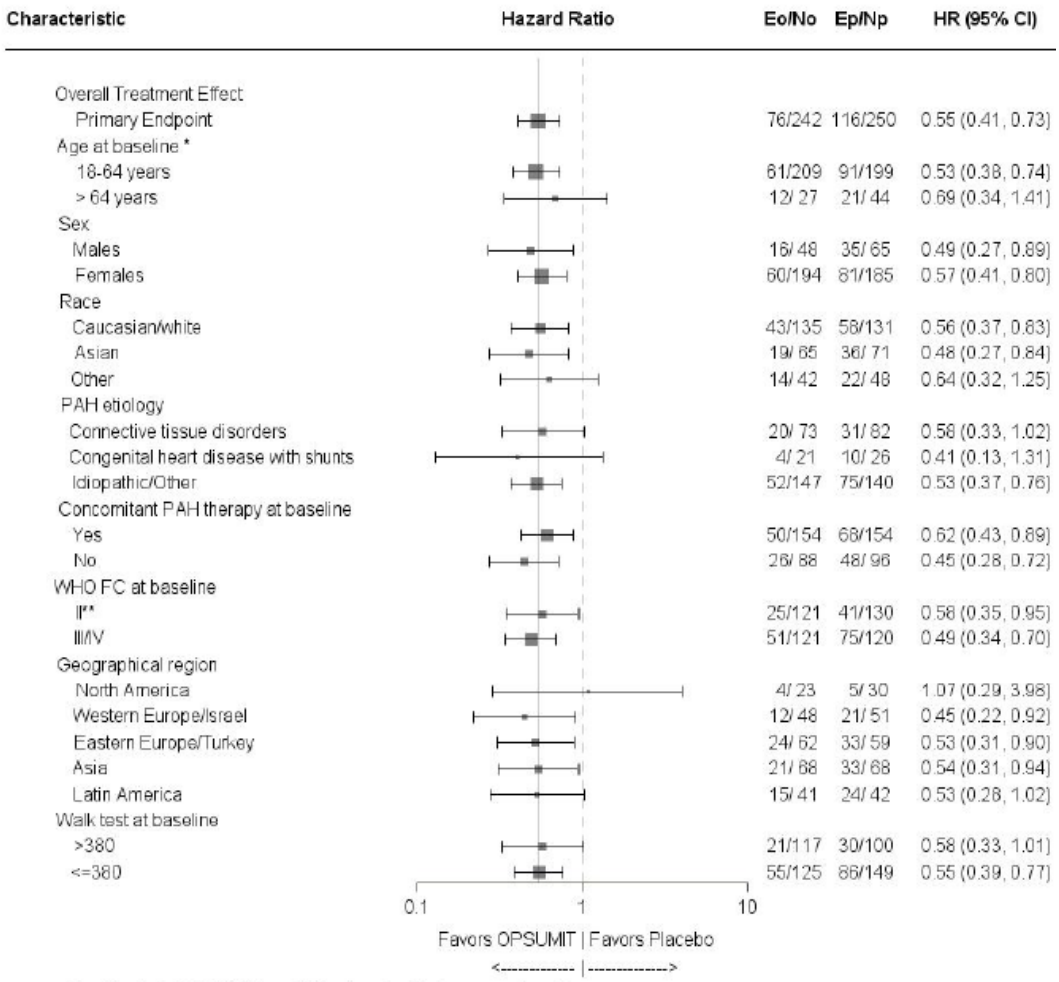
	Placebo N = 250 n (%)	OPSUMIT 10 mg N = 242 n (%)	Treatment Comparison: OPSUMIT 10 mg vs Placebo		
			Relative Risk Reduction (97.5% CI)	HR (97.5% CI)	Log rank p-value
Patients with a primary endpoint event	116 (46.4)	76 (31.4)	45% (24%; 61%)	0.55 (0.39; 0.76)	< 0.0001
Component as first event[§]					
Death	17 (6.8)	16 (6.6)			
Worsening PAH	93 (37.2)	59 (24.4)			
i.v./s.c. Prostanoid	6 (2.4)	1 (0.4)			

[§] Due to competing risks, HR and p-values are not provided for the component events; No patients experienced an event of lung transplantation or atrial septostomy in the placebo or OPSUMIT 10 mg treatment groups.

Subgroup analyses were performed to examine their influence on outcome as shown in Figure 2. Consistent efficacy of OPSUMIT 10 mg on the primary endpoint was seen across subgroups of age,

sex, race, aetiology, by monotherapy or in combination with another PAH therapy, baseline 6MWD, and baseline WHO FC.

Figure 2 Subgroup analysis of the SERAPHIN study



Eo = Number of events OPSUMIT 10 mg; No = Number of patients randomized to OPSUMIT 10 mg
Ep = Number of events placebo; Np = Number of patients randomized to placebo

The SERAPHIN study was not powered to assess the effect on mortality. Treatment with OPSUMIT 10 mg resulted in a statistically non-significant 36% relative risk reduction (HR 0.64, 97.5% CI 0.29-1.42; logrank p=0.2037) in the occurrence of death of all causes up to EOT regardless of prior worsening. The number of deaths of all causes up to EOS on macitentan 10 mg was 35 versus 44 on placebo (HR 0.77; 97.5% CI: 0.46 to 1.28; logrank p=0.2509).

The risk of PAH-related death or hospitalisation for PAH up to the end of double-blind treatment was reduced by 50% in patients receiving macitentan 10 mg (50 events) (HR 0.50; 97.5% CI 0.34–0.75; logrank p < 0.0001) compared to placebo (84 events) [Figure 3 and Table 8].

Figure 3 **Kaplan-Meier estimates of risk of death due to PAH or hospitalization for PAH in SERAPHIN**

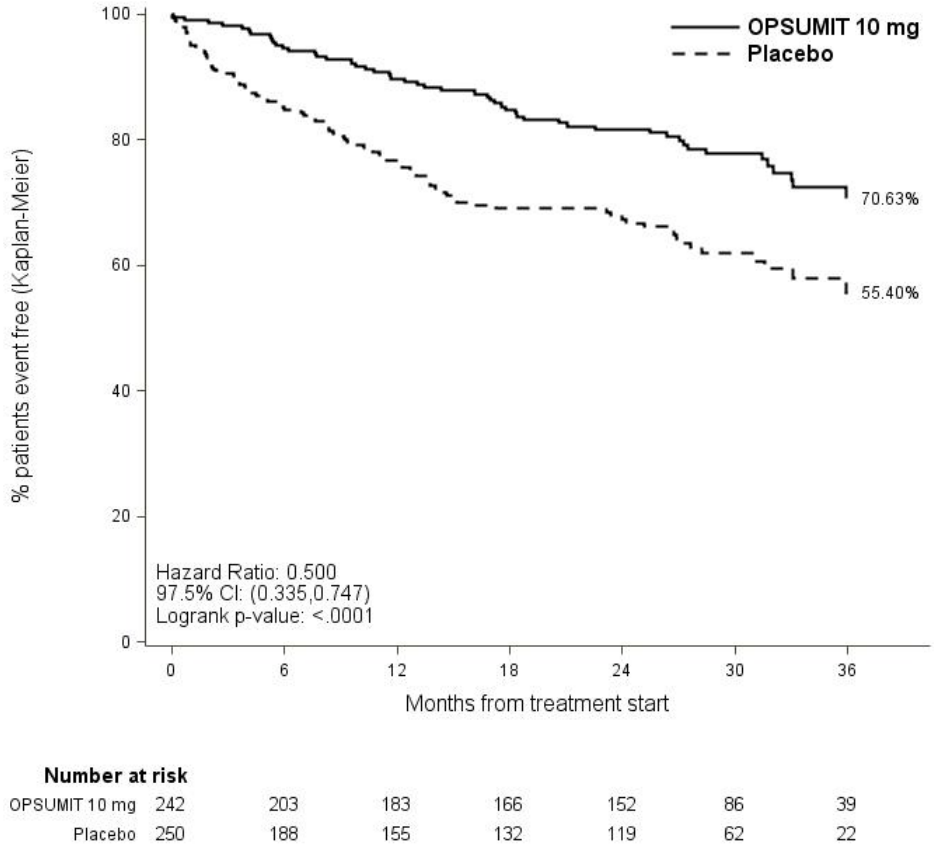


Table 8 **Summary of Death due to PAH and Hospitalisation due to PAH**

	Placebo (N=250) n (%)	**OPSUMIT 10 mg (N=242) n (%)**
Death due to PAH or hospitalisation for PAH	84 (33.6)	50 (20.7)
Component as first event		
Death due to PAH	5 (2.0)	5 (2.1)
Hospitalisation for PAH	79 (31.6)	45 (18.6)

Symptomatic endpoints

Exercise capacity was evaluated as a secondary endpoint. Treatment with macitentan 10 mg at Month 6 resulted in a placebo-corrected mean increase in Six Minute Walk Distance (6MWD) of 22 metres (97.5% CI 3–41). Evaluation of 6MWD by functional class resulted in a placebo-corrected mean increase from baseline to Month 6 in FC III/IV patients of 37 metres (97.5% CI 5–69) and in FC I/II of 12 metres (97.5% CI –8–33). The increase in 6MWD achieved with macitentan was maintained for the duration of the study.

Treatment with macitentan 10 mg led to a 74% higher chance of WHO FC improvement relative to placebo (risk ratio 1.74; 97.5% CI 1.10–2.74). Treatment with macitentan 10 mg led to an improvement

of at least one WHO FC at Month 6 in 22% of patients compared to 13% of patients treated with placebo.

Macitentan 10 mg improved quality of life assessed by the SF-36 questionnaire.

Haemodynamic endpoints
Haemodynamic parameters were assessed in a subset of patients (placebo, N = 67, macitentan 10 mg, N = 57) after 6 months of treatment. Patients treated with macitentan 10 mg achieved a median reduction of 36.5% (CI 21.7–49.2%) in pulmonary vascular resistance and an increase of 0.58 L/min/m^2 (CI 0.28–0.93 L/min/m^2) in cardiac index compared to placebo.

Long-term treatment of PAH
In long-term follow-up of patients who were treated with OPSUMIT 10 mg in the double-blind / open-label extension studies (N=242), Kaplan-Meier estimates of survival at 1, 2, 3, 5 and 7 years were 95%, 89%, 84%, 73% and 63%. The median follow-up time was 5.9 years. Without a control group, these data must be interpreted cautiously.

Efficacy in paediatric patients with pulmonary arterial hypertension
A multi-centre, open-label, randomised, Phase 3 study with an open-label single-arm extension period (AC-055-312/TOMORROW) was conducted to assess pharmacokinetics and efficacy in paediatric patients with symptomatic PAH.

The primary endpoint was the characterisation of pharmacokinetics (see Section 5.2 PHARMACOKINETIC PROPERTIES).

The key secondary endpoint was the time to first Clinical Events Committee (CEC) confirmed disease progression occurring between randomisation and the end of the core period (EOCP) visit defined as, deaths (all causes), or atrial septostomy or Potts' anastomosis, or registration on lung transplant list, or hospitalisation due to worsening PAH or clinical worsening of PAH. Clinical worsening of PAH was defined as: need for, or initiation of new PAH-specific therapy or IV diuretics or continuous oxygen use AND at least 1 of the following: worsening in WHO FC, or new occurrence or worsening of syncope, or 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.

Other secondary endpoints included time to first CEC-confirmed hospitalisation for PAH, time to CEC-confirmed death due to PAH both between randomisation and EOCP, time to all cause death between randomisation and EOCP, change in WHO FC, and N-terminal prohormone of brain natriuretic peptide (NT-proBNP) data.

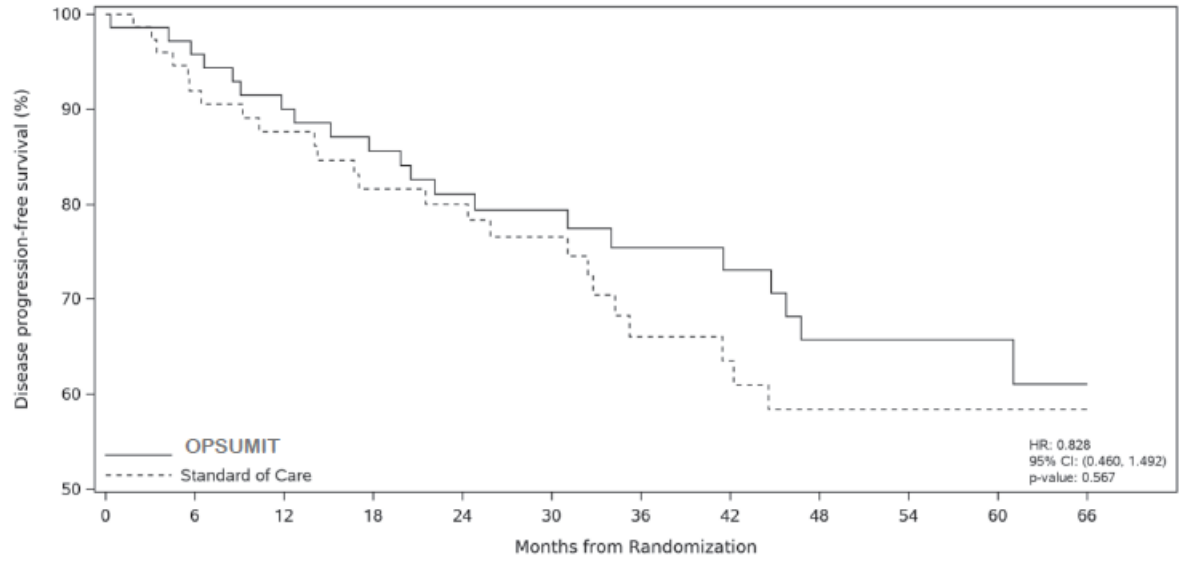
Paediatric population (aged ≥ 2 years to less than 18 years)
A total of 148 patients aged ≥ 2 years to less than 18 years were randomised 1:1 to receive either OPSUMIT or Standard of Care (SoC). In the TOMORROW study, OPSUMIT doses were given based on weight (3.5 mg for ≥ 10-< 15 kg, 5 mg for ≥ 15-< 25 kg, 7.5 mg for ≥ 25-< 50 kg and 10.0 mg for ≥50 kg)*. The majority of patients received at least one PAH-specific concomitant therapy (82.2% OPSUMIT, 100% SoC). The most common therapies were sildenafil (72.6% OPSUMIT, 92.0% SoC), tadalafil (11.0% OPSUMIT, 5.3% SoC), and bosentan (4.1% OPSUMIT, 48.0% SoC). The mean age was 9.8 years (range 2.1 years 17.9 years), with 35 (23.6%) aged ≥ 2 to < 6 years, 61 (41.2%) aged ≥ 6 to < 12 years, and 52 (35.1%) aged ≥ 12 to < 18 years. The majority of patients were white (51.4%) and female (59.5%). Patients were either WHO FC I (25.0%), FC II (56.1%), or FC III (18.9%).

**The doses recommended for clinical use (see Section 4.2 DOSE AND METHOD OF ADMINISTRATION) slightly differ from those used in the TOMORROW study because PK modelling indicated that administering slightly higher doses will result in better exposure matching to the exposure achieved in adults.*

Idiopathic PAH was the most common aetiology in the study population (48.0%), followed by PAH associated with post-operative congenital heart disease (28.4%), PAH with co-incidental congenital heart disease (17.6%), heritable PAH (4. 1%) and PAH associated with connective tissue disease (2.0%). The mean treatment duration in the randomised study was 183.4 weeks in the OPSUMIT arm and 130.6 weeks in the SoC arm.

Treatment with OPSUMIT exhibited a trend toward clinical benefit for time to first CEC-confirmed disease progression (HR 0.828; 95% CI 0.460; 1.492; 2-sided stratified p-value = 0.567) [Figure 4], as compared to the SoC arm. The same number of events for first-confirmed hospitalisation for PAH were observed in both groups (OPSUMIT 11 vs SoC 11; adjusted HR 0.912; 95% CI 0.393; 2.118; 2-sided stratified p-value = 0.882) [Figure 5] .

Figure 4 **Kaplan-Meier curves of time to first CEC-confirmed disease progression event for subjects ≥ 2 years old (key secondary endpoint)**



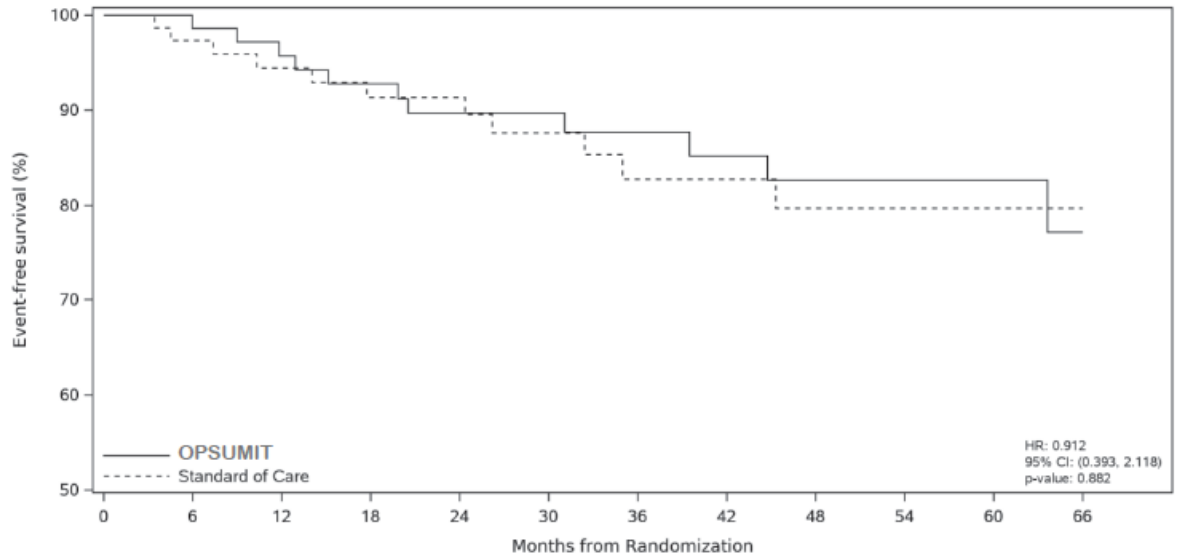
OPSUMIT

at risk	73	68	62	58	51	43	35	30	25	24	18	9
event(s)	0	3	7	10	13	14	16	17	20	20	20	21
censored	0	2	4	5	9	16	22	26	28	29	35	43

Standard of Care

at risk	75	67	60	54	48	41	28	25	19	17	11	4
event(s)	0	6	9	13	14	16	21	22	24	24	24	24
censored	0	2	6	8	13	18	26	28	32	34	40	47

Figure 5 **Kaplan-Meier curves of time to first CEC-confirmed hospitalisation for PAH for subjects ⩾ 2 years old (secondary endpoint)**



OPSUMIT												
at risk	73	70	66	62	55	47	38	34	29	28	20	11
event(s)	0	1	3	5	7	7	8	9	10	10	10	11
censored	0	2	4	6	11	19	27	30	34	35	43	51
Standard of Care												
at risk	75	71	63	59	50	43	30	29	23	21	13	5
event(s)	0	2	4	6	6	8	10	10	11	11	11	11
censored	0	2	8	10	19	24	35	36	41	43	51	59

Other secondary efficacy analyses

In terms of the time to CEC-confirmed death due to PAH and death from all causes, a total of 7 deaths (6 of which were due to PAH as per CEC) were observed in the macitentan arm compared to 6 deaths (4 of which were due to PAH as per CEC) in the SoC arm. The interpretation of mortality results is difficult due to limited number of deaths.

OPSUMIT exhibited a beneficial trend for WHO FC score I or II compared to SoC at week 12 (88.7% in macitentan arm versus 81.7% in SoC arm) and at week 24 (90.0% in macitentan arm versus 82.5% in SoC arm).

OPSUMIT treatment tended to reduce the percent of baseline NT-proBNP (pmol/L) at Week 12 compared with the SoC arm (geometric mean ratio equal to 0.72; 95% CI 0.49 to 1.05) but the results were not statistically significant (2-sided p-value of 0.086). The non-significant trend was less pronounced at Week 24 (geometric mean ratio equal to 0.97; 95% CI 0.66 to 1.43; 2-sided p-value of 0.884).

Paediatric population (aged ≥ 1 month less than 2 years)

An additional 11 patients, aged ≥ 1 month to less than 2 years old were enrolled to receive OPSUMIT without randomisation, 9 patients from the open-label arm of the TOMORROW study and 2 Japanese patients from the PAH3001 study. PAH3001 was a multi-centre, open-label, single arm, Phase 3 study in Japanese paediatric participants (between ≥ 3 months and < 15 years of age) with PAH, conducted to assess the pharmacokinetics and efficacy of macitentan.

At baseline, 6 patients from the TOMORROW study were on phosphodiesterase-5 inhibitors (PDE5i) therapy. At enrolment, the age of the patients ranged from 1.2 years - 1.9 years. Patients were either WHO FC II (4 patients) or FC I (5 patients). PAH associated with congenital heart disease was the most common aetiology (5 patients), followed by idiopathic PAH (4 patients). The initially administered daily dose was 2.5 mg macitentan until the patients reached the 2 years of age. After a median follow-up of 37.3 weeks, none of the patients had experienced a CEC-confirmed disease progression event, a CEC-confirmed hospitalisation for PAH, a CEC-confirmed death due to PAH, or an event of death from all causes. NT-proBNP was reduced by 42.9% (n = 6) at Week 12, 53.2% (n = 5) at Week 24 and 26.1% (n = 6) at Week 36.

At baseline, 1 Japanese patient from the PAH3001 study was on PDE5i therapy. Both Japanese patients were male and their ages at enrolment were 21 months and 22 months. Both patients were in Panama FC I and II and the leading aetiology was post-operative PAH. At week 24, a reduction in baseline NT-proBNP levels of -3.894 pmol/L and -16.402 pmol/L was observed.

Exposure-matching to adult patients was not established in this age group (see Section 4.2 DOSE AND METHOD OF ADMINISTRATION and 5.2 PHARMACOKINETIC PROPERTIES) .

5.2 PHARMACOKINETIC PROPERTIES

The pharmacokinetics of macitentan and its active metabolite aprocitentan have mainly been documented in healthy adult subjects. Exposure to macitentan in patients with PAH was approximately 1.2-fold greater than in healthy subjects. The exposure to the active metabolite in patients, which is approximately 5-fold less potent than macitentan, was approximately 1.3-fold higher than in healthy subjects. The pharmacokinetics of macitentan in PAH patients were not influenced by the severity of the disease.

After repeated administration, the pharmacokinetics of macitentan are dose-proportional up to and including 30 mg.

Absorption
Maximum plasma concentrations of macitentan are achieved about 8 to 9 hours after administration for film-coated tablets and dispersible tablets. The absolute bioavailability after oral administration is not known. Thereafter, plasma concentrations of macitentan and its active metabolite decrease slowly, with an apparent elimination half-life of approximately 16 hours and 48 hours, respectively.

In healthy subjects, the exposure to macitentan and its active metabolite is unchanged in the presence of food and, therefore, macitentan may be taken with or without food.

Distribution
Macitentan and its active metabolite aprocitentan are highly bound to plasma proteins (> 99%), primarily to albumin and to a lesser extent to alpha-1-acid glycoprotein. The apparent volumes of distribution (Vss/F) of macitentan and its active metabolite were about 50 L and 40 L, respectively, in healthy subjects.

Metabolism
Macitentan has four primary metabolic pathways. The most important is oxidative depropylation of the sulfamide to yield a pharmacologically active metabolite aprocitentan. This reaction is dependent on the cytochrome P450 system, mainly CYP3A4 (approximately 99%) with minor contributions from

CYP2C8, CYP2C9 and CYP2C19. The active metabolite circulates in human plasma and may contribute to the pharmacological effect.

Other metabolic pathways yield products without pharmacological activity. For these pathways, CYP2C9 plays a predominant role with minor contributions from CYP2C8, CYP2C19 and CYP3A.

Excretion
Macitentan is only excreted after extensive metabolism. The major excretion route is via urine, accounting for about 50% of the dose.

Comparison between film-coated tablet and dispersible tablet formulations
Bioequivalence of macitentan 10 mg was established between the film-coated tablet and 4 x 2.5 mg dispersible tablets in a study with 28 healthy subjects.

Special populations
For film-coated tablets, there is no clinically relevant effect of age, sex or ethnic origin on the pharmacokinetics of macitentan and its active metabolite.

Similarly, for dispersible tablets, sex or ethnic origin do not have a clinically relevant impact on the pharmacokinetics of macitentan and its active metabolite.

Paediatrics (aged ≥ 1 month to less than 18 years)
Pharmacokinetics of macitentan and its active metabolite aprocitentan were characterised in 47 paediatric patients ≥ 2 years or older and in 11 patients who are ≥ 1 month to less than 2 years old. Weight-based dose regimens of macitentan resulted in observed / simulated exposures in paediatric patients aged 2 years to less than 18 years that were comparable to exposures observed in adult PAH patients and healthy subjects who received 10 mg once daily.

Exposures of macitentan comparable to that of adult PAH patients receiving 10 mg once daily were not achieved for the age group of ≥ 1 month to less than 2 years old (see Section 4.2 DOSE AND METHOD OF ADMINISTRATION).

Renal impairment
Exposure to macitentan and its active metabolite was increased by 1.3- and 1.6-fold, respectively, in adult patients with severe renal impairment.

Hepatic impairment
Exposure to macitentan was decreased by 21%, 34%, and 6% and for the active metabolite by 20%, 25%, and 25% in adult subjects with mild, moderate or severe hepatic impairment, respectively.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity
Macitentan was not genotoxic in a standard battery of in vitro and in vivo assays.

Carcinogenicity
Studies of 2 years duration did not reveal a carcinogenic potential at exposures 18-fold and 116-fold the human exposure in rats and mice, respectively.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Film-coated tablets

Tablet core

Lactose monohydrate
Microcrystalline cellulose
Sodium starch glycollate Type A
Povidone
Magnesium stearate
Polysorbate 80

Film coating

OPADRY AMB complete film coating system OY-B-28920 White, ARTG PI No. 4271

Dispersible tablets

Croscarmellose sodium
Isomalt
Magnesium stearate
Mannitol

6.2 INCOMPATIBILITIES

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store OPSUMIT below 30˚C, protect from moisture.

6.5 NATURE AND CONTENTS OF CONTAINER

Film-coated tablets

Blisters: PVC/PE/PVdC/Aluminium foil blisters in cartons containing 3^, 6^, 9 or 30 film-coated tablets.

Dispersible tablets

Aluminium cold form blisters with integrated desiccant and an aluminium push-through lidding foil in cartons containing 30 tablets.

^ Not marketed

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

No special precautions for disposal.

6.7 PHYSICOCHEMICAL PROPERTIES

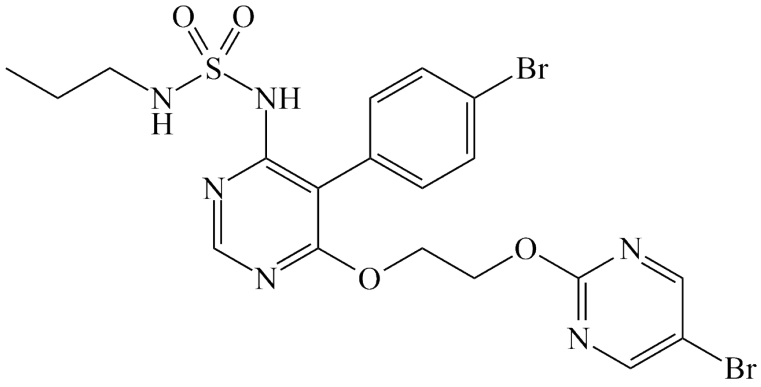
Active: macitentan

OPSUMIT is the brand name for macitentan and is a dual ETA and ETB endothelin receptor antagonist. The chemical name of macitentan is N-[5-(4-Bromophenyl)-6-[2-[(5-bromo-2-pyrimidinyl)oxy]ethoxy]-4-pyrimidinyl]-N'-propylsulfamide.

The molecular formula: $C_{19}H_2OBr_2N_6O_4S$

Relative molecular mass: 588.3 g/mol, the molecule is achiral.

Chemical structure



CAS number

441798-33-0.

Macitentan is a white to off-white crystalline powder that is insoluble in water and slightly soluble in ethanol (approx 2 mg/mL). In the solid state macitentan is very stable, is not hygroscopic, and is not light sensitive. The melting temperature of macitentan is 135 °C, Partition coefficient (1-octanol / aqueous phosphate buffer, pH 7.4): log D = 2.9 and ionization constant pKa is 6.2.

7 MEDICINE SCHEDULE (POISONS STANDARD)

SCHEDULE 4 - Prescription Only Medicine

8 SPONSOR

JANSSEN-CILAG Pty Ltd
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Macquarie Park NSW 2113 Australia
Telephone: 1800 226 334

NZ Office: Auckland New Zealand

9 DATE OF FIRST APPROVAL

5 February 2014

10 DATE OF REVISION

14 August 2025

SUMMARY TABLE OF CHANGES

Section Changed	Summary of new information
Section 2, 3, 4.1, 4.2, 4.4, 4.8, 4.9, 5.1, 5.2, 6.1 and 6.5	Addition of dispersible tablets and use in paediatric population.