ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Opsumit 10 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 10 mg macitentan.

Excipients with known effect

Each film-coated tablet contains approximately 37 mg of lactose (as monohydrate) and approximately 0.06 mg of soya bean lecithin (E322).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet (tablet).

5.5 mm, round, biconvex, white to off-white film-coated tablets, debossed with “10” on both sides.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Adults

Opsumit, as monotherapy or in combination, is indicated for the long-term treatment of pulmonary arterial hypertension (PAH) in adult patients of WHO Functional Class (FC) II to III (see section 5.1).

Paediatric population

Opsumit, as monotherapy or in combination, is indicated for the long-term treatment of pulmonary arterial hypertension (PAH) in paediatric patients aged less than 18 years and bodyweight ≥ 40 kg with WHO Functional Class (FC) II to III (see section 5.1).

4.2 Posology and method of administration

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

Posology

Adults and paediatric patients aged less than 18 years of age weighing at least 40 kg
The recommended dose is 10 mg once daily. Opsumit should be taken every day at about the same time.

If the patient misses a dose of Opsumit, the patient should be told to take it as soon as possible and then take the next dose at the regularly scheduled time. The patient should be told not to take two doses at the same time if a dose has been missed.

The 10 mg film-coated tablets are only recommended in paediatric patients weighing at least 40 kg. For paediatric patients weighing less than 40 kg, a lower strength of dispersible tablets of 2.5 mg is available. Please refer to the Opsumit dispersible tablets Summary of Product Characteristics.

Special populations

Elderly
No dose adjustment is required in patients over the age of 65 years (see section 5.2).

Hepatic impairment
Based on pharmacokinetic (PK) data, no dose adjustment is required in patients with mild, moderate or severe hepatic impairment (see sections 4.4 and 5.2). However, there is no clinical experience with the use of macitentan in PAH patients with moderate or severe hepatic impairment. Opsumit must not be initiated in patients with severe hepatic impairment, or clinically significant elevated hepatic aminotransferases (greater than 3 times the Upper Limit of Normal (> 3 × ULN); see sections 4.3 and 4.4).

Renal impairment
Based on PK data, no dose adjustment is required in patients with renal impairment. There is no clinical experience with the use of macitentan in PAH patients with severe renal impairment. The use of Opsumit is not recommended in patients undergoing dialysis (see sections 4.4 and 5.2).

Paediatric population
Dosing and efficacy of macitentan in children below 2 years of age have not been established. Currently available data are described in sections 4.8, 5.1 and 5.2 but no recommendation on a posology can be made.

Method of administration

The film-coated tablets are not breakable and are to be swallowed whole, with water. They may be taken with or without food.

4.3 Contraindications

- Hypersensitivity to the active substance, soya or to any of the excipients listed in section 6.1.
- Pregnancy (see section 4.6).
- Women of childbearing potential who are not using reliable contraception (see sections 4.4 and 4.6).
- Breastfeeding (see section 4.6).
- Patients with severe hepatic impairment (with or without cirrhosis) (see section 4.2).
- Baseline values of hepatic aminotransferases (aspartate aminotransferases (AST) and/or alanine aminotransferases (ALT) > 3 × ULN) (see sections 4.2 and 4.4).

4.4 Special warnings and precautions for use

The benefit/risk balance of macitentan has not been established in patients with WHO class I functional status of pulmonary arterial hypertension.

Liver function

Elevations of liver aminotransferases (AST, ALT) have been associated with PAH and with endothelin receptor antagonists (ERAs). Opsumit is not to be initiated in patients with severe hepatic impairment or elevated aminotransferases (> 3 × ULN) (see sections 4.2 and 4.3) and is not recommended in patients with moderate hepatic impairment. Liver enzyme tests should be obtained prior to initiation of Opsumit.

Patients should be monitored for signs of hepatic injury and monthly monitoring of ALT and AST is recommended. If sustained, unexplained, clinically relevant aminotransferase elevations occur, or if elevations are accompanied by an increase in bilirubin > 2 × ULN, or by clinical symptoms of liver injury (e.g., jaundice), Opsumit treatment should be discontinued.

Reinitiation of Opsumit may be considered following the return of hepatic enzyme levels to within the normal range in patients who have not experienced clinical symptoms of liver injury. The advice of a hepatologist is recommended.

Haemoglobin concentration

Decrease in haemoglobin concentrations has been associated with endothelin receptor antagonists (ERAs) including macitentan (see section 4.8). 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 macitentan and other ERAs. Initiation of Opsumit is not recommended in patients with severe anaemia. It is recommended that haemoglobin concentrations be measured prior to initiation of treatment and tests repeated during treatment as clinically indicated.

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 macitentan is administered in patients with PAH, the possibility of pulmonary veno-occlusive disease should be considered.

Use in women of childbearing potential

Opsumit treatment should only be initiated in women of childbearing potential when the absence of pregnancy has been verified, appropriate advice on contraception provided, and reliable contraception is practised (see sections 4.3 and 4.6). Women should not become pregnant for 1 month after discontinuation of Opsumit. Monthly pregnancy tests during treatment with Opsumit are recommended to allow the early detection of pregnancy.

Concomitant use with strong CYP3A4 inducers

In the presence of strong CYP3A4 inducers reduced efficacy of macitentan could occur. The combination of macitentan with strong CYP3A4 inducers (e.g., rifampicin, St. John's wort, carbamazepine, and phenytoin) should be avoided (see section 4.5).

Concomitant use with strong CYP3A4 inhibitors

Caution should be exercised when macitentan is administered concomitantly with strong CYP3A4 inhibitors (e.g., itraconazole, ketoconazole, voriconazole, clarithromycin, telithromycin, nefazodone, ritonavir, and saquinavir) (see section 4.5).

Concomitant use with moderate dual or combined CYP3A4 and CYP2C9 inhibitors

Caution should be exercised when macitentan is administered concomitantly with moderate dual inhibitors of CYP3A4 and CYP2C9 (e.g., fluconazole and amiodarone) (see section 4.5).

Caution should also be exercised when macitentan is administered concomitantly with both a moderate CYP3A4 inhibitor (e.g., ciprofloxacin, cyclosporine, diltiazem, erythromycin, verapamil) and moderate CYP2C9 inhibitor (e.g., miconazole, piperine) (see section 4.5).

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 macitentan in PAH patients with severe renal impairment. Caution is recommended in this population. There is no experience with the use of

macitentan in patients undergoing dialysis, therefore Opsumit is not recommended in this population (see sections 4.2 and 5.2).

Excipients with known effects

Opsumit contains lactose. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

Opsumit contains soya bean lecithin. If a patient is hypersensitive to soya, Opsumit must not be used (see section 4.3).

Other excipients

This medicinal product contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially 'sodium-free'.

4.5 Interaction with other medicinal products and other forms of interaction

In vitro studies

The cytochrome P450 CYP3A4 is the main enzyme involved in the metabolism of macitentan and in the formation of its active metabolite, with minor contribution from CYP2C8, CYP2C9, and CYP2C19 enzymes (see section 5.2). Macitentan and its active metabolite do not have clinically relevant inhibitory or inducing effects on cytochrome P450 enzymes.

Macitentan and its active metabolite are not inhibitors of hepatic or renal uptake transporters at clinically relevant concentrations, including the organic anion transporting polypeptides (OATP1B1 and OATP1B3). Macitentan and its active metabolite are not relevant substrates of OATP1B1 and OATP1B3 but enter the liver by passive diffusion.

Macitentan and its active metabolite are not inhibitors of hepatic or renal efflux pumps at clinically relevant concentrations, including the multi-drug resistance protein (P-gp, MDR-1) and multidrug and toxin extrusion transporters (MATE1 and MATE2-K). Macitentan is not a substrate for P-gp/MDR-1.

At clinically relevant concentrations, macitentan and its active metabolite do not interact with proteins involved in hepatic bile salt transport, i.e., the bile salt export pump (BSEP) and the sodium-dependent taurocholate co-transporting polypeptide (NTCP).

In vivo studies

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 should be avoided (see section 4.4).

Ketoconazole
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. The uncertainties of such modelling should be considered. Exposure to the active metabolite of macitentan was reduced by 26%. Caution should be exercised when macitentan is administered concomitantly with strong CYP3A4 inhibitors (see section 4.4).

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 PBPK modelling. However, there was no clinically relevant change in exposure to the active metabolite of macitentan. The uncertainties of such modelling should be considered. Caution should be exercised when macitentan is administered concomitantly with moderate dual inhibitors of CYP3A4 and CYP2C9 (e.g., fluconazole and amiodarone) (see section 4.4).

Caution should also be exercised when macitentan is administered concomitantly with both a moderate CYP3A4 inhibitor (e.g., ciprofloxacin, cyclosporine, diltiazem, erythromycin, verapamil) and moderate CYP2C9 inhibitor (e.g., miconazole, piperine) (see section 4.4).

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 three times a day 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.

Cyclosporine A
Concomitant treatment with cyclosporine A 100 mg twice daily, a combined CYP3A4 and OATP inhibitor, did not alter the steady-state exposure to macitentan and its active metabolite to a clinically relevant extent.

Hormonal contraceptives
Macitentan 10 mg once daily did not affect the pharmacokinetics 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 a BCRP substrate drug (riociguat 1 mg; rosuvastatin 10 mg).

Paediatric population

Interaction studies have only been performed in adults.

4.6 Fertility, pregnancy, and lactation

Use in women of childbearing potential/Contraception in males and females

Opsumit treatment should only be initiated in women of childbearing potential when the absence of pregnancy has been verified, appropriate advice on contraception provided, and reliable contraception is practised (see sections 4.3 and 4.4). Women should not become pregnant for 1 month after discontinuation of Opsumit. Monthly pregnancy tests during treatment with Opsumit are recommended to allow the early detection of pregnancy.

Pregnancy

There are no data from the use of macitentan in pregnant women. Studies in animals have shown reproductive toxicity (see section 5.3). The potential risk for humans is still unknown. Opsumit is contraindicated during pregnancy and in women of childbearing potential who are not using reliable contraception (see section 4.3).

Breastfeeding

It is unknown whether macitentan is excreted in human milk. In rats, macitentan and its metabolites are excreted into milk during lactation (see section 5.3). A risk to the breastfeeding child cannot be excluded. Opsumit is contraindicated during breastfeeding (see section 4.3).

Male fertility

The development of testicular tubular atrophy in male animals was observed after treatment with macitentan (see section 5.3). Decreases in sperm count have been observed in patients taking ERAs. Macitentan, like other ERAs, may have an adverse effect on spermatogenesis in men.

4.7 Effects on ability to drive and use machines

Macitentan has minor influence on the ability to drive and use machines. No studies on the effects on the ability to drive and use machines have been performed. However, undesirable effects may occur (e.g., headache, hypotension) that may influence the ability to drive and use machines (see section 4.8).

4.8 Undesirable effects

Summary of the safety profile.

The most commonly reported adverse reactions in the SERAPHIN study were nasopharyngitis (14%), headache (13.6%) and anaemia (13.2%, see section 4.4).

Tabulated list of adverse reactions

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. Adverse reactions associated with macitentan obtained from this clinical study are tabulated below. Post-marketing adverse reactions are also included.

Frequencies are defined as: very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1 000 to < 1/100); rare (≥ 1/10 000 to < 1/1 000); very rare (< 1/10 000); not known (cannot be estimated from the available data).

System organ class	Frequency	Adverse reaction
Infections and infestations	Very common	Nasopharyngitis
	Very common	Bronchitis
	Common	Pharyngitis
	Common	Influenza
	Common	Urinary tract infection
Blood and lymphatic system disorders	Very common	Anaemia, haemoglobin decrease[5]
	Common	Leukopenia[6]
	Common	Thrombocytopenia[7]
Immune system disorders	Uncommon	Hypersensitivity reactions (e.g., angioedema, pruritus, rash)[1]
Nervous system disorders	Very common	Headache
Vascular disorders	Common	Hypotension[2], flushing
Respiratory, thoracic and mediastinal disorders	Common	Nasal congestion[1]
Hepatobiliary disorders	Common	Aminotransferase elevations[4]
Reproductive system and breast disorders	Common	Increased uterine bleeding[8]
General disorders and administration site conditions	Very common	Oedema, fluid retention[3]

[1] Data derived from pooled placebo-controlled studies.

[8] Includes PTs of heavy menstrual bleeding, abnormal uterine bleeding, intermenstrual bleeding, uterine/vaginal haemorrhage, polymennorhoea and menstruation irregular. Frequency based on exposure in females.

Description of selected adverse reactions

[2] Hypotension has been associated with the use of ERAs including macitentan. In SERAPHIN, a long-term double-blind study in patients with PAH, hypotension was reported for 7.0% and 4.4% of patients on macitentan 10 mg and placebo, respectively. This corresponded to 3.5 events / 100 patient-years on macitentan 10 mg compared to 2.7 events / 100 patient-years on placebo.

[3] Oedema/fluid retention has been associated with the use of ERAs including macitentan. 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. In a double-blind study in adult patients with idiopathic pulmonary fibrosis, the incidence of peripheral oedema AEs in the macitentan and placebo treatment groups was 11.8% and 6.8%, respectively. In two double-blind clinical studies in adult patients with digital ulcers associated with systemic sclerosis, the incidences of peripheral oedema AEs ranged from 13.4% to 16.1% in the macitentan 10 mg groups and from 6.2% to 4.5% in the placebo groups.

Laboratory abnormalities

[4] Liver aminotransferases

The incidence of aminotransferase elevations (ALT/AST) > 3 × ULN was 3.4% on macitentan 10 mg and 4.5% on placebo in SERAPHIN, a double-blind study in patients with PAH. Elevations > 5 × ULN occurred in 2.5% of patients on macitentan 10 mg versus 2% of patients on placebo.

[5] 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 1 g/dL. A decrease from baseline in haemoglobin concentration to below 10 g/dL was reported in 8.7% of patients treated with macitentan 10 mg and 3.4% of placebo-treated patients.

[6] 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.

[7] 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

Of the 742 patients who participated in the pivotal SERAPHIN double-blind study, 550 patients entered a long-term open-label (OL) extension study. (The OL cohort included 182 patients who continued on macitentan 10 mg and 368 patients who received placebo or macitentan 3 mg and crossed over to macitentan 10 mg.)

Long-term follow-up of these 550 patients for a median exposure of 3.3 years and a maximum exposure of 10.9 years showed a safety profile that was consistent as described above during the SERAPHIN double-blind phase.

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

The safety of macitentan was evaluated in TOMORROW, a Phase 3 study in 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. In addition to the adverse reactions tabulated above, the following paediatric adverse reactions were reported: upper respiratory tract infection (31.9%), rhinitis (8.3%), and gastroenteritis (11.1%).

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

An additional 11 patients, aged ≥ 1 month to less than 2 years old were enroled 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, however, very limited clinical safety data are available to establish a robust safety conclusion in paediatric population below 2 years.

The safety of macitentan in children below 2 years of age has not been established (see section 4.2).

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation 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 via the national reporting system listed in Appendix V.

4.9 Overdose

Macitentan has been administered as a single dose of up to 600 mg to healthy adult subjects. Adverse reactions 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.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: anti-hypertensives, anti-hypertensives for pulmonary arterial hypertension. ATC code: C02KX04.

Mechanism of action

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

Macitentan is an orally active potent endothelin receptor antagonist, active on both ET_A and ET_B receptors and approximately 100-fold more selective for ET_A as compared to ET_B *in vitro*. Macitentan displays high affinity and sustained occupancy of the ET receptors in human pulmonary arterial smooth muscle cells. This prevents endothelin-mediated activation of second messenger systems that result in vasoconstriction and smooth muscle cell proliferation.

Clinical efficacy and safety

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 endpoint was the time to first occurrence of a morbidity or mortality event, up to the end of double-blind treatment, 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 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.

All patients were followed up to end-of-study (EOS) for vital status. EOS was declared when the predefined number of primary endpoint events was reached. In the period between end-of-treatment (EOT) and EOS, patients could receive open-label macitentan 10 mg or alternative PAH therapy. The overall median double-blind treatment duration was 115 weeks (up to a maximum of 188 weeks on macitentan).

The mean age of all patients was 46 years (range 12–85 years of age, including 20 patients below 18, 706 patients between 18–74 years, and 16 patients aged 75 and older) 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.

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 corrected simple congenital heart disease (8%), and PAH associated with other aetiologies (medicinal products and toxins [3%] and HIV [1%]).

Outcome endpoints

Treatment with macitentan 10 mg resulted in a 45% risk reduction (hazard ratio [HR] 0.55; 97.5% CI: 0.39 to 0.76; logrank $p < 0.0001$) of the composite morbidity-mortality endpoint up to EOT when compared to placebo [Figure 1 and Table 1]. The treatment effect was established early and was sustained.

Efficacy of macitentan 10 mg on the primary endpoint was consistent across subgroups of age, sex, ethnic origin, geographical region, aetiology, by monotherapy or in combination with another PAH therapy and by WHO FC (I/II and III/IV).

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

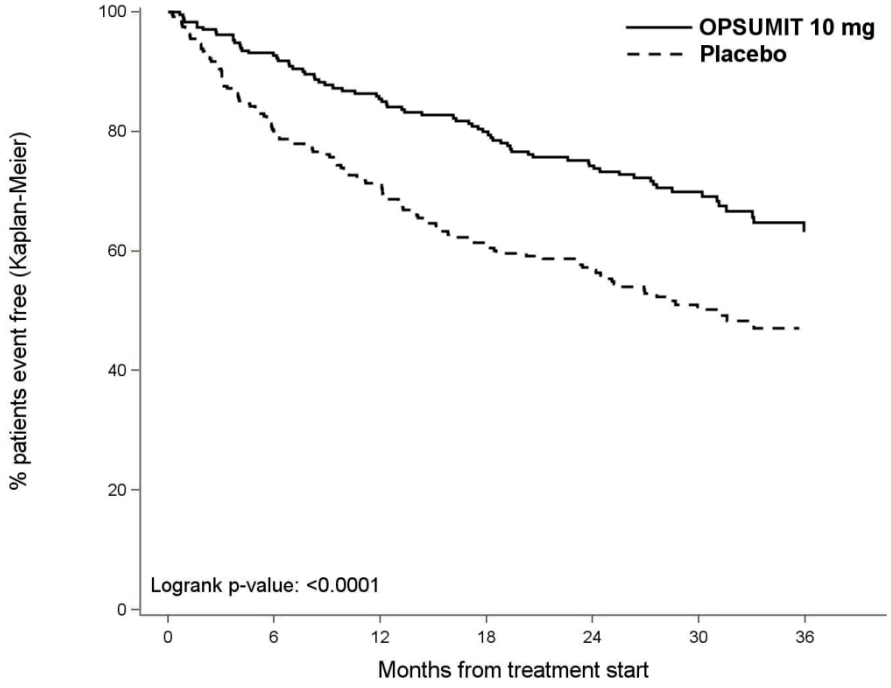

Table 1: Summary of outcome events

Endpoints & statistics	Patients with events		Treatment comparison: macitentan 10 mg vs placebo			
	Placebo (N = 250)	Macitentan 10 mg (N = 242)	Absolute risk reduction	Relative risk reduction (97.5% CI)	HR [a] (97.5% CI)	Logrank p-value
Morbidity-mortality event [b]	53%	37%	16%	45% (24%; 61%)	0.55 (0.39; 0.76)	< 0.0001
Death [c] **n (%)**	19 (7.6%)	14 (5.8%)	2%	36% (−42%; 71%)	0.64 (0.29; 1.42)	0.20
Worsening of PAH n (%)	93 (37.2%)	59 (24.4%)	13%	49% (27%; 65%)	0.51 (0.35; 0.73)	< 0.0001
i.v./s.c. prostanoid initiation n (%)	6 (2.4%)	1 (0.4%)	2%			

[a] = based on Cox's Proportional Hazards Model
[b] = % of patients with an event at 36 months = 100 × (1 - KM estimate)
[c] = all cause death 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).

The risk of PAH-related death or hospitalisation for PAH up to EOT was reduced by 50% (HR 0.50; 97.5% CI: 0.34 to 0.75; logrank $p < 0.0001$) in patients receiving macitentan 10 mg (50 events) compared to placebo (84 events). At 36 months, 44.6% of patients on placebo and 29.4% of patients on macitentan 10 mg (Absolute Risk Reduction = 15.2%) had been hospitalised for PAH or died from a PAH-related cause.

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 6MWD of 22 meters (97.5% CI: 3 to 41; $p = 0.0078$). 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 meters (97.5% CI: 5 to 69) and in FC I/II of 12 meters (97.5% CI: −8 to 33). The increase in 6MWD achieved with macitentan was maintained for the duration of the study.

Treatment with macitentan 10 mg at Month 6 led to a 74% higher chance of WHO FC improvement relative to placebo (risk ratio 1.74; 97.5% CI: 1.10 to 2.74; $p = 0.0063$).

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% (97.5% CI: 21.7 to 49.2%) in pulmonary vascular resistance and an increase of 0.58 L/min/m^2 (97.5% CI: 0.28 to 0.93 L/min/m^2) in cardiac index compared to placebo.

Long-term data in PAH

In long-term follow-up of 242 patients who were treated with macitentan 10 mg in the double-blind (DB) phase of the SERAPHIN study, 182 of which continued with macitentan in the open-label (OL) extension study (SERAPHIN OL) (DB/OL cohort), Kaplan-Meier estimates of survival at 1, 2, 5, 7 and 9 years were 95%, 89%, 73%, 63% and 53%, respectively. The median follow-up time was 5.9 years.

Paediatric population

Efficacy in paediatric population is mainly based in an extrapolation exercise based upon exposure-matching to the adult efficacious dose range given the similarity of the disease in children and adults, as well as on supportive efficacy and safety data from the TOMORROW phase 3 study described below.

A multi-centre, open-label, randomised, Phase 3 study with an open-label single-arm extension period (TOMORROW) was conducted to assess pharmacokinetics, efficacy and safety of macitentan in paediatric patients with symptomatic PAH.

The primary endpoint was the characterisation of pharmacokinetics (see section 5.2).

The key secondary combined 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 < 18 years were randomised 1:1 to receive either macitentan or Standard of Care (SoC). SoC included PAH non-specific treatment and/or up to 2 PAH-specific medications (including another ERA) and excluding macitentan and IV/SC prostanoids. 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%).

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%). Co-incidental CHD only included typically small coincidental defects such as pre-tricuspid, post-tricuspid shunts, atrial septal defect, ventricular septal defect, patent ductus arteriosus, none considered causative of the degree of PAH.

The mean treatment duration in the randomised study was 183.4 weeks in the macitentan arm and 130.6 weeks in the SoC arm.

Fewer events for the key secondary endpoint of CEC-confirmed disease progression were observed in the macitentan arm (21 events/73 patients, 29%) versus the SoC arm (24 events/75 patients, 32%),

absolute risk reduction of 3%. The hazard ratio was 0.828 (95% CI 0.460; 1.492; 2-sided stratified p-value = 0.567). The numerical trend towards benefit was mainly driven by the clinical worsening of PAH.

Other secondary efficacy analyses

The same number of events for first-confirmed hospitalisation for PAH were observed in both groups (macitentan 11 vs. SoC 11; adjusted HR=0.912, 95% CI= [0.393; 2.118]). 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.

There was a numerically higher proportion of patients at WHO FC I or II reported at Week 12 in the macitentan arm compared with the SoC arm (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).

Macitentan treatment tended to reduce the percent of baseline NT-proBNP (pmol/L) at Week 12 compared with the SoC arm (geometric mean ratio: 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: 0.97;95% CI: 0.66 to 1.43;2-sided p-value of 0.884).

Efficacy results from patients aged ≥ 2 years to less than 18 years were similar to those of adult patients.

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

An additional 11 patients, aged ≥ 1 month to less than 2 years old were enroled to receive macitentan 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 PDE5i therapy. At enrolment, the age range of the patients ranged from 1.2 years-1.9 years. Patients were either WHO FC II (4) or FC I (5). 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 sections 4.2 and 5.2).

5.2 Pharmacokinetic properties

The pharmacokinetics of macitentan and its active metabolite 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 8-9 hours after administration for film-coated tablets and dispersible tablets. 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 are highly bound to plasma proteins (> 99%), primarily to albumin and to a lesser extent to alpha1-acid glycoprotein. Macitentan and its active metabolite ACT-132577 are well distributed into tissues as indicated by an apparent volume of distribution (Vss/F) of approximately 50 L and 40 L for macitentan and ACT-132577, respectively.

Biotransformation

Macitentan has four primary metabolic pathways. Oxidative depropylation of the sulfamide yields a pharmacologically active metabolite. This reaction is dependent on the cytochrome P450 system, mainly CYP3A4 (approximately 99%) with minor contributions of 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 CYP3A4.

Elimination

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

There is no clinically relevant effect of age, sex or ethnic origin on the pharmacokinetics of macitentan and its active metabolite.

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. This increase is not considered clinically relevant (see sections 4.2 and 4.4).

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. This decrease is not considered clinically relevant (see sections 4.2 and 4.4).

Paediatric population (aged ≥ 1 month to less than 18 years)

Pharmacokinetics of macitentan and its active metabolite aprocitentan were characterised in 47 paediatric patients who were ≥ 2 years and in 11 patients who were ≥ 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).

5.3 Preclinical safety data

In dogs, macitentan decreased blood pressure at exposures similar to the therapeutic human exposure. Intimal thickening of coronary arteries was observed at 17-fold the human exposure after 4 to 39 weeks of treatment. Due to the species-specific sensitivity and the safety margin, this finding is considered not relevant for humans.

Increased liver weight and hepatocellular hypertrophy were observed in mice, rats and dogs after treatment with macitentan. These changes were largely reversible and considered non-adverse adaptations of the liver to increased metabolic demand.

Macitentan induced minimal to slight mucosal hyperplasia and inflammatory infiltration in the submucosa of the nasal cavity in the mouse carcinogenicity study at all doses. No nasal cavity findings were noted in the 3-month mouse toxicity study or in rat and dog studies.

Macitentan was not genotoxic in a standard battery of *in vitro* and *in vivo* assays. Macitentan was not phototoxic *in vivo* after single dose at exposures of up to 24-fold the human exposure.
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.

Testicular tubular dilatation was observed in chronic toxicity studies with male rats and dogs with safety margins of 11.6 and 5.8, respectively. Tubular dilatation was fully reversible. After 2 years of treatment, testicular tubular atrophy was seen in rats at 4-fold the human exposure.
Hypospermatogenesis was observed in the life-long carcinogenicity study in rats and in the repeat-dose toxicity studies in dogs at exposures that provide safety margins of 9.7 in rats and 23 in dogs. The safety margins for fertility were 18 for male and 44 for female rats. No testicular findings were noted in mice after treatment up to 2 years.

Macitentan was teratogenic in rabbits and rats at all doses tested. In both species there were cardiovascular and mandibular arch fusion abnormalities.

Administration of macitentan to female rats from late pregnancy through lactation at maternal exposures 5-fold the human exposure, caused reduced pup survival and impairment of the reproductive capability of the offspring, which was exposed to macitentan during late intrauterine life and via the milk during the suckling period.

Treatment of juvenile rats from postnatal Day 4 to Day 114 caused reduced body weight gain leading to secondary effects on development (slight delay of descensus testis, reversible reduction of long-bone length, prolonged estrous cycle). Slightly increased pre- and post-implantation loss, decreased mean number of pups, and decreased testis and epididymis weights, were observed at exposures 7-fold the human exposure. Testicular tubular atrophy, and minimal effects on reproductive variables and sperm morphology were recorded at exposures 3.8-fold the human exposure.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core
Lactose monohydrate
Microcrystalline cellulose (E460i)
Sodium starch glycolate Type A
Povidone
Magnesium stearate (E470b)
Polysorbate 80 (E433)

Film coating
Poly(vinyl-alcohol) (E1203)
Titanium dioxide (E171)
Talc (E553b)
Soya bean lecithin (E322)
Xanthan gum (E415)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

5 years.

6.4 Special precautions for storage

Do not store above 30°C.

6.5 Nature and contents of container

White, opaque PVC/PE/PVdC/Aluminium blisters in cartons containing 15 or 30 film-coated tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

No special requirements.

7. MARKETING AUTHORISATION HOLDER

Janssen-Cilag International NV
Turnhoutseweg 30
B 2340 Beerse
Belgium

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/13/893/001
EU/1/13/893/002

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 20 December 2013
Date of latest renewal: 23 August 2018

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency https://www.ema.europa.eu.

1. NAME OF THE MEDICINAL PRODUCT

Opsumit 2.5 mg dispersible tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each dispersible tablet contains 2.5 mg macitentan.

Excipients with known effect

Each dispersible tablet contains approximately 25 mg of isomalt.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Dispersible tablet.

Round (9 mm) white to almost white dispersible tablet, debossed with a “2.5” on one side and with “Mn” on the other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Opsumit, as monotherapy or in combination, is indicated for the long-term treatment of pulmonary arterial hypertension (PAH) in paediatric patients aged 2 years to less than 18 years with WHO Functional Class (FC) II to III (see section 5.1).

4.2 Posology and method of administration

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

Posology

Paediatric population (aged ≥ 2 years to less than 18 years)
The recommended daily dose of Opsumit is based on body weight (Table 1). Opsumit should be taken every day at about the same time.

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 × 2.5 mg
≥ 20 and < 40	7.5 mg	3 × 2.5 mg
≥ 40	10 mg	4 × 2.5 mg*

*Opsumit is also available as a 10 mg film-coated tablet. Opsumit administered in the form of one 10 mg film-coated tablet is bioequivalent to four 2.5 mg dispersible tablets. Therefore, one film-coated tablet may be used as a direct replacement for paediatric patients who weigh at least 40 kg and are aged 2 years and older (see section 5.2). Please refer to the Opsumit film-coated tablets Summary of Product Characteristics.

If the patient misses a dose of Opsumit, administer it as soon as possible and then take the next dose at the regularly scheduled time. The patient should not take two doses at the same time if a dose has been missed.

Special populations

Elderly
No dose adjustment is required in patients over the age of 65 years (see section 5.2).

Hepatic impairment
Based on pharmacokinetic (PK) data, no dose adjustment is required in patients with mild, moderate or severe hepatic impairment (see sections 4.4 and 5.2). However, there is no clinical experience with the use of macitentan in PAH patients with moderate or severe hepatic impairment. Opsumit must not be initiated in patients with severe hepatic impairment, or clinically significant elevated hepatic aminotransferases (greater than 3 times the Upper Limit of Normal (> 3 × ULN); see sections 4.3 and 4.4).

Renal impairment
Based on PK data, no dose adjustment is required in patients with renal impairment. There is no clinical experience with the use of macitentan in PAH patients with severe renal impairment. The use of Opsumit is not recommended in patients undergoing dialysis (see sections 4.4 and 5.2).

Paediatric population
Dosing and efficacy of macitentan in children below 2 years of age have not been established. Currently available data are described in sections 4.8, 5.1 and 5.2 but no recommendation on a posology can be made.

Method of administration

Opsumit should be taken orally once a day 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 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 (see section 6.6).

Administration by a spoon
The prescribed daily dose of dispersible tablet(s) should be added to room temperature drinking water in a 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 or 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 (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 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

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
- Pregnancy (see section 4.6).
- Women of childbearing potential who are not using reliable contraception (see sections 4.4 and 4.6).
- Breastfeeding (see section 4.6).
- Patients with severe hepatic impairment (with or without cirrhosis) (see section 4.2).
- Baseline values of hepatic aminotransferases (aspartate aminotransferases (AST) and/or alanine aminotransferases (ALT) > 3 × ULN) (see sections 4.2 and 4.4).

4.4 Special warnings and precautions for use

The benefit/risk balance of macitentan has not been established in patients with WHO class I functional status of pulmonary arterial hypertension.

Liver function

Elevations of liver aminotransferases (AST, ALT) have been associated with PAH and with endothelin receptor antagonists (ERAs). Opsumit is not to be initiated in patients with severe hepatic impairment or elevated aminotransferases (> 3 × ULN) (see sections 4.2 and 4.3) and is not recommended in patients with moderate hepatic impairment. Liver enzyme tests should be obtained prior to initiation of Opsumit.

Patients should be monitored for signs of hepatic injury and monthly monitoring of ALT and AST is recommended. If sustained, unexplained, clinically relevant aminotransferase elevations occur, or if elevations are accompanied by an increase in bilirubin > 2 × ULN, or by clinical symptoms of liver injury (e.g., jaundice), Opsumit treatment should be discontinued.

Reinitiation of Opsumit may be considered following the return of hepatic enzyme levels to within the normal range in patients who have not experienced clinical symptoms of liver injury. The advice of a hepatologist is recommended.

Haemoglobin concentration

Decrease in haemoglobin concentrations has been associated with endothelin receptor antagonists (ERAs) including macitentan (see section 4.8). 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 macitentan and other ERAs. Initiation of Opsumit is not recommended in patients with severe anaemia. It is recommended that haemoglobin concentrations be measured prior to initiation of treatment and tests repeated during treatment as clinically indicated.

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 macitentan is administered in patients with PAH, the possibility of pulmonary veno-occlusive disease should be considered.

Use in women of childbearing potential

Opsumit treatment should only be initiated in women of childbearing potential when the absence of pregnancy has been verified, appropriate advice on contraception provided, and reliable contraception is practised (see sections 4.3 and 4.6). Women should not become pregnant for 1 month after discontinuation of Opsumit. Monthly pregnancy tests during treatment with Opsumit are recommended to allow the early detection of pregnancy.

Concomitant use with strong CYP3A4 inducers

In the presence of strong CYP3A4 inducers reduced efficacy of macitentan could occur. The combination of macitentan with strong CYP3A4 inducers (e.g., rifampicin, St. John's wort, carbamazepine, and phenytoin) should be avoided (see section 4.5).

Concomitant use with strong CYP3A4 inhibitors

Caution should be exercised when macitentan is administered concomitantly with strong CYP3A4 inhibitors (e.g., itraconazole, ketoconazole, voriconazole, clarithromycin, telithromycin, nefazodone, ritonavir, and saquinavir) (see section 4.5).

Concomitant use with moderate dual or combined CYP3A4 and CYP2C9 inhibitors

Caution should be exercised when macitentan is administered concomitantly with moderate dual inhibitors of CYP3A4 and CYP2C9 (e.g., fluconazole and amiodarone) (see section 4.5).

Caution should also be exercised when macitentan is administered concomitantly with both a moderate CYP3A4 inhibitor (e.g., ciprofloxacin, cyclosporine, diltiazem, erythromycin, verapamil) and moderate CYP2C9 inhibitor (e.g., miconazole, piperine) (see section 4.5).

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 macitentan in PAH patients with severe renal impairment. Caution is recommended in this population. There is no experience with the use of macitentan in patients undergoing dialysis, therefore Opsumit is not recommended in this population (see sections 4.2 and 5.2).

Excipients with known effects

Opsumit dispersible tablets contain isomalt. Patients with rare hereditary problems of fructose intolerance should not take this medicine.

Other excipients

This medicinal product contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially 'sodium-free'.

4.5 Interaction with other medicinal products and other forms of interaction

In vitro studies

The cytochrome P450 CYP3A4 is the main enzyme involved in the metabolism of macitentan and in the formation of its active metabolite, with minor contribution from CYP2C8, CYP2C9, and CYP2C19 enzymes (see section 5.2). Macitentan and its active metabolite do not have clinically relevant inhibitory or inducing effects on cytochrome P450 enzymes.

Macitentan and its active metabolite are not inhibitors of hepatic or renal uptake transporters at clinically relevant concentrations, including the organic anion transporting polypeptides (OATP1B1 and OATP1B3). Macitentan and its active metabolite are not relevant substrates of OATP1B1 and OATP1B3 but enter the liver by passive diffusion.

Macitentan and its active metabolite are not inhibitors of hepatic or renal efflux pumps at clinically relevant concentrations, including the multi-drug resistance protein (P-gp, MDR-1) and multidrug and toxin extrusion transporters (MATE1 and MATE2-K). Macitentan is not a substrate for P-gp/MDR-1.

At clinically relevant concentrations, macitentan and its active metabolite do not interact with proteins involved in hepatic bile salt transport, i.e., the bile salt export pump (BSEP) and the sodium-dependent taurocholate co-transporting polypeptide (NTCP).

In vivo studies

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 should be avoided (see section 4.4).

Ketoconazole
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. The uncertainties of such modelling should be considered. Exposure to the active metabolite of macitentan was reduced by 26%. Caution should be exercised when macitentan is administered concomitantly with strong CYP3A4 inhibitors (see section 4.4).

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 PBPK modelling. However, there was no clinically relevant change in exposure to the active metabolite of macitentan. The uncertainties of such modelling should be considered. Caution should be exercised when macitentan is administered concomitantly with moderate dual inhibitors of CYP3A4 and CYP2C9 (e.g., fluconazole and amiodarone) (see section 4.4).

Caution should also be exercised when macitentan is administered concomitantly with both a moderate CYP3A4 inhibitor (e.g., ciprofloxacin, cyclosporine, diltiazem, erythromycin, verapamil) and moderate CYP2C9 inhibitor (e.g., miconazole, piperine) (see section 4.4).

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 three times a day 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 adult patients with PAH, the efficacy and safety of macitentan in combination with sildenafil were demonstrated.

Cyclosporine A
Concomitant treatment with cyclosporine A 100 mg twice daily, a combined CYP3A4 and OATP inhibitor, did not alter the steady-state exposure to macitentan and its active metabolite to a clinically relevant extent.

Hormonal contraceptives
Macitentan 10 mg once daily did not affect the pharmacokinetics 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 a BCRP substrate drug (riociguat 1 mg; rosuvastatin 10 mg).

Paediatric population

Interaction studies have only been performed in adults.

4.6 Fertility, pregnancy, and lactation

Use in women of childbearing potential/Contraception in males and females

Opsumit treatment should only be initiated in women of childbearing potential when the absence of pregnancy has been verified, appropriate advice on contraception provided, and reliable contraception is practised (see sections 4.3 and 4.4). Women should not become pregnant for 1 month after discontinuation of Opsumit. Monthly pregnancy tests during treatment with Opsumit are recommended to allow the early detection of pregnancy.

Pregnancy

There are no data from the use of macitentan in pregnant women. Studies in animals have shown reproductive toxicity (see section 5.3). The potential risk for humans is still unknown. Opsumit is contraindicated during pregnancy and in women of childbearing potential who are not using reliable contraception (see section 4.3).

Breastfeeding

It is unknown whether macitentan is excreted in human milk. In rats, macitentan and its metabolites are excreted into milk during lactation (see section 5.3). A risk to the breastfeeding child cannot be excluded. Opsumit is contraindicated during breastfeeding (see section 4.3).

Male fertility

The development of testicular tubular atrophy in male animals was observed after treatment with macitentan (see section 5.3). Decreases in sperm count have been observed in patients taking ERAs. Macitentan, like other ERAs, may have an adverse effect on spermatogenesis in men.

4.7 Effects on ability to drive and use machines

Macitentan has minor influence on the ability to cycle, drive and use machines. No studies on the effects on the ability to drive and use machines have been performed. However, undesirable effects may occur (e.g., headache, hypotension) that may influence the ability to cycle, drive and use machines (see section 4.8).

4.8 Undesirable effects

Summary of the safety profile.

The most commonly reported adverse reactions in the SERAPHIN study were nasopharyngitis (14%), headache (13.6%) and anaemia (13.2%, see section 4.4).

Tabulated list of adverse reactions

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. Adverse reactions associated with macitentan obtained from this clinical study are tabulated below. Post-marketing adverse reactions are also included.

Frequencies are defined as: very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1 000 to < 1/100); rare (≥ 1/10 000 to < 1/1 000); very rare (< 1/10 000); not known (cannot be estimated from the available data).

System organ class	Frequency	Adverse reaction
Infections and infestations	Very common	Nasopharyngitis
	Very common	Bronchitis
	Common	Pharyngitis
	Common	Influenza
	Common	Urinary tract infection
Blood and lymphatic system disorders	Very common	Anaemia, haemoglobin decrease[5]
	Common	Leukopenia[6]
	Common	Thrombocytopenia[7]
Immune system disorders	Uncommon	Hypersensitivity reactions (e.g., angioedema, pruritus, rash)[1]
Nervous system disorders	Very common	Headache
Vascular disorders	Common	Hypotension[2], flushing
Respiratory, thoracic and mediastinal disorders	Common	Nasal congestion[1]
Hepatobiliary disorders	Common	Aminotransferase elevations[4]
Reproductive system and breast disorders	Common	Increased uterine bleeding[8]
General disorders and administration site conditions	Very common	Oedema, fluid retention[3]

[1] Data derived from pooled placebo-controlled studies.

[8] Includes PTs of heavy menstrual bleeding, abnormal uterine bleeding, intermenstrual bleeding, uterine/vaginal haemorrhage, polymennorhoea and menstruation irregular. Frequency based on exposure in females.

Description of selected adverse reactions

[2] Hypotension has been associated with the use of ERAs including macitentan. In SERAPHIN, a long-term double-blind study in patients with PAH, hypotension was reported for 7.0% and 4.4% of patients on macitentan 10 mg and placebo, respectively. This corresponded to 3.5 events / 100 patient-years on macitentan 10 mg compared to 2.7 events / 100 patient-years on placebo.

[3] Oedema/fluid retention has been associated with the use of ERAs including macitentan. 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. In a double-blind study in adult patients with idiopathic pulmonary fibrosis, the incidence of peripheral oedema AEs in the macitentan and placebo treatment groups was 11.8% and 6.8%, respectively. In two double-blind clinical studies in adult patients with digital ulcers associated with systemic sclerosis, the incidences of peripheral oedema AEs ranged from 13.4% to 16.1% in the macitentan 10 mg groups and from 6.2% to 4.5% in the placebo groups.

Laboratory abnormalities

[4] Liver aminotransferases

The incidence of aminotransferase elevations (ALT/AST) > 3 × ULN was 3.4% on macitentan 10 mg and 4.5% on placebo in SERAPHIN, a double-blind study in adult patients with PAH. Elevations > 5 × ULN occurred in 2.5% of patients on macitentan 10 mg versus 2% of patients on placebo.

[5] Haemoglobin

In SERAPHIN, a double-blind study in adult patients with PAH, macitentan 10 mg was associated with a mean decrease in haemoglobin versus placebo of 1 g/dL. A decrease from baseline in haemoglobin concentration to below 10 g/dL was reported in 8.7% of patients treated with macitentan 10 mg and 3.4% of placebo-treated patients.

[6] White blood cells

In SERAPHIN, a double-blind study in adult 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.

[7] Platelets

In SERAPHIN, a double-blind study in adult 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

Of the 742 patients who participated in the pivotal SERAPHIN double-blind study, 550 patients entered a long-term open-label (OL) extension study. (The OL cohort included 182 patients who continued on macitentan 10 mg and 368 patients who received placebo or macitentan 3 mg and crossed over to macitentan 10 mg.)

Long-term follow-up of these 550 patients for a median exposure of 3.3 years and a maximum exposure of 10.9 years showed a safety profile that was consistent as described above during the SERAPHIN double-blind phase.

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

The safety of macitentan was evaluated in TOMORROW, a Phase 3 study in 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. In addition to the adverse reactions tabulated above, the following paediatric adverse reactions were reported: upper respiratory tract infection (31.9%), rhinitis (8.3%), and gastroenteritis (11.1%).

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

An additional 11 patients, aged ≥ 1 month to less than 2 years old were enroled 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, however, very limited clinical safety data are available to establish a robust safety conclusion in paediatric population below 2 years.

The safety of macitentan in children below 2 years of age has not been established (see section 4.2).

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation 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 via the national reporting system listed in Appendix V.

4.9 Overdose

Macitentan has been administered as a single dose of up to 600 mg to healthy adult subjects. Adverse reactions 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.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: anti-hypertensives, anti-hypertensives for pulmonary arterial hypertension. ATC code: C02KX04.

Mechanism of action

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

Macitentan is an orally active potent endothelin receptor antagonist, active on both ET_A and ET_B receptors and approximately 100-fold more selective for ET_A as compared to ET_B *in vitro*. Macitentan displays high affinity and sustained occupancy of the ET receptors in human pulmonary arterial smooth muscle cells. This prevents endothelin-mediated activation of second messenger systems that result in vasoconstriction and smooth muscle cell proliferation.

Clinical efficacy and safety

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 endpoint was the time to first occurrence of a morbidity or mortality event, up to the end of double-blind treatment, 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 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.

All patients were followed up to end-of-study (EOS) for vital status. EOS was declared when the predefined number of primary endpoint events was reached. In the period between end-of-treatment (EOT) and EOS, patients could receive open-label macitentan 10 mg or alternative PAH therapy. The overall median double-blind treatment duration was 115 weeks (up to a maximum of 188 weeks on macitentan).

The mean age of all patients was 46 years (range 12–85 years of age, including 20 patients below 18, 706 patients between 18–74 years, and 16 patients aged 75 and older) 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.

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 corrected simple congenital heart disease (8%), and PAH associated with other aetiologies (medicinal products and toxins [3%] and HIV [1%]).

Outcome endpoints

Treatment with macitentan 10 mg resulted in a 45% risk reduction (hazard ratio [HR] 0.55; 97.5% CI: 0.39 to 0.76; logrank $p < 0.0001$) of the composite morbidity-mortality endpoint up to EOT when compared to placebo [Figure 1 and Table 2]. The treatment effect was established early and was sustained.

Efficacy of macitentan 10 mg on the primary endpoint was consistent across subgroups of age, sex, ethnic origin, geographical region, aetiology, by monotherapy or in combination with another PAH therapy and by WHO FC (I/II and III/IV).

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

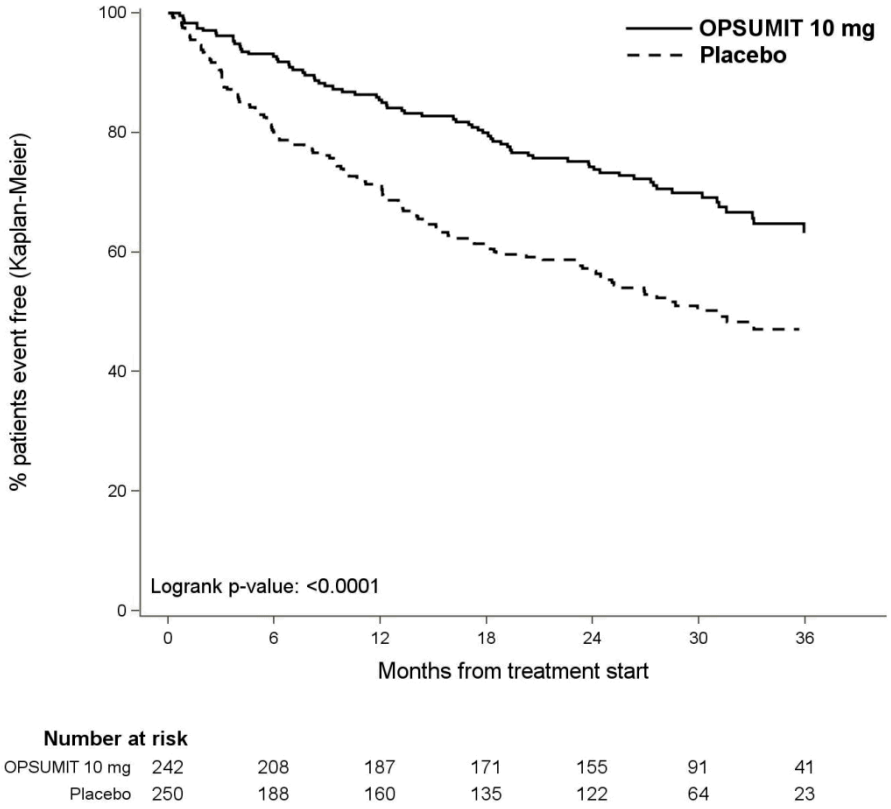

Table 2: Summary of outcome events

Endpoints & statistics	Patients with events		Treatment comparison: macitentan 10 mg vs placebo			
	Placebo (N = 250)	Macitentan 10 mg (N = 242)	Absolute risk reduction	Relative risk reduction (97.5% CI)	HR [a] (97.5% CI)	Logrank p-value
Morbidity-mortality event [b]	53%	37%	16%	45% (24%; 61%)	0.55 (0.39; 0.76)	< 0.0001
Death [c] **n (%)**	19 (7.6%)	14 (5.8%)	2%	36% (−42%; 71%)	0.64 (0.29; 1.42)	0.20
Worsening of PAH n (%)	93 (37.2%)	59 (24.4%)	13%	49% (27%; 65%)	0.51 (0.35; 0.73)	< 0.0001
i.v./s.c. prostanoid initiation n (%)	6 (2.4%)	1 (0.4%)	2%			

[a] = based on Cox's Proportional Hazards Model
[b] = % of patients with an event at 36 months = 100 × (1 – KM estimate)
[c] = all cause death 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).

The risk of PAH-related death or hospitalisation for PAH up to EOT was reduced by 50% (HR 0.50; 97.5% CI: 0.34 to 0.75; logrank p < 0.0001) in patients receiving macitentan 10 mg (50 events) compared to placebo (84 events). At 36 months, 44.6% of patients on placebo and 29.4% of patients

on macitentan 10 mg (Absolute Risk Reduction = 15.2%) had been hospitalised for PAH or died from a PAH-related cause.

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 6MWD of 22 meters (97.5% CI: 3 to 41; p = 0.0078). 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 meters (97.5% CI: 5 to 69) and in FC I/II of 12 meters (97.5% CI: −8 to 33). The increase in 6MWD achieved with macitentan was maintained for the duration of the study.

Treatment with macitentan 10 mg at Month 6 led to a 74% higher chance of WHO FC improvement relative to placebo (risk ratio 1.74; 97.5% CI: 1.10 to 2.74; p = 0.0063).

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% (97.5% CI: 21.7 to 49.2%) in pulmonary vascular resistance and an increase of 0.58 L/min/m^2 (97.5% CI: 0.28 to 0.93 L/min/m^2) in cardiac index compared to placebo.

Long-term data in PAH

In long-term follow-up of 242 patients who were treated with macitentan 10 mg in the double-blind (DB) phase of the SERAPHIN study, 182 of which continued with macitentan in the open-label (OL) extension study (SERAPHIN OL) (DB/OL cohort), Kaplan-Meier estimates of survival at 1, 2, 5, 7 and 9 years were 95%, 89%, 73%, 63% and 53%, respectively. The median follow-up time was 5.9 years.

Paediatric population

Efficacy in paediatric population is mainly based in an extrapolation exercise based upon exposure-matching to the adult efficacious dose range given the similarity of the disease in children and adults, as well as on supportive efficacy and safety data from the TOMORROW phase 3 study described below.

A multi-centre, open-label, randomised, Phase 3 study with an open-label single-arm extension period (TOMORROW) was conducted to assess pharmacokinetics, efficacy and safety of macitentan in paediatric patients with symptomatic PAH.

The primary endpoint was the characterisation of pharmacokinetics (see section 5.2).

The key secondary combined 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 < 18 years were randomised 1:1 to receive either macitentan or Standard of Care (SoC). SoC included PAH non-specific treatment and/or up to 2 PAH-specific medications (including another ERA) and excluding macitentan and IV/SC prostanoids. 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%).

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%). Co-incidental CHD only included typically small coincidental defects such as pre-tricuspid, post-tricuspid shunts, atrial septal defect, ventricular septal defect, patent ductus arteriosus, none considered causative of the degree of PAH.

The mean treatment duration in the randomised study was 183.4 weeks in the macitentan arm and 130.6 weeks in the SoC arm.

Fewer events for the key secondary endpoint of CEC-confirmed disease progression were observed in the macitentan arm (21 events/73 patients, 29%) versus the SoC arm (24 events/75 patients, 32%), absolute risk reduction of 3%. The hazard ratio was 0.828 (95% CI 0.460; 1.492; 2-sided stratified p-value = 0.567). The numerical trend towards benefit was mainly driven by the clinical worsening of PAH.

Other secondary efficacy analyses

The same number of events for first-confirmed hospitalisation for PAH were observed in both groups (macitentan 11 vs. SoC 11; adjusted HR=0.912, 95% CI= [0.393; 2.118]). 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.

There was a numerically higher proportion of patients at WHO FC I or II reported at Week 12 in the macitentan arm compared with the SoC arm (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).

Macitentan treatment tended to reduce the percent of baseline NT-proBNP (pmol/L) at Week 12 compared with the SoC arm (geometric mean ratio: 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: 0.97;95% CI: 0.66 to 1.43;2-sided p-value of 0.884).

Efficacy results from patients aged ≥ 2 years to less than 18 years were similar to those of adult patients.

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

An additional 11 patients, aged ≥ 1 month to less than 2 years old were enroled to receive macitentan 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 PDE5i therapy. At enrolment, the age range of the patients ranged from 1.2 years-1.9 years. Patients were either WHO FC II (4) or FC I (5). 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 sections 4.2 and 5.2).

5.2 Pharmacokinetic properties

The pharmacokinetics of macitentan and its active metabolite have mainly been documented in healthy adult subjects. Exposure to macitentan in adult 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 8-9 hours after administration for film-coated tablets and dispersible tablets. 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 adult 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 are highly bound to plasma proteins (> 99%), primarily to albumin and to a lesser extent to alpha1-acid glycoprotein. Macitentan and its active metabolite ACT-132577 are well distributed into tissues as indicated by an apparent volume of distribution (Vss/F) of approximately 50 L and 40 L for macitentan and ACT-132577, respectively.

Biotransformation

Macitentan has four primary metabolic pathways. Oxidative depropylation of the sulfamide yields a pharmacologically active metabolite. This reaction is dependent on the cytochrome P450 system, mainly CYP3A4 (approximately 99%) with minor contributions of 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 CYP3A4.

Elimination

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

There is no clinically relevant effect of sex or ethnic origin on the pharmacokinetics of macitentan and its active metabolite.

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. This increase is not considered clinically relevant (see sections 4.2 and 4.4).

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. This decrease is not considered clinically relevant (see sections 4.2 and 4.4).

Paediatric population (aged ≥ 1 month to less than 18 years)

Pharmacokinetics of macitentan and its active metabolite aprocitentan were characterised in 47 paediatric patients who were ≥ 2 years and in 11 patients who were ≥ 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).

5.3 Preclinical safety data

In dogs, macitentan decreased blood pressure at exposures similar to the therapeutic human exposure. Intimal thickening of coronary arteries was observed at 17-fold the human exposure after 4 to 39 weeks of treatment. Due to the species-specific sensitivity and the safety margin, this finding is considered not relevant for humans.

Increased liver weight and hepatocellular hypertrophy were observed in mice, rats and dogs after treatment with macitentan. These changes were largely reversible and considered non-adverse adaptations of the liver to increased metabolic demand.

Macitentan induced minimal to slight mucosal hyperplasia and inflammatory infiltration in the submucosa of the nasal cavity in the mouse carcinogenicity study at all doses. No nasal cavity findings were noted in the 3-month mouse toxicity study or in rat and dog studies.

Macitentan was not genotoxic in a standard battery of *in vitro* and *in vivo* assays. Macitentan was not phototoxic *in vivo* after single dose at exposures of up to 24-fold the human exposure.
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.

Testicular tubular dilatation was observed in chronic toxicity studies with male rats and dogs with safety margins of 11.6 and 5.8, respectively. Tubular dilatation was fully reversible. After 2 years of treatment, testicular tubular atrophy was seen in rats at 4-fold the human exposure. Hypospermatogenesis was observed in the life-long carcinogenicity study in rats and in the repeat-dose toxicity studies in dogs at exposures that provide safety margins of 9.7 in rats and 23 in dogs. The safety margins for fertility were 18 for male and 44 for female rats. No testicular findings were noted in mice after treatment up to 2 years.

Macitentan was teratogenic in rabbits and rats at all doses tested. In both species there were cardiovascular and mandibular arch fusion abnormalities.

Administration of macitentan to female rats from late pregnancy through lactation at maternal exposures 5-fold the human exposure, caused reduced pup survival and impairment of the reproductive capability of the offspring, which was exposed to macitentan during late intrauterine life and via the milk during the suckling period.

Treatment of juvenile rats from postnatal Day 4 to Day 114 caused reduced body weight gain leading to secondary effects on development (slight delay of descensus testis, reversible reduction of long-bone length, prolonged estrous cycle). Slightly increased pre- and post-implantation loss, decreased mean number of pups, and decreased testis and epididymis weights, were observed at exposures 7-fold the human exposure. Testicular tubular atrophy, and minimal effects on reproductive variables and sperm morphology were recorded at exposures 3.8-fold the human exposure.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Mannitol (E421)
Isomalt (E953)
Croscarmellose sodium (E468)
Magnesium stearate (E470b)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years.

6.4 Special precautions for storage

Store in original package to protect from moisture.

This medicinal product does not require any special temperature storage conditions.

6.5 Nature and contents of container

30 x 1 dispersible tablets in Alu/Alu perforated unit dose blisters consisting of an aluminium cold form film with integrated desiccant and an aluminium push through lidding foil.

6.6 Special precautions for disposal and other handling

The oral suspension must be prepared by adding the dispersible tablet(s) to a little room temperature liquid on a spoon or in a small glass to make a liquid medicine. When the tablet has fully dispersed, give the resulting liquid to the patient (see section 4.2).

Hands must be thoroughly washed and dried before and after preparation of the medicine.

7. MARKETING AUTHORISATION HOLDER

Janssen-Cilag International NV
Turnhoutseweg 30
B 2340 Beerse
Belgium

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/13/893/004

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 20 December 2013
Date of latest renewal: 23 August 2018

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency https://www.ema.europa.eu.

ANNEX II

A. MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

A. MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer(s) responsible for batch release

Janssen Pharmaceutica NV
Turnhoutseweg 30
B-2340 Beerse
Belgium

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic safety update reports (PSURs)**

The requirements for submission of PSURs for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk management plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:
- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

- **Additional risk minimisation measures**

The MAH shall ensure that in each Member State where Opsumit is marketed, all patients who are expected to use Opsumit are provided with the following educational material:

- Patient Card

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON for BLISTERS

1. NAME OF THE MEDICINAL PRODUCT

Opsumit 10 mg film-coated tablets
macitentan

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains 10 mg macitentan.

3. LIST OF EXCIPIENTS

Also contains lactose and soya bean lecithin (E322). See package leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Film-coated tablet

15 film-coated tablets
30 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Do not store above 30°C.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Janssen-Cilag International NV
Turnhoutseweg 30
B 2340 Beerse
Belgium

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/13/893/001
EU/1/13/893/002

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Opsumit 10 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC
SN
NN

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON for BLISTERS

1. NAME OF THE MEDICINAL PRODUCT

Opsumit 2.5 mg dispersible tablets
macitentan

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each dispersible tablet contains 2.5 mg macitentan.

3. LIST OF EXCIPIENTS

Also contains isomalt. See package leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Dispersible tablet

30 x 1 dispersible tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in original package to protect from moisture.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Janssen-Cilag International NV
Turnhoutseweg 30
B 2340 Beerse
Belgium

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/13/893/004

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Opsumit 2.5 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTERS

1. NAME OF THE MEDICINAL PRODUCT

Opsumit 10 mg tablets
macitentan

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Janssen-Cilag Int

3. EXPIRY DATE

EXP

4. BATCH NUMBER, DONATION AND PRODUCT CODES

Lot

5. OTHER

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTERS

1. NAME OF THE MEDICINAL PRODUCT

Opsumit 2.5 mg dispersible tablets
macitentan

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Janssen-Cilag Int

3. EXPIRY DATE

EXP

4. BATCH NUMBER, DONATION AND PRODUCT CODES

Lot

5. OTHER

Patient Card

Page 1

Patient Card

This card contains important safety information you need to be aware of when receiving treatment with Opsumit. Carry this card with you at all times and show it to any doctor involved in your medical care.

Opsumit®
macitentan

EN

Page 2

It is important that you report immediately to your prescribing doctor pregnancy or any side effects that may occur during treatment with Opsumit.

Treatment centre: _____

Name of prescribing doctor: _____

Phone number of prescribing doctor: _____

Page 3

Pregnancy
Opsumit may harm the development of the foetus. Therefore you must not take Opsumit if you are pregnant and you must also not become pregnant while taking Opsumit. Moreover, if you are suffering from pulmonary arterial hypertension, the occurrence of a pregnancy can severely deteriorate the symptoms of your disease.

Contraception
You need to use a reliable form of birth control (contraception) while you are taking Opsumit. Be sure to discuss any questions you may have with your doctor.

Page 4

You should have a pregnancy test before initiation of Opsumit and every month during treatment even if you think that you are not pregnant.

Like other medicines of this class, Opsumit can have effects on the liver. Your doctor will take blood test before you start treatment with Opsumit and during treatment to test whether your liver is working properly.

Page 5

Signs that your liver may not be working properly include:

- nausea (urge to vomit)
- vomiting
- fever (high temperature)
- pain in your stomach (abdomen)
- jaundice (yellowing of your skin or the whites of your eyes)
- dark-coloured urine
- itching of your skin
- lethargy or fatigue (unusual tiredness or exhaustion)
- flu-like syndrome (joint and muscle pain with fever)

Page 6

If you notice any of these signs, tell your doctor immediately. If you have any question about your treatment, ask your doctor or pharmacist.

B. PACKAGE LEAFLET

Package leaflet: information for the user

Opsumit 10 mg film-coated tablets
macitentan

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Opsumit is and what it is used for

Opsumit contains the active substance macitentan, which belongs to the class of medicines called "endothelin receptor antagonists".

Opsumit is used for the long-term treatment of pulmonary arterial hypertension (PAH):
- in adults of WHO Functional Class (FC) II to III
- in children under 18 years and body weight of at least 40 kg with WHO Functional Class (FC) II to III.

It can be used on its own or with other medicines for PAH. PAH is high blood pressure in the blood vessels that carry blood from the heart to the lungs (the pulmonary arteries). In people with PAH, these arteries get narrower, so the heart has to work harder to pump blood through them. This causes people to feel tired, dizzy, and short of breath.

Opsumit widens the pulmonary arteries, making it easier for the heart to pump blood through them. This lowers the blood pressure, relieves the symptoms and improves the course of the disease.

2. What you need to know before you take Opsumit

Do not take Opsumit
- if you are allergic to macitentan, soya or any of the other ingredients of this medicine (listed in section 6).
- if you are pregnant, if you are planning to become pregnant, or if you could become pregnant because you are not using reliable birth control (contraception). See section 'Pregnancy and breastfeeding'.
- if you are breastfeeding. See section 'Pregnancy and breastfeeding'.
- if you have liver disease or if you have very high levels of liver enzymes in your blood. Talk to your doctor, who will decide whether this medicine is suitable for you.

If any of these apply to you, please tell your doctor.

Warnings and precautions

Talk to your doctor or pharmacist before taking Opsumit.

<u>You will need blood tests, as indicated by your doctor</u>:
Your doctor will take blood test before you start treatment with Opsumit and during treatment to test:
- whether you have anaemia (a reduced number of red blood cells)
- whether your liver is working properly

If you have anaemia (a reduced number of red blood cells), you may have the following signs:
- dizziness
- fatigue/malaise/weakness
- fast heart rate, palpitations
- pallor

If you notice any of these signs, **tell your doctor.**

Signs that your liver may not be working properly include:
- feeling sick (nausea)
- vomiting
- fever
- pain in your stomach (abdomen)
- yellowing of your skin or the whites of your eyes (jaundice)
- dark-coloured urine
- itching of your skin
- unusual tiredness or exhaustion (lethargy or fatigue)
- flu-like syndrome (joint and muscle pain with fever)

If you notice any of these signs, **tell your doctor immediately**.

If you have kidney problems, talk to your doctor before using Opsumit. Macitentan may lead to more reduction of blood pressure and decrease in haemoglobin in patients with kidney problems.

In patients with pulmonary veno-occlusive disease (obstruction of the lung veins), the use of medicines for treatment of PAH, including Opsumit, may lead to pulmonary oedema. If you have signs of pulmonary oedema when using Opsumit, such as a sudden, important increase in breathlessness and low oxygen, **tell your doctor immediately**. Your doctor may perform additional tests, and will determine what treatment regimen is most suitable for you.

Children and adolescents
Do not give this medicine to children below 2 years of age because efficacy and safety have not been established.

Other medicines and Opsumit
Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicine. Opsumit can affect other medicines.

If you take Opsumit together with other medicines including those listed below, the effects of Opsumit or the other medicines might be altered. Please talk to your doctor or pharmacist if you are taking any of the following medicines:

- rifampicin, clarithromycin, telithromycin, ciprofloxacin, erythromycin (antibiotics used to treat infections),
- phenytoin (a medicine used to treat seizures),
- carbamazepine (used to treat depression and epilepsy),
- St. John’s Wort (an herbal preparation used to treat depression),
- ritonavir, saquinavir (used to treat HIV infections),

- nefazodone (used to treat depression),
- ketoconazole (except shampoo), fluconazole, itraconazole, miconazole, voriconazole (medicines used against fungal infections),
- amiodarone (to control the heartbeat),
- cyclosporine (used to prevent organ rejection after transplant),
- diltiazem, verapamil (to treat high blood pressure or specific heart problems)

Opsumit with food
If you are taking piperine as a dietary supplement, this may alter how the body responds to some medicinal products, including Opsumit. Please talk to your doctor or pharmacist should this be the case.

Pregnancy and breastfeeding
If you are pregnant or breastfeeding, think you may be pregnant or are planning to have a baby, ask your doctor for advice before taking this medicine.

Opsumit may harm unborn babies conceived before, during or soon after treatment.

- If it is possible you could become pregnant, use a reliable form of birth control (contraception) while you are taking Opsumit. Talk to your doctor about this.
- Do not take Opsumit if you are pregnant or planning to become pregnant.
- If you become pregnant or think that you may be pregnant while you are taking Opsumit, or shortly after stopping Opsumit (up to 1 month), see your doctor immediately.

If you are a woman who could become pregnant, your doctor will ask you to take a pregnancy test before you start taking Opsumit and regularly (once a month) while you are taking Opsumit.

It is not known if Opsumit is transferred to breast milk. Do not breastfeed while you are taking Opsumit. Talk to your doctor about this.

Fertility
If you are a man taking Opsumit, it is possible that this medicine may lower your sperm count. Talk to your doctor if you have any questions or concerns about this.

Driving and using machines
Opsumit can cause side effects such as headaches and hypotension (listed in section 4), and the symptoms of your condition can also make you less fit to drive or use machines.

Opsumit contains lactose, lecithin from soya and sodium
Opsumit contains a sugar called lactose. If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicine.

Opsumit contains lecithin derived from soya. If you are allergic to soya, do not use this medicine (see section 2 ‘Do not take Opsumit’).

This medicine contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially ‘sodium-free’.

3. How to take Opsumit

Opsumit should only be prescribed by a doctor experienced in the treatment of pulmonary arterial hypertension.

Always take this medicine exactly as your doctor has told you. Check with your doctor if you are not sure.

Adults and children aged less than 18 years weighing at least 40 kg
The recommended dose of Opsumit is one 10 mg tablet, once a day. Swallow the whole tablet, with a glass of water, do not chew or break the tablet. You can take Opsumit with or without food. It is best to take the tablet at the same time each day.

For children weighing less than 40 kg, Opsumit is available as 2.5 mg dispersible tablets. Your doctor will advise you on your dosing.

If you take more Opsumit than you should
If you have taken more tablets than you have been told to take, you may experience headache, nausea, or vomiting. Ask your doctor for advice.

If you forget to take Opsumit
If you forget to take Opsumit, take a dose as soon as you remember, then continue to take your tablets at the usual times. Do not take a double dose to make up for a forgotten tablet.

If you stop taking Opsumit
Opsumit is a treatment that you will need to keep on taking to control your PAH. Do not stop taking Opsumit unless you have agreed this with your doctor.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Uncommon serious side effects (may affect up to 1 in 100 people)
- Allergic reactions (swelling around the eyes, face, lips, tongue or throat, itching and/or rash)

If you notice any of these signs, tell your doctor immediately.

Very common side effects (may affect more than 1 in 10 people)
- Anaemia (low number of red blood cells) or reduced haemoglobin
- Headache
- Bronchitis (inflammation of the airways)
- Nasopharyngitis (inflammation of the throat and nasal passages)
- Oedema (swelling), especially of the ankles and feet

Common side effects (may affect up to 1 in 10 people)
- Pharyngitis (inflammation of the throat)
- Influenza (flu)
- Urinary tract infection (bladder infection)
- Hypotension (low blood pressure)
- Nasal congestion (blocked nose)
- Elevated liver tests
- Leukopenia (decreased white blood cell counts)
- Thrombocytopenia (decreased blood platelet counts)
- Flushing (redness of the skin)
- Increased uterine bleeding

Side effects in children and adolescents
The side effects listed above may also be seen in children. Additional side effects very commonly seen in children include upper respiratory tract infection (infected nose sinuses, or throat) and gastroenteritis (inflamed stomach and gut). Rhinitis (itchy, runny, or blocked nose) was seen commonly in children.

Reporting of side effects
If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Opsumit

Keep this medicine out of the sight and reach of children.

Do not use Opsumit after the expiry date which is stated on the carton and blister after "EXP". The expiry date refers to the last day of that month.

Do not store above 30°C.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer require. These measures will help to protect the environment.

6. Contents of the pack and other information

What Opsumit contains
- The active substance is macitentan. Each tablet contains 10 mg macitentan.
- The other ingredients are lactose monohydrate (see section 2 "Opsumit contains lactose, lecithin from soya and sodium"), microcrystalline cellulose (E460i), povidone, sodium starch glycolate Type A (see section 2 "Opsumit contains lactose, lecithin from soya and sodium"), magnesium stearate (E470b), polysorbate 80 (E433), polyvinyl alcohol (E1203), titanium dioxide (E171), talc (E553b), soya bean lecithin (E322) (see section 2 "Opsumit contains lactose, lecithin from soya and sodium") and xanthan gum (E415).

What Opsumit looks like and contents of the pack
Opsumit 10 mg film-coated tablets are white to off-white, biconvex, round, with "10" on both sides.

Opsumit is supplied as 10 mg film-coated tablets in blister packs of 15 or 30 tablets.

Not all pack sizes may be marketed.

Marketing Authorisation Holder
Janssen-Cilag International NV
Turnhoutseweg 30
B-2340 Beerse
Belgium

Manufacturer
Janssen Pharmaceutica NV
Turnhoutseweg 30
B-2340 Beerse
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This leaflet was last revised in

Detailed information on this medicine is available on the European Medicines Agency web site: https://www.ema.europa.eu.

Package leaflet: information for the user

Opsumit 2.5 mg dispersible tablets
macitentan

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you. This leaflet has been written for the patient ("you") and the parent or caregiver who will give this medicine to the child.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Opsumit is and what it is used for

Opsumit contains the active substance macitentan, which belongs to the class of medicines called "endothelin receptor antagonists".

Opsumit is used for the long-term treatment of pulmonary arterial hypertension (PAH) in children aged 2 years to less than 18 years with WHO Functional Class (FC) II to III.

It can be used on its own or with other medicines for PAH. PAH is high blood pressure in the blood vessels that carry blood from the heart to the lungs (the pulmonary arteries). In people with PAH, these arteries get narrower, so the heart has to work harder to pump blood through them. This causes people to feel tired, dizzy, and short of breath.

Opsumit widens the pulmonary arteries, making it easier for the heart to pump blood through them. This lowers the blood pressure, relieves the symptoms and improves the course of the disease.

2. What you need to know before you take or give Opsumit

Do not take or give Opsumit
- if you are allergic to macitentan or any of the other ingredients of this medicine (listed in section 6).
- if you are pregnant, if you are planning to become pregnant, or if you could become pregnant because you are not using reliable birth control (contraception). See section 'Pregnancy and breastfeeding'.
- if you are breastfeeding. See section 'Pregnancy and breastfeeding'.
- if you have liver disease or if you have very high levels of liver enzymes in your blood. Talk to your doctor, who will decide whether this medicine is suitable for you.

If any of these apply to you, please tell your doctor.

Warnings and precautions

Talk to your doctor or pharmacist before taking or giving Opsumit.

<u>You will need blood tests, as indicated by your doctor</u>:
Your doctor will take blood before and during treatment with Opsumit to test:
- whether you have anaemia (a reduced number of red blood cells)
- whether your liver is working properly

If you have anaemia (a reduced number of red blood cells), you may have the following signs:
- dizziness
- fatigue/malaise/weakness
- fast heart rate, palpitations
- pallor

If you notice any of these signs, **tell your doctor.**

Signs that your liver may not be working properly include:
- feeling sick (nausea)
- vomiting
- fever
- pain in your stomach (abdomen)
- yellowing of your skin or the whites of your eyes (jaundice)
- dark-coloured urine
- itching of your skin
- unusual tiredness or exhaustion (lethargy or fatigue)
- flu-like syndrome (joint and muscle pain with fever)

If you notice any of these signs, **tell your doctor immediately**.

If you have kidney problems, talk to your doctor before using Opsumit. Macitentan may lead to more reduction of blood pressure and decrease in haemoglobin in patients with kidney problems.

In patients with pulmonary veno-occlusive disease (obstruction of the lung veins), the use of medicines for treatment of PAH, including Opsumit, may lead to pulmonary oedema. If you have signs of pulmonary oedema when using Opsumit, such as a sudden, important increase in breathlessness and low oxygen, **tell your doctor immediately**. Your doctor may perform additional tests, and will determine what treatment regimen is most suitable for you.

Children and adolescents
Do not give this medicine to children below 2 years of age because efficacy and safety have not been established.

Other medicines and Opsumit
Tell your doctor or pharmacist if you or the child are taking, have recently taken or might take any other medicine.
Opsumit can affect other medicines.

If you take or give Opsumit together with other medicines including those listed below, the effects of Opsumit or the other medicines might be altered. Please talk to your doctor or pharmacist if you are taking any of the following medicines:

- rifampicin, clarithromycin, telithromycin, ciprofloxacin, erythromycin (antibiotics used to treat infections),
- phenytoin (a medicine used to treat seizures),
- carbamazepine (used to treat depression and epilepsy),
- St. John’s Wort (an herbal preparation used to treat depression),

- ritonavir, saquinavir (used to treat HIV infections),
- nefazodone (used to treat depression),
- ketoconazole (except shampoo), fluconazole, itraconazole, miconazole, voriconazole (medicines used against fungal infections),
- amiodarone (to control the heartbeat),
- cyclosporine (used to prevent organ rejection after transplant),
- diltiazem, verapamil (to treat high blood pressure or specific heart problems)

Opsumit with food
If you are taking piperine as a dietary supplement, this may alter how the body responds to some medicinal products, including Opsumit. Please talk to your doctor or pharmacist should this be the case.

Pregnancy and breastfeeding
If you are pregnant or breastfeeding, think you may be pregnant or are planning to have a baby, ask your doctor for advice before taking this medicine.

Opsumit may harm unborn babies conceived before, during or soon after treatment.

- If it is possible you could become pregnant, use a reliable form of birth control (contraception) while you are taking Opsumit. Talk to your doctor about this.
- Do not take Opsumit if you are pregnant or planning to become pregnant.
- If you become pregnant or think that you may be pregnant while you are taking Opsumit, or shortly after stopping Opsumit (up to 1 month), see your doctor immediately.

If you are a woman who could become pregnant, your doctor will ask you to take a pregnancy test before you start taking Opsumit and regularly (once a month) while you are taking Opsumit.

It is not known if Opsumit is transferred to breast milk. Do not breastfeed while you are taking Opsumit. Talk to your doctor about this.

Fertility
If you are a man taking Opsumit, it is possible that this medicine may lower your sperm count. Talk to your doctor if you have any questions or concerns about this.

Driving and using machines
Opsumit can cause side effects such as headaches and hypotension (listed in section 4), and the symptoms of your condition can also make you less fit to cycle, drive or use machines.

Opsumit contains isomalt and sodium
Opsumit contains a sugar substitute called isomalt. If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicine.

This medicine contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially ‘sodium-free’.

3. How to take or give Opsumit

Opsumit should only be prescribed by a doctor experienced in the treatment of pulmonary arterial hypertension.

Always take or give this medicine exactly as your doctor has told you. Check with your doctor if you are not sure.

Recommended dose
Your doctor will determine the number of tablets of Opsumit depending on the body weight of the child.

How to take or give this medicine
- Take or give Opsumit dispersible tablets once a day.
- Take or give them at about the same time every day.
- They can be taken or given with or without food.

Take or give Opsumit dispersible tablets as an oral suspension only
Opsumit dispersible tablets must be dispersed in liquids to form an oral suspension before they can be given to patients. The oral suspension can be prepared in either a spoon or in a small glass. Take care that the entire dose is swallowed. Hands must be thoroughly washed and dried before and after preparation of the medicine.

How to prepare and take or give the oral suspension using a spoon
1. Prepare the oral suspension by adding the prescribed number of dispersible tablets to room temperature drinking water in a spoon.
2. Gently stir the liquid for 1 to 3 minutes using the tip of a knife. Either give the resulting white cloudy liquid to the child right away or mix it further with a small portion of apple sauce or yoghurt to aid with administration.
3. Add a little more water or apple sauce or yogurt to the spoon and have the child swallow it to make sure all the medicine has been taken.
4. If not taken right away, discard the medicine and prepare a new dose.

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

How to prepare and take or give the oral suspension using a small glass
1. Prepare the oral suspension by adding the prescribed number of dispersible tablets to a small amount (maximum 100 mL) of room temperature drinking water in a small glass.
2. Gently stir with a spoon for 1 to 2 minutes. Have the child drink the resulting white cloudy liquid right away.
3. Add a little more water to the small glass and stir with the same spoon and have the child drink the entire contents of the glass to make sure all the medicine has been taken.
4. If not taken right away, discard the medicine and prepare a new dose.

Special information for caregivers
Caregivers are advised to avoid contact with suspensions of Opsumit dispersible tablets. Wash hands thoroughly before and after preparation of the suspension.

If you take or give more Opsumit than you should
If you have taken or given more tablets than you have been told to take, you may experience headache, nausea, or vomiting. Ask your doctor for advice.

If you forget to take or give Opsumit
If you forget to take or give Opsumit, take or give a dose as soon as you remember, then continue to take or give the tablets at the usual times. Do not take or give a double dose to make up for a forgotten tablets.

If you stop taking or giving Opsumit
Opsumit is a treatment that you will need to keep on taking to control your PAH. Do not stop taking or giving Opsumit unless you have agreed this with your doctor.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Uncommon serious side effects (may affect up to 1 in 100 people)
- Allergic reactions (swelling around the eyes, face, lips, tongue or throat, itching and/or rash)

If you notice any of these signs, tell your doctor immediately.

Very common side effects (may affect more than 1 in 10 people)
- Anaemia (low number of red blood cells) or reduced haemoglobin
- Headache
- Bronchitis (inflammation of the airways)
- Nasopharyngitis (inflammation of the throat and nasal passages)
- Oedema (swelling), especially of the ankles and feet

Common side effects (may affect up to 1 in 10 people)
- Pharyngitis (inflammation of the throat)
- Influenza (flu)
- Urinary tract infection (bladder infection)
- Hypotension (low blood pressure)
- Nasal congestion (blocked nose)
- Elevated liver tests
- Leukopenia (decreased white blood cell counts)
- Thrombocytopenia (decreased blood platelet counts)
- Flushing (redness of the skin)
- Increased uterine bleeding

Side effects in children and adolescents
The side effects listed above may also be seen in children. Additional side effects very commonly seen in children include upper respiratory tract infection (infected nose sinuses, or throat) and gastroenteritis (inflamed stomach and gut). Rhinitis (itchy, runny, or blocked nose) was seen commonly in children.

Reporting of side effects
If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Opsumit

Keep this medicine out of the sight and reach of children.

Do not use Opsumit after the expiry date which is stated on the carton and blister after “EXP”. The expiry date refers to the last day of that month.

Store in original package to protect from moisture.

This medicinal product does not require any special temperature storage conditions.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer require. These measures will help to protect the environment.

6. Contents of the pack and other information

What Opsumit contains
- The active substance is macitentan. Each dispersible tablet contains 2.5 mg macitentan.
- The other ingredients are mannitol (E421), isomalt (E953), croscarmellose sodium (E468), magnesium stearate (E470b) (see section 2 “Opsumit contains isomalt and sodium”).

What Opsumit looks like and contents of the pack
Opsumit 2.5 mg dispersible tablets are white to almost white, round, with a “2.5” on one side and with “Mn” on the other side.

Opsumit is supplied as 2.5 mg dispersible tablets in perforated unit dose blisters (Aluminium/Aluminium) containing 30 x 1 dispersible tablets.

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Detailed information on this medicine is available on the European Medicines Agency web site: https://www.ema.europa.eu.