SUMMARY OF PRODUCT CHARACTERISTICS

▼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
MASILVA 10 mg Film Coated Tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION
Each film-coated tablet contains:
Active substance:
Macitentan_____10 mg
Excipient(s) with known effect:
Lactose monohydrate (from cow milk)_____40.96 mg
For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM
Film-coated tablets.
White to off-white, biconvex, round film-coated tablets.

4. CLINICAL PARTICULARS
4.1 Therapeutic indications
MASILVA is indicated for the long-term treatment of pulmonary arterial hypertension (PAH, WHO Group 1) 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 must be initiated and monitored by a physician experienced in the treatment of PAH.

Posology/duration and frequency of administration
The recommended dose is 10 mg once daily administered orally.

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.

MASILVA should be taken every day at about the same time. If the patient misses a dose of MASILVA, 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.

Additional information on special populations
Renal failure
Based on pharmacokinetic data, no dose adjustment is required in patients with renal failure. There is no clinical experience with the use of macitentan in PAH patients with severe renal failure. The use of MASILVA is not recommended in patients undergoing dialysis (see sections 4.4 and 5.2).

Hepatic failure
Based on pharmacokinetic data, no dose change is required in patients with mild, moderate or severe hepatic failure (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 failure. MASILVA must not be initiated in patients with severe hepatic failure, or clinically significant elevated hepatic aminotransferases (greater than 3 times the Upper Limit of Normal (>3×ULN); see sections 4.3 and 4.4).

Pediatric population
The safety and efficacy of macitentan in children have not yet been established. Therefore, it should not be used in children under 18 years of age.

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

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 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 warning 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). MASILVA 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 MASILVA.

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), MASILVA treatment should be discontinued.

Reinitiation of MASILVA 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.

Hemoglobin concentration
Decrease in hemoglobin concentrations has been associated with endothelin receptor antagonists (ERAs) including macitentan (see section 4.8). In placebo-controlled studies, macitentan-related decreases in hemoglobin concentration were not progressive, stabilized after the first 4–12 weeks of treatment and remained stable during chronic treatment. Cases of anemia requiring blood cell transfusion have been reported with macitentan and other ERAs. Initiation of MASILVA is not recommended in patients with severe anemia. It is recommended that hemoglobin concentrations be measured prior to initiation of treatment and tests repeated during treatment as clinically indicated.

Pulmonary veno-occlusive disease

Cases of pulmonary edema have been reported with vasodilators (mainly prostacyclins) when used in patients with pulmonary veno-occlusive disease. Consequently, if signs of pulmonary edema 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
MASILVA 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 MASILVA. Monthly pregnancy tests during treatment with MASILVA 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 anemia during treatment with macitentan. Therefore, monitoring of blood pressure and hemoglobin 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 MASILVA is not recommended in this population (see sections 4.2 and 5.2).

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

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
Interaction studies have only been performed in adults.

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 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 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.

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 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.

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).

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).

Hormonal contraceptives: Macitentan 10 mg once daily did not affect the pharmacokinetics of an oral contraceptive (norethisterone 1 mg and ethinyl estradiol 35 mcg).

Pediatric population

Interaction studies have only been performed in adults.

4.6 Fertility, pregnancy and lactation

General principles

Pregnancy category is “X”.

Women of childbearing potential/Contraception

MASILVA 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 MASILVA. Monthly pregnancy tests during treatment with MASILVA are recommended to allow the early detection of pregnancy.

Pregnancy

There are no data from the use of macitentan in pregnant women. Based on non-clinical data, macitentan is suspected of causing serious birth defects if administered during pregnancy. Studies in animals have shown reproductive toxicity (see section 5.3). The potential risk for humans is still unknown. MASILVA is contraindicated during pregnancy and in women of childbearing potential who are not using reliable contraception (see section 4.3). Women of childbearing potential must use effective contraception during treatment (and for up to 1 month following treatment).

Lactation

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. MASILVA 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). A decrease in sperm count has been observed in patients receiving ERA. 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. The patient's clinical status and adverse reaction profile of macitentan (e.g., headache, hypotension) should be considered when assessing the patient's 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 are nasopharyngitis (14%), headache (13.6%) and anemia (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 (SERAPHIN) 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.

The following terms have been used to classify the occurrence of undesirable effects: 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).

MedDRA 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	Anemia, hemoglobin 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]
Respiratory, thoracic and mediastinal disorders	Common	Nasal congestion[1]
Hepatobiliary disorders	Common	Aminotransferase elevations[4]
General disorders and administration site conditions	Very common	Edema, 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 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] Edema/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 edema 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 edema 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 edema 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 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] Hemoglobin

In a double-blind study in patients with PAH, macitentan 10 mg was associated with a mean decrease in hemoglobin versus placebo of 1 g/dL. A decrease from baseline in hemoglobin 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 17×10^9/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.

Pediatric population

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

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorization 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 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, 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 (PAH)

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 receiving 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 etiologies (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

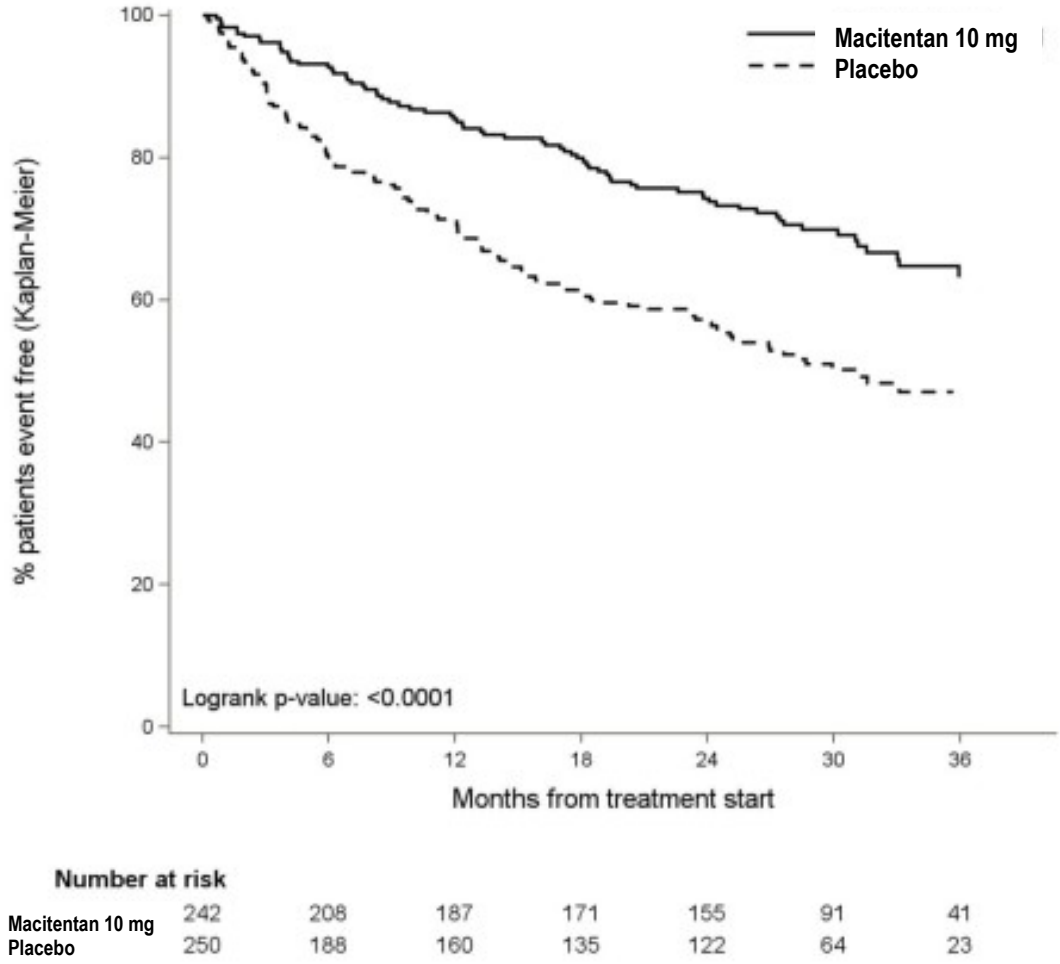

Table 1. Summary of outcome events

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 hospitalization 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 hospitalized 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.

Hemodynamic endpoints
Hemodynamic parameters were assessed in a subset of patients (placebo [N = 67], macitentan 10 mg [N = 57]) after 6 months of treatment. Patients received 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 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.

5.2. Pharmacokinetic properties
General 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 is 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. 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.

Linearity/Non-linearity
No data available.

Characteristics in patients
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 has been increased by 1.3- and 1.6-fold, respectively, in patients with severe renal impairment. This increase is not considered to be clinically significant (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 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

Lactose monohydrate (from cow milk)
Microcrystalline cellulose (PH 101) (E460)
Povidone K30 (E 1201)
Polysorbate 80 (E 433)
Microcrystalline cellulose (PH 102) (E 460)
Croscarmellose sodium (E 468)
Magnesium stearate (E 572)

Opadry ® AMB-II 88A180040 White (Film coating)
Polyvinyl alcohol-Partial hydrolysis (E 1203)
Talc (E 553b)
Titanium dioxide (E 171)
GMCC Type 1/Glycerol Fatty Acids
Sodium Lauryl Sulphate

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

24 months.

6.4 Special precautions for storage
Store at room temperature below 30°C and in its original package.

6.5 Nature and contents of container
Opaque PVC/PCTFE (PVC/Aclar) blister and aluminum foil are used as the primary packaging material of our product. Blisters are packed in a cardboard box. In a cardboard box, 4 blisters (7 tablets in each blister) with a total of 28 tablets and a package leaflet are presented.

6.6 Special precautions for disposal and other handling
Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORIZATION HOLDER

DEVA Holding A.Ş.
Halkalı Merkez Mah. Basın Ekspres Cad. No:1
34303 Küçükçekmece – İSTANBUL / TÜRKİYE

8. MARKETING AUTHORIZATION NUMBER

2022/75

9. DATE OF FIRST AUTHORIZATION/RENEWAL OF THE AUTHORIZATION

Date of first authorization : 11.02.2022
Date of last renewal :

10. DATE OF REVISION OF THE TEXT