1. NAME OF THE MEDICINAL PRODUCT

Opsumit® 10mg film-coated tablet

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 lecithin (soya) (E322).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated 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

Long-term treatment of pulmonary arterial hypertension (PAH) in patients of WHO Functional Class (FC) II to III to reduce the morbidity and the risk of mortality.

Macitentan is effective when used as monotherapy or in combination with phosphodiesterase-5 inhibitor or inhaled/oral prostanoids.

Efficacy has been shown in a PAH population including idiopathic and heritable PAH, PAH associated with connective tissue disorders, and PAH associated with corrected simple congenital heart disease.

4.2 Posology and method of administration

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

Posology

The recommended dose is 10 mg once daily

Special populations

Elderly

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

Hepatic impairment

Based on pharmacokinetic (PK) data, no dose adjustment is required in patients with mild, moderate or severe hepatic impairment. 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).

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.

Paediatric population

The safety and efficacy of macitentan in children and adolescents *below the age of 18 years* have not yet been established. No data are available

Method of administration

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

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 (aspartate aminotransferase [AST], alanine aminotransferase [ALT]) have been associated with pulmonary hypertension (PAH) and with endothelin receptor antagonists (ERAs) (see *Adverse Reactions*). 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

As with other ERAs, treatment with macitentan has been associated with a decrease in haemoglobin concentration (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. Opsumit can increase the risk in groups with initial Hb level under 13 g/dL and if other medical condition which have impact in decrease Hb (ex: bleeding).

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).

Patients with 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

Opsumit tablets contain lactose. Patients with rare hereditary problems of galactose intolerance, Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

Opsumit tablets contain lecithin derived from soya. If a patient is hypersensitive to soya, Opsumit must not be used (see section 4.3).

4.5 Interaction with other medicinal products and other forms of interaction

***In vitro* studies**

The cytochrome P450 enzymes CYP3A4, CYP2C8, CYP2C9, and CYP2C19 are involved in the metabolism of macitentan and formation of its metabolites (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 (MATEI and MATE2-K). Macitentan is not a substrate for Pgp/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**

Interaction studies have only been performed in adults.

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 Normalized Ratio (INR) was not affected by macitentan. The pharmacokinetics of macitentan and its active metabolite were not affected by warfarin.

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

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 (e.g., itraconazole, ketoconazole, voriconazole, clarithromycin, telithromycin, nefazodone, ritonavir, and saquinavir) (see section 4.4).

Fluconazole: In the presence of fluconazole 400 mg daily, a moderate dual inhibitor of CYP3A4 and CYP2C9, exposure to Opsumit® may increase approximately 3.8-fold based on physiologically based pharmacokinetic (PBPK) modelling. However, there was no clinically relevant change in exposure to the active metabolite of Opsumit®. Caution should be exercised when Opsumit® is administered concomitantly with moderate dual inhibitors of CYP3A4 and CYP2C9 (e.g., fluconazole and amiodarone).

Caution should also be exercised when Opsumit® is administered concomitantly with both a moderate CYP3A4 inhibitor (e.g., ciprofloxacin, cyclosporine, diltiazem, erythromycin, verapamil) and moderate CYP2C9 inhibitor (e.g., miconazole, piperine). *Cyclosporine A:* Concomitant treatment with cyclosporine A 100 mg b.i.d., a combined CYP3A4 and OATP inhibitor, did not alter the steady-state exposure to macitentan and its active metabolite to a clinically relevant extent.

Strong CYP3A4 inducers: Concomitant treatment with rifampicin 600 mg daily, a potent inducer of CYP3A4, reduced the steady-state exposure to macitentan by 79% but did not affect the exposure to the active metabolite. Reduced efficacy of macitentan in the presence of a potent inducer of CYP3A4 such as rifampicin should be considered. The combination of macitentan with strong CYP3A4 inducers should be avoided (see section 4.4).

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).

4.6 Fertility, pregnancy and lactation

Pregnancy

PAH is a contra-indication to pregnancy, due to a high mortality risk to both mother and fetus. There are limited data from the use of macitentan in pregnant women. The potential risk for humans is still unknown. Animal studies have shown teratogenicity. Women receiving macitentan must be advised of the risk of harm to the fetus. Macitentan is contraindicated during pregnancy.

Contraception

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 4.4). 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.

Breastfeeding

It is not known whether macitentan is excreted into human breast 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).

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. Opsumit, like other ERAs, may have an adverse effect on spermatogenesis in men.

4.7 Effects on ability to drive and use machines

Macitentan may have a minor influence on the ability to drive and use machines. The clinical status of the patient and the adverse reaction profile of macitentan (such as headache, hypotension) should be kept in mind when considering the patient's ability to drive and use machines.

4.8 Undesirable effects

Summary of the safety profile.

The most commonly reported adverse reactions are nasopharyngitis (14%), headache (13,6%) and anaemia (13,2%, see section 4.4). The majority of adverse reactions are mild to moderate in intensity.

Tabulated list of adverse reactions

The safety of macitentan has been evaluated in a long-term placebo-controlled trial of 742 patients with symptomatic PAH. 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 (≥ 1/1000 to <1/100); rare (≥ 1/10000 to <1/1000); very rare (<1/10000); 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 elevations4
General disorders and administration site conditions	Very common	Oedema, fluid retention[3]

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

Description of selected adverse reactions

[2]Hypotension has been associated with the use of ERAs including macitentan. In a long-term doubleblind 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 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 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 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 x ULN was 3.4% on macitentan 10 mg and 4.5% on placebo in a double-blind study in patients with PAH. Elevations > 5 x ULN occurred in 2.5% of patients on macitentan 10 mg versus 2% of patients on placebo. The incidence of elevated aminotransferases of >8 x ULN was 2.1% on macitentan 10 mg versus 0.4% in the placebo group.

[5]***Haemoglobin***

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

Paediatric population

The safety of macitentan in children and adolescents below 18 years has not yet been established.

Long-term safety

Of the 742 patients who participated in the pivotal SERAPHIN double-blind study, 550 patients entered a long-term open-label extension study (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 patients treated with macitentan 10 mg in the double-blind / open-label extension studies (N=242) for a median exposure of 4.6 years and a maximum exposure of 11.8 years showed a safety profile that was consistent as described above.

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.

4.9 Overdose

Macitentan has been administered as a single dose of up to and including 600 mg to healthy subjects. Adverse events 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: other anti-hypertensives for pulmonary arterial hypertension, ATC code: C02KX04.

Mechanism of action

Endothelin (ET)-1 and its receptors (ETA and ETB) mediate a variety of deleterious 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, dual ETA and ETB receptor antagonist that prevents the binding of ET-1 to its receptors. 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 multicenter, 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 randomized 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 enrolled patients (64%) were treated with a stable dose of specific therapy for PAH, either oral phosphodiesterase inhibitors (61%) and/or inhaled/oral prostanoids (6%). The primary study endpoint was the time to first occurrence of a morbidity or mortality event, up to end of treatment (EOT), defined as death, or atrial septostomy, or lung transplantation, or initiation of intravenous (i.v.) or subcutaneous (s.c.) prostanoids, or other worsening of PAH. Other worsening of PAH was defined as the presence of all of the three following components: a sustained decrease in 6-minute walk distance (6MWD) of at least 15% from baseline; worsening of PAH symptoms (worsening of WHO Functional Class [FC] or right heart failure); and need for new treatment for PAH. All events were confirmed by an independent adjudication committee, blinded to treatment allocation.

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

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

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

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

Outcome endpoints

Treatment with macitentan10 mg resulted in a 45% risk reduction (hazard ratio [HR] 0.55; 97.5% CI 0.39–0.76; log rank $p < 0.0001$) of the occurrence of morbidity or mortality events up to EOT compared to placebo [Figure 1 and Table 2]. The treatment effect was established early and sustained for a median duration of 2 years.

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

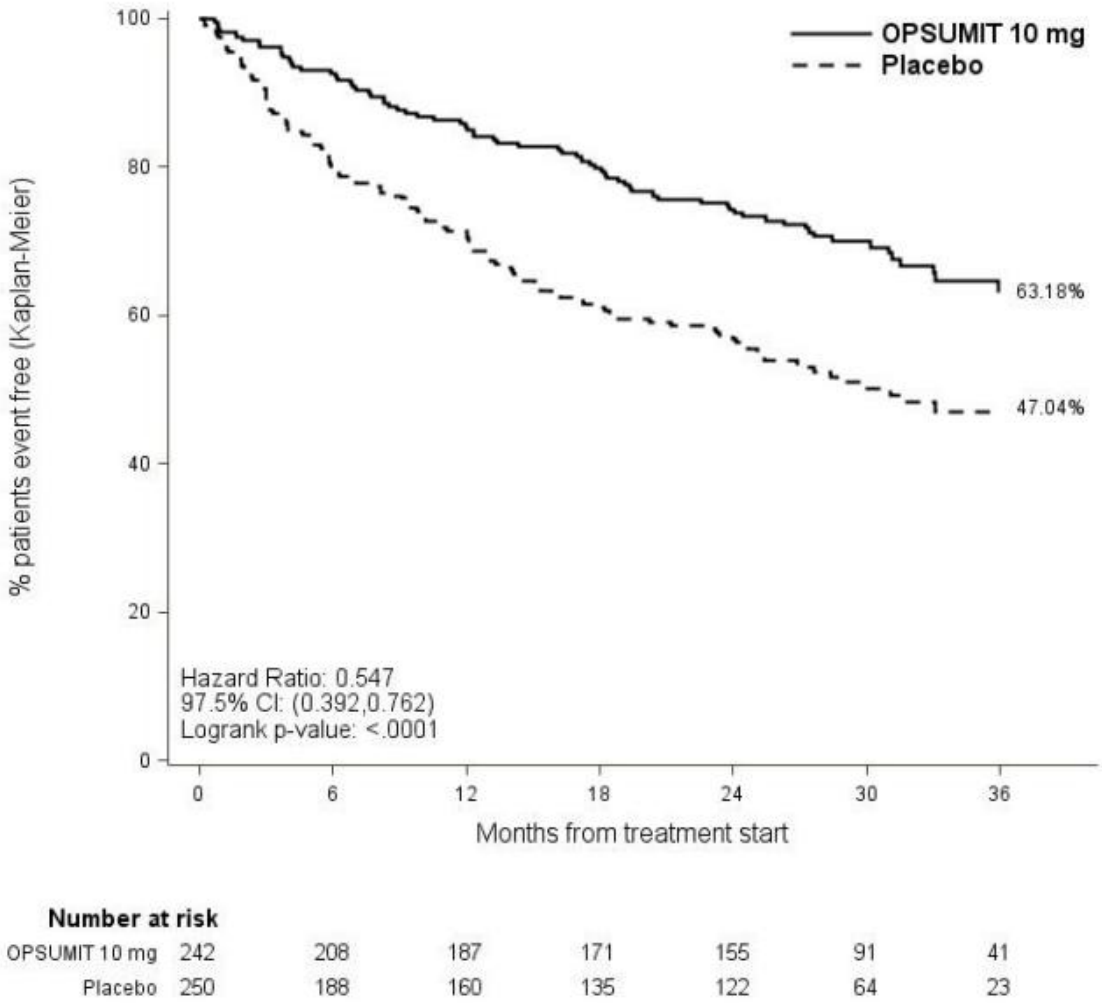


Table 2 Summary of outcome events

Endpoints & Statistics	Patients with events		Treatment Comparison: Macitentan 10 mg vs Placebo			
	Placebo (N = 250)	Macitentan 10 mg (N = 242)	Absolute Risk Reduction (97.5% CI)	Relative Risk Reduction (97.5% CI)	HR[a] (97.5% CI)	Log rank 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 x (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 3–41; 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 5–69, p= 0.0088) and in FC I/II of 12 meters (97.5% CI −8–33, p = 0.1762). The increase in 6MWD achieved with macitentan was maintained for the duration of the study.

Treatment with macitentan 10 mg led to a 74% higher chance of WHO FC improvement relative to placebo (risk ratio 1.74; 97.5% CI 1.10–2.74; p = 0.0063). Treatment with macitentan 10 mg led to an improvement of at least one WHO FC at Month 6 in 22% of patients compared to 13% of patients treated with placebo.

Macitentan 10 mg improved quality of life assessed by the SF-36 questionnaire. Improvements compared to placebo were observed in 7 out of 8 domains at 6 months, including physical functioning, role-physical, bodily pain, vitality, social functioning, emotional, and mental health domains of the SF-36 questionnaire.

Haemodynamic endpoints

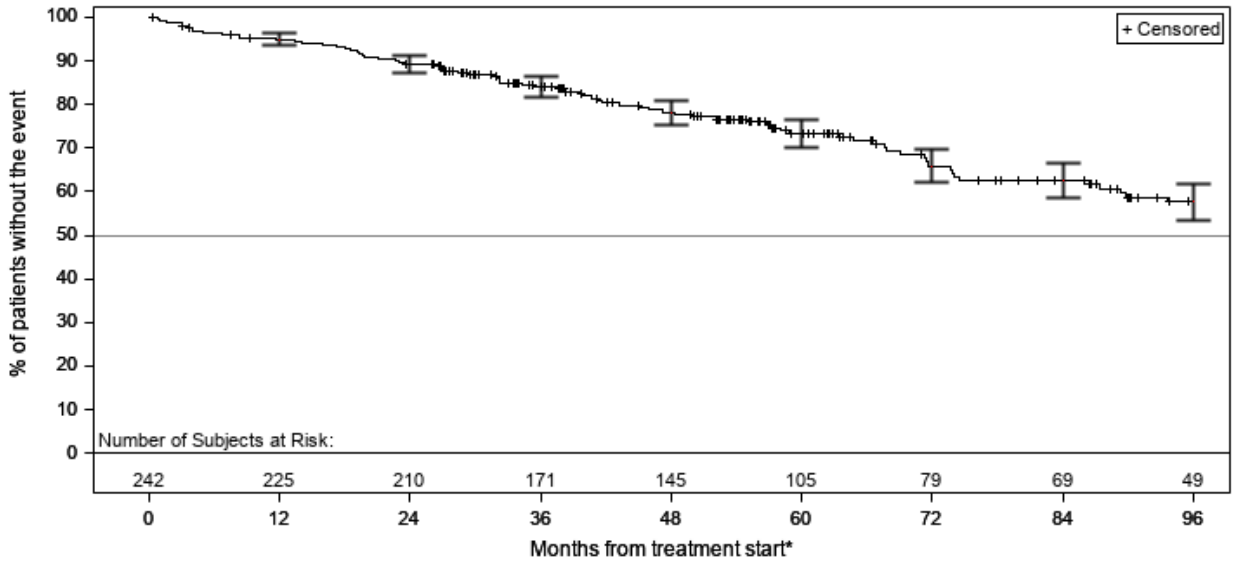
Hemodynamic parameters were assessed in a subset of patients (placebo, N = 67, macitentan10 mg, N = 57) after 6 months of treatment. Patients treated with macitentan 10 mg achieved a median reduction of 36.5% (CI 21.7-49.2%) in pulmonary vascular resistance and an increase of 0.58 L/min/m^2 (CI 0.28-0.93 L/min/m^2) in cardiac index compared to placebo.

Paediatric population

The European Medicines Agency has deferred the obligation to submit the results of studies with macitentan in all subsets of the paediatric population in PAH (see section 4.2 for information on paediatric use).

Long-term treatment of PAH
In long-term follow-up of patients who were treated with macitentan 10 mg in the double-blind / open-label extension studies (N=242), Kaplan-Meier estimates of survival at 1, 2, 3, 4, 5, 6, 7, 8 and 9 years were 95%, 89%, 84%, 78%, 73%, 66%, 63%, 58% and 53% respectively [Figure 2]. The median follow-up time was 5.9 years. Without a control group, these data must be interpreted cautiously.

Figure 2: Kaplan-Meier estimates of time to death (all-cause) in SERAPHIN and its long-term OL extension from treatment start up to study closure, 10 mg DB/OL, Safety analysis set



Note: Survival curves are presented up to the time when more than 10% of the subjects are still at risk.
Error bars show Kaplan-Meier estimate +- standard error.
*Treatment start corresponds to the start of double-blind macitentan 10 mg in AC-055-302

5.2 Pharmacokinetic properties

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

Metabolism

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

Other metabolic pathways yield products without pharmacological activity. For these pathways, CYP2C9 plays a predominant role with minor contributions from CYP2C8, CYP2C19 and CYP3A4

Excretion

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

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 patients with severe renal impairment. This increase is not considered clinically relevant.

Hepatic impairment

Exposure to macitentan was decreased by 21%, 34% and 6% and for the active metabolite by 20%, 25% and 25% in subjects with mild, moderate or severe hepatic impairment, respectively. This decrease is not considered clinically relevant.

5.3 Preclinical safety data

No adverse effects were observed in repeated dose toxicity studies in mice, rats, and dogs up to 39 weeks of treatment at exposures of 2- to 6-fold the human exposure at 10 mg/day.

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.

Carcinogenicity and Mutagenicity

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.

Reproductive Toxicology and Fertility

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 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. The effect of macitentan on human male fertility is not known (section 4.6).
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
Sodium starch glycolate Type A
Povidone
Magnesium stearate
Polysorbate 80

Film coat
Polyvinyl alcohol
Titanium dioxide
Talc
Soya lecithin
Xanthan gum

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

5 years. See expiry date on the outer pack.

6.4 Special precautions for storage

The drug product must be stored at a temperature not exceeding 30°C.
Keep out of the sight and reach of children.

6.5 Nature and contents of container

PVC/PE/PVdC/Aluminum foil blisters in cartons containing 30 film-coated tablets.

6.6 Special precautions for disposal and other handling

No special requirements.

HOW SUPPLIED
OPSUMIT® Film-coated Tablet
Box @ 2 blister @15 film-coated tablets
Reg. No.: DKI2152500217A1

HARUS DENGAN RESEP DOKTER

Registered by PT Integrated Healthcare Indonesia, Jakarta – Indonesia
Manufactured by Excella GmbH & Co. KG, Nümberger Str. 12, 90537 Feucht, Germany
Packed by Patheon France, 40, Boulevard de Champaret, 38300 Bourgoin Jallieu, France
Released by Actelion Pharmaceuticals Ltd., Hegenheimermattweg 167c, 4123 Allschwil, Switzerland

For adverse event and product quality complaint, please contact: drugsafety@jacid.jnj.com or (021) 2935-3935

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