▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

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 lecithin (soya) (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 one 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 adult patients of WHO Functional Class (FC) II to III.

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 (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

Opsumit is to be taken orally at a dose of 10 mg once daily, with or without food. The film-coated tablets are not breakable and are to be swallowed whole, with water.

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.

Elderly

No dose adjustment is required in patients over the age of 65 years (see section 5.2). There is limited clinical experience in patients over the age of 75 years. Therefore Opsumit should be used with caution in this population (see section 4.4).

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

The safety and efficacy of macitentan in children have not yet been established.

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

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.

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).

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).

Elderly

There is limited clinical experience with macitentan in patients over the age of 75 years, therefore Opsumit should be used with caution in this population (see section 4.2).

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 (MATE1 and MATE2-K). Macitentan inhibits the breast cancer resistance protein (BCRP) at clinically relevant intestinal concentrations. 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

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 (see section 4.4).

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).

4.6 Fertility, pregnancy, and lactation

Pregnancy

There are no data on the use of macitentan in pregnant women. Animal studies 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).

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).

Male fertility

The development of testicular tubular atrophy in male animals was observed after treatment with macitentan (see section 5.3). The relevance of this finding to humans is unknown, but a deterioration of spermatogenesis cannot be excluded.

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 drug reactions are nasopharyngitis (14.0%), 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.

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).

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
Immune system disorders	Uncommon	Hypersensitivity reactions (e.g., angioedema, pruritus, rash)*
Nervous system disorders	Very Common	Headache
Vascular disorders	Common	Hypotension**
Respiratory, thoracic and mediastinal disorders	Common	Nasal congestion*
General disorders and administration site conditions	Very common	Oedema, fluid retention***

* Data derived from pooled placebo-controlled studies.

Description of selected adverse reactions

** Hypotension has been associated with the use of ERAs. In 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.

*** Oedema/fluid retention has been associated with the use of ERAs. 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

Liver aminotransferases

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

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.

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.

Platelets
In 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.

Paediatric population

The safety and efficacy of macitentan in children have not yet been established.

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 below.

United Kingdom
Yellow Card Scheme
Website: www.mhra.gov.uk/yellowcard

Ireland
HPRA Pharmacovigilance
Earlsfort Terrace
IRL - Dublin 2
Tel: +353 1 6764971
Fax: +353 1 6762517
Website: www.hpra.ie
e-mail: medsafety@hpra.ie

Malta
ADR Reporting
Website: www.medicinesauthority.gov.mt/adrportal

4.9 Overdose

Macitentan has been administered as a single dose of up to 600 mg to healthy 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: other anti-hypertensives, 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 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 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 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 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 (drugs 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

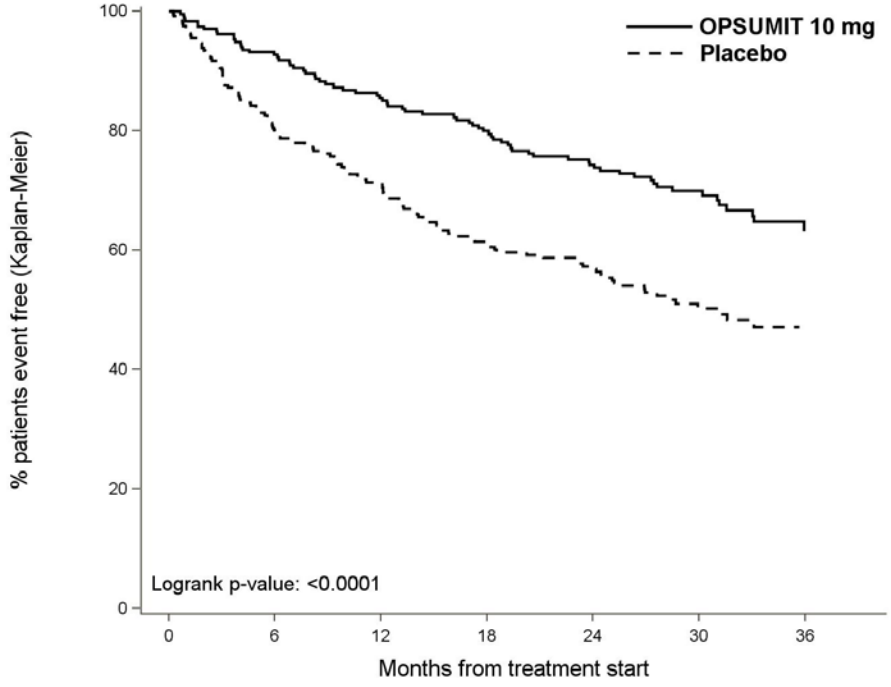

Table 1 Summary of outcome events

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.

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 for PAH (see section 4.2 for information on paediatric use).

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 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. Several members of the CYP2C family, namely CYP2C8, CYP2C9 and CYP2C19, as well as CYP3A4, are involved in the formation of these metabolites.

Elimination

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 (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 subjects with mild, moderate or severe hepatic impairment, respectively. This decrease is not considered clinically relevant (see sections 4.2 and 4.4).

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 23in 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 (E460i)
Sodium starch glycolate Type A
Povidone
Magnesium stearate (E572)
Polysorbate 80 (E433)

Film coat
Polyvinyl alcohol (E1203)
Titanium dioxide (E171)
Talc (E553b)
Lecithin, soybean (E322)
Xanthan gum (E415)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

4 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 foil blisters in cartons containing 15 or 30 film-coated tablets.

White high-density polyethylene bottles with a silica gel desiccant, in cartons containing 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

Actelion Registration Ltd
Chiswick Tower 13th Floor
389 Chiswick High Road
London W4 4AL
United Kingdom

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/13/893/001

EU/1/13/893/002

EU/1/13/893/003

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 20 December 2013

10. DATE OF REVISION OF THE TEXT

March 2016

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