Summary of Product Characteristics for Pharmaceutical Products

1. Name of the medicinal product:

PLATERO (Macitentan Tablets 10mg)

2. Qualitative and quantitative composition

Each film-coated tablet contains, Macitentan 10mg
Excipients with known effect
Each film-coated tablet contains approximately 37 mg of lactose (as monohydrate) and approximately 0.06 mg of soya bean lecithin (E322).
For the full list of excipients, see section 6.1.

3. Pharmaceutical form

Dosage form: Film coated Tablets
White colored, round, biconvex, film coated tablets debossed with "HM" on one side and "21" on other side.
Drug description
Macitentan is an endothelin receptor antagonist. The chemical name of macitentan is N-[5-(4Bromophenyl)-6-[2-[(5-bromo-2-pyrimidinyl)oxy]ethoxy]-4-pyrimidinyl] N'propylsulfamide. It has a molecular formula of $C_{19}H_{20}Br_2N_6O_4S$ and a molecular weight of 588.28.

Macitentan is a crystalline powder that is insoluble in water. Soluble in Dimethyl sulfoxide and slightly soluble in methanol. In the solid state macitentan is very stable, is not hygroscopic, and is not light sensitive. Macitentan is available as a 10 mg film-coated tablet for once daily oral administration. The tablets include the following inactive ingredients: Lactose Monohydrate (Pharmatose 200M), Sodium Starch Glycolate Type A (Primojel), Povidone (Kollidon 30), Polysorbate 80 (Crillet 4), Purified water, Sodium Stearyl Fumarate.
Colorant
Opadry AMB White (OY-B-28920) Composition: Polyvinyl Alcohol, Soya Lecithin, Talc, Titanium dioxide and Xanthan gum.

4. Clinical particulars

4.1 Therapeutic indications

Pulmonary Arterial Hypertension

Macitentan is an endothelin receptor antagonist (ERA) indicated for the treatment of pulmonary arterial hypertension (PAH, WHO Group I) to reduce the risks of disease progression and hospitalization for PAH.
Effectiveness was established in a long-term study in PAH patients with predominantly WHO Functional Class II–III symptoms treated for an average of 2 years. Patients had idiopathic and heritable PAH (57%), PAH caused by connective tissue disorders (31%), and PAH caused by congenital heart disease with repaired shunts (8%).

4.2 Posology and method of administration

Recommended Dosage
The recommended dosage of Macitentan is 10 mg once daily for oral administration.
Doses higher than 10 mg once daily have not been studied in patients with PAH and are not recommended.
Pregnancy Testing in Females of Reproductive Potential
Obtain a pregnancy test in females of reproductive potential prior to Macitentan treatment, monthly during treatment and one month after stopping Macitentan. Initiate treatment with Macitentan in females of reproductive potential only after a negative pregnancy test.
Dosage forms and strengths
Tablets: 10 mg, bi-convex film-coated, round, white, and debossed with "10" on both sides.

4.3 Contraindications

Pregnancy
Macitentan may cause fetal harm when administered to a pregnant woman. Macitentan is contraindicated in females who are pregnant. Macitentan was consistently shown to have teratogenic effects when administered to animals. If Macitentan is used during pregnancy, advise the patient of the potential risk to a fetus.
Hypersensitivity
Macitentan is contraindicated in patients with a history of a hypersensitivity reaction to macitentan or any component of the product.

4.4 Special warnings and precautions for use

Embryo-fetal Toxicity

Macitentan may cause fetal harm when administered during pregnancy and is contraindicated for use in females who are pregnant. In females of reproductive potential, exclude pregnancy prior to initiation of therapy, ensure use of acceptable contraceptive methods and obtain monthly pregnancy tests.
Females of reproductive potential must comply with the pregnancy testing and contraception requirements.
Pharmacies must be certified with the program and must only dispense to patients who are authorized to receive Macitentan.
Macitentan REMS Program
For all females, Macitentan is available only through a restricted program called the Macitentan REMS Program, because of the risk of embryo-fetal toxicity.
Notable requirements of the Macitentan REMS Program include the following:
Prescribers must be certified with the Macitentan REMS Program by enrolling and completing training.
All females, regardless of reproductive potential, must enroll in the Macitentan REMS Program prior to initiating Macitentan. Male patients are not enrolled in the REMS.
Hepatotoxicity
ERAs have caused elevations of aminotransferases, hepatotoxicity, and liver failure. The incidence of elevated aminotransferases in the study of Macitentan in PAH is shown in Table1.
Table 1: Incidence of Elevated Aminotransferases in the SERAPHIN Study

	Macitentan 10 mg (N=242)	Placebo (N=249)
>3 × ULN	3.4%	4.5%
>8 × ULN	2.1%	0.4%

In the placebo-controlled study of Macitentan, discontinuations for hepatic adverse events were 3.3% in the Macitentan 10 mg group vs. 1.6% for placebo.
Obtain liver enzyme tests prior to initiation of Macitentan and repeat during treatment as clinically indicated.
Advise patients to report symptoms suggesting hepatic injury (nausea, vomiting, right upper quadrant pain, fatigue, anorexia, jaundice, dark urine, fever, or itching). If clinically relevant aminotransferase elevations occur, or if elevations are accompanied by an increase in bilirubin >2 × ULN, or by clinical symptoms of hepatotoxicity, discontinue Macitentan. Consider reinitiation of Macitentan when hepatic enzyme levels normalize in patients who have not experienced clinical symptoms of hepatotoxicity.
Fluid Retention

Peripheral edema and fluid retention are known clinical consequences of PAH and known effects of ERAs. In the placebo-controlled study of Macitentan in PAH, the incidence of edema was 21.9% in the Macitentan 10 mg group and 20.5% in the placebo group.
Patients with underlying left ventricular dysfunction may be at particular risk for developing significant fluid retention after initiation of ERA treatment. In a small study of Macitentan in patients with pulmonary hypertension because of left ventricular dysfunction, more patients in the Macitentan group developed significant fluid retention and had more hospitalizations because of worsening heart failure compared to those randomized to placebo. Post marketing cases of edema and fluid retention occurring within weeks of starting Macitentan, some requiring intervention with a diuretic or hospitalization for decompensated heart failure, have been reported.
Monitor for signs of fluid retention after Macitentan initiation. If clinically significant fluid retention develops, evaluate the patient to determine the cause, such as Macitentan or underlying heart failure, and the possible need to discontinue Macitentan.
Haemoglobin Decrease
Decreases in haemoglobin concentration and haematocrit have occurred following administration of other ERAs and were observed in clinical studies with Macitentan. These decreases occurred early and stabilized thereafter. In the placebo-controlled study of Macitentan in PAH, Macitentan 10 mg caused a mean decrease in haemoglobin from baseline to up to 18 months of about 1.0 g/dL compared to no change in the placebo group. A decrease in haemoglobin to below 10.0 g/dL was reported in 8.7% of the Macitentan 10 mg group and in 3.4% of the placebo group. Decreases in haemoglobin seldom require transfusion. Initiation of Macitentan is not recommended in patients with severe anaemia. Measure haemoglobin prior to initiation of treatment and repeat during treatment as clinically indicated.
Pulmonary Edema with Pulmonary Veno-occlusive Disease (PVOD)
Should signs of pulmonary edema occur, consider the possibility of associated PVOD. If confirmed, discontinue Macitentan.
Decreased Sperm Counts
Macitentan, like other ERAs, may have an adverse effect on spermatogenesis. Counsel men about potential effects on fertility.
Adverse reactions
Clinically significant adverse reactions that appear in other sections of the labelling include:
Embryo-fetal Toxicity
Hepatotoxicity

Fluid Retention
Decrease in Haemoglobin

4.5 Interaction with other medicinal products and other forms of interaction

Strong CYP3A4 Inducers
Strong inducers of CYP3A4 such as rifampin significantly reduce macitentan exposure.
Concomitant use of Macitentan with strong CYP3A4 inducers should be avoided.
Strong CYP3A4 Inhibitors
Concomitant use of strong CYP3A4 inhibitors like ketoconazole approximately double macitentan exposure. Many HIV drugs like ritonavir are strong inhibitors of CYP3A4. Avoid concomitant use of Macitentan with strong CYP3A4 inhibitors. Use other PAH treatment options when strong CYP3A4 inhibitors are needed as part of HIV treatment.
Moderate Dual or Combined CYP3A4 and CYP2C9 Inhibitors
Concomitant use of moderate dual inhibitors of CYP3A4 and CYP2C9 such as fluconazole is predicted to increase macitentan exposure approximately 4-fold based on physiologically based pharmacokinetic (PBPK) modelling. Avoid concomitant use of Macitentan with moderate dual inhibitors of CYP3A4 and CYP2C9 (such as fluconazole and amiodarone).
Concomitant treatment of both a moderate CYP3A4 inhibitor and moderate CYP2C9 inhibitor with Macitentan should also be avoided.

4.6 Pregnancy and Lactation

Pregnancy
Risk Summary
Based on data from animal reproduction studies, Macitentan may cause embryo-fetal toxicity, including birth defects and fetal death, when administered to a pregnant female and is contraindicated during pregnancy. There are risks to the mother and the fetus associated with pulmonary arterial hypertension in pregnancy. There are limited data on Macitentan use in pregnant women. Macitentan was teratogenic in rabbits and rats at all doses tested. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, advise the patient of the risk to a fetus.

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2–4% and 15–20%, respectively.

Clinical Considerations

Disease-associated Maternal and/or Embryo/Fetal Risk

In patients with pulmonary arterial hypertension, pregnancy is associated with an increased rate of maternal and fetal morbidity and mortality, including spontaneous abortion, intrauterine growth restriction and premature labour.

Data

Animal Data

In both rabbits and rats, there were cardiovascular and mandibular arch fusion abnormalities. Administration of macitentan to female rats from late pregnancy through lactation caused reduced pup survival and impairment of the male fertility of the offspring at all dose levels tested.

Lactation

Risk Summary

There are no data on the presence of macitentan in human milk, the effects on the breastfed infant, or the effect on milk production. Because of the potential for serious adverse reactions in breastfed infants from Macitentan advise women not to breastfeed during treatment with Macitentan.

Females and Males of Reproductive Potential

Pregnancy Testing

Verify the pregnancy status of females of reproductive potential prior to initiating Macitentan, monthly during treatment and one month after stopping treatment with Macitentan. The patient should contact her physician immediately for pregnancy testing if onset of menses is delayed or pregnancy is suspected. If the pregnancy test is positive, the physician and patient must discuss the risks to her, the pregnancy, and the fetus.

Contraception

Female patients of reproductive potential must use acceptable methods of contraception during treatment with Macitentan and for 1 month after treatment with Macitentan. Patients may choose one highly effective form of contraception (intrauterine devices (IUD), contraceptive implants or tubal sterilization) or a combination of methods (hormone method with a barrier method or two barrier methods). If a partner's vasectomy is the chosen method of contraception, a hormone or barrier method must be used along with this method. Counsel patients on pregnancy planning and prevention, including

emergency contraception, or designate counseling by another healthcare provider trained in contraceptive counselling.

Infertility

Based on findings in animals, Macitentan may impair fertility in males of reproductive potential. It is not known whether effects on fertility would be reversible.

Pediatric Use

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

Geriatric Use

Of the total number of subjects in the clinical study of Macitentan for PAH, 14% were 65 and over. No overall differences in safety or effectiveness were observed between these subjects and younger subjects. Clinical Trial Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

Safety data for Macitentan were obtained primarily from one placebo-controlled clinical study in 742 patients with PAH (SERAPHIN study)

The exposure to Macitentan in this trial was up to 3.6 years with a median exposure of about 2 years (N=542 for 1 year; N=429 for 2 years; and N=98 for more than 3 years).

The overall incidence of treatment discontinuations because of adverse events was similar across Macitentan 10 mg and placebo treatment groups (approximately 11%).

Table 2: Adverse Reactions more frequent on Macitentan than on placebo by ≥3%.

Adverse Reaction	Macitentan 10 mg (N=242) (%)	Placebo (N=249) (%)
Anemia	13	3
Nasopharyngitis/pharyngitis	20	13
Bronchitis	12	6
Headache	14	9
Influenza	6	2
Urinary tract infection	9	6

Post marketing Experience

The following adverse reactions have been identified during post-approval use of Macitentan. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.
Immune system disorders: hypersensitivity reactions (angioedema, pruritus and rash)
Vascular disorders: flushing Respiratory, thoracic and mediastinal disorders: nasal congestion
Gastrointestinal disorders: Elevations of liver aminotransferases (ALT, AST) and liver injury have been reported with Macitentan use; in most cases alternative causes could be identified (heart failure, hepatic congestion, autoimmune hepatitis). Endothelin receptor antagonists have been associated with elevations of aminotransferases, hepatotoxicity, and cases of liver failure.
General disorders and administration site conditions: edema/fluid retention. Cases of edema and fluid retention occurred within weeks of starting Macitentan, some requiring intervention with a diuretic, fluid management or hospitalization for decompensated heart failure.
Cardiac disorders: symptomatic hypotension.

4.7 Effects on ability to drive and use machines

None.

4.8 Undesirable effects

Embryo-fetal Toxicity
Hepatotoxicity
Fluid Retention
Decrease in Haemoglobin

4.9 Overdose

Macitentan has been administered as a single dose of up to and including 600 mg to healthy subjects (60 times the approved dosage). Adverse reactions of headache, nausea and vomiting were observed. In the event of an overdose, standard supportive measures should be taken, as required. Dialysis is unlikely to be effective because macitentan is highly protein-bound.
Clinical Studies Pulmonary Arterial Hypertension
The effect of macitentan on progression of PAH was demonstrated in a multi-center, long-term (average duration of exposure approximately 2 years), placebo-controlled study in 742 patients with symptomatic [WHO functional

class (FC) II–IV] PAH who were randomized to placebo (n=250), 3 mg macitentan (n=250), or 10 mg macitentan (n=242) once daily. Patients were treated with macitentan monotherapy or in combination with phosphodiesterase-5 inhibitors or inhaled prostanoids.

The primary study endpoint was time to the first occurrence of death, a significant morbidity event, defined as atrial septostomy, lung transplantation, initiation of IV or subcutaneous (SC) prostanoids, or "other worsening of PAH" during double-blind treatment plus 7 days. Other worsening was defined as all of the following: 1) a sustained ≥15% decrease from baseline in 6minute walk distance (6MWD), 2) worsening of PAH symptoms (worsening of WHO FC), and 3) need for additional treatment for PAH. All of these other worsening events were confirmed by an independent adjudication committee, blinded to treatment allocation. A critical secondary endpoint was time to PAH death or PAH hospitalization.

The mean patient age was 46 years (14% were age 65 or above). Most patients were white (55%) or Asian (29%) 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 caused by connective tissue disorders (31%), PAH caused by congenital heart disease with repaired shunts (8%), and PAH caused by other etiologies [drugs and toxins (3%) and HIV (1%)].

At baseline, the majority of enrolled patients (64%) were being treated with a stable dose of specific therapy for PAH, either oral phosphodiesterase inhibitors (61%) and/or inhaled/oral prostanoids (6%).

Study results are described for the placebo and Macitentan 10 mg groups. The median treatment durations were 101 and 118 weeks in the placebo and Macitentan 10 mg groups, respectively, up to a maximum of 188 weeks.

Treatment with Macitentan 10 mg resulted in a 45% reduction (HR 0.55, 97.5% CI 0.39–0.76; logrank $p<0.0001$) in the occurrence of the primary endpoint up to end of double-blind treatment compared to placebo (Table 3 and Figure 2). The beneficial effect of Macitentan 10 mg was primarily attributable to a reduction in clinical worsening events (deterioration in 6MWD and worsening of PAH symptoms and need for additional PAH treatment).

Macitentan10mg	242	208	187	171	155	91	41
Placebo	250	188	160	135	122	64	23

Table 3: Summary of Primary Endpoint Events

	Placebo N=250 n (%)	Macitentan 10 mg N=242 n (%)
Patients with a primary endpoint event	116 (46.4)	76 (31.4)
Component as first event		
Worsening PAH	93 (37.2)	59 (24.4)
Death	17 (6.8)	16 (6.6)
IV/SC prostanoid	6 (2.4)	1 (0.4)

*No patients experienced an event of lung transplantation or atrial septostomy in the placebo or Macitentan 10 mg treatment groups.

Subgroup analyses were performed to examine their influence on outcome as shown in Figure 3. Consistent efficacy of Macitentan 10 mg on the primary endpoint was seen across subgroups of age, sex, race, etiology, by monotherapy or in combination with another PAH therapy, baseline 6MWD, and baseline WHO FC.

PAH related death or hospitalization for PAH was assessed as a secondary endpoint.

The risk of PAH related death or hospitalization for PAH was reduced by 50% in patients receiving Macitentan 10 mg compared to placebo (HR 0.50, 97.5% CI 0.34–0.75; log rank p<0.0001).

Number at risk

Macitentan10mg	242	203	183	166	152	86	39
Placebo	250	188	155	132	119	62	22

Table 4: Summary of Death due to PAH and Hospitalization due to PAH

	Placebo (N=250) n (%)	Macitentan 10 mg (N=242) n (%)
Death due to PAH or hospitalization for PAH	84 (33.6)	50 (20.7)
Component as first event		

Death due to PAH	5 (2.0)	5 (2.1)
Hospitalization for PAH	79 (31.6)	45 (18.6)

Treatment with Macitentan 10 mg resulted in a placebo-corrected mean increase in 6MWD of 22 meters at Month 6 (97.5% CI 3–41; p=0.0078), with significant improvement in 6MWD by Month 3. 6MWD increased more in patients with worse baseline WHO Functional Class (37 meters and 12 meters' placebo-corrected mean increase in WHO FC III/IV and FC I/II, respectively). The increase in 6MWD achieved with Macitentan was maintained for the duration of the study.

Treatment with Macitentan 10 mg led to an improvement of at least one WHO Functional Class at Month 6 in 22% of patients compared to 13% of patients treated with placebo.

Long-Term Treatment of PAH

In long-term follow-up of patients who were treated with Macitentan 10 mg in the placebo controlled study (N=242) and the open-label extension study, Kaplan-Meier estimates of survival at 1, 2, 5, and 7 years were 95%, 89%, 73%, and 63% respectively. The median exposure to Macitentan was 4.6 years. These uncontrolled observations do not allow comparison with a group not given Macitentan and cannot be used to determine the long termeffect of Macitentan on mortality.

5. Pharmacological properties

5.1 Pharmacodynamic properties

Mechanism of Action

Endothelin (ET)-1 and its receptors (ET_A and ET_B) 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 endothelin receptor antagonist that inhibits the binding of ET-1 to both ET_A and ET_B receptors. Macitentan displays high affinity and sustained occupancy of the ET receptors in human pulmonary arterial smooth muscle cells. One of the metabolites of macitentan is also pharmacologically active at the ET receptors and is estimated to be about 20% as potent as the parent drug in vitro. The clinical impact of dual endothelin blockage is unknown.

Pulmonary Hemodynamics

The clinical efficacy study in patients with pulmonary arterial hypertension assessed hemodynamic parameters in a subset of patients after 6 months of treatment. Patients treated with Macitentan 10 mg (N=57) achieved a median reduction of 37% (95% CI 22– 49) in pulmonary vascular resistance and an increase of 0.6 L/min/m^2 (95% CI 0.3–0.9) in cardiac index compared to placebo (N=67).

Cardiac Electrophysiology

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

5.2 Pharmacokinetic properties

The pharmacokinetics of macitentan and its active metabolite have been studied primarily in healthy subjects. The pharmacokinetics of macitentan are dose proportional over a range from 1 mg to 30 mg after once daily administration.

A cross study comparison shows that the exposures to macitentan and its active metabolite in patients with PAH are similar to those observed in healthy subjects.

Absorption and Distribution

The maximum plasma concentration of macitentan is achieved about 8 hours after oral administration. The absolute bioavailability after oral administration is not known. In a study in healthy subjects, the exposure to macitentan and its active metabolite were unchanged after a high fat breakfast. Macitentan may therefore be taken with or without food.

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

Metabolism and Elimination

Following oral administration, the apparent elimination half-lives of macitentan and its active metabolite are approximately 16 hours and 48 hours, respectively. Macitentan is metabolized primarily by oxidative depropylation of the sulfamide to form the pharmacologically active metabolite. This reaction is dependent on the cytochrome P450 (CYP) system, mainly CYP3A4 with minor contributions of CYP2C8, CYP2C9, and CYP2C19. At steady state in PAH patients, the systemic exposure to the active metabolite is 3-times the exposure to macitentan and is expected to contribute approximately 40% of the total pharmacologic activity. In a study in healthy subjects with radiolabeled

macitentan, approximately 50% of radioactive drug material was eliminated in urine but none was in the form of unchanged drug or the active metabolite. About 24% of the radioactive drug material was recovered from feces.

Special Populations

There are no clinically relevant effects of age, sex, or race on the pharmacokinetics of macitentan and its active metabolite.

Renal Impairment

Exposure to macitentan and its active metabolite in patients with severe renal impairment (CrCl 15–29 mL/min) compared to healthy subjects was increased by 30% and 60%, respectively.

This increase is not considered clinically relevant.

Hepatic Impairment

Exposure to macitentan was decreased by 21%, 34%, and 6% and exposure to the active metabolite was decreased by 20%, 25%, and 25% in subjects with mild, moderate, or severe hepatic impairment (Child-Pugh Class A, B, and C), respectively. This decrease is not considered clinically relevant.

Drug Interactions

In Vitro Studies

At plasma levels obtained with dosing at 10 mg once daily, macitentan has no relevant inhibitory or inducing effects on CYP enzymes. Macitentan is not a substrate or inhibitor of multi-drug resistance protein (P-gp, MDR-1). The active metabolite of macitentan also is not an inhibitor of P-gp/MDR-1 at clinically relevant concentrations.

Macitentan and its active metabolite are not expected to have significant interaction with drug transporters such as organic anion transporting polypeptide (OATP1B1, OATP1B3), multidrug and toxin extrusion protein (MATE-1, MATE-2K), bile salt export pump (BSEP), sodiumtaurocholate co-transporting polypeptide (NTCP), organic cation transporter (OCT-1, OCT-3), organic anion transporter (OAT-1, OAT-3) or BCRP transporter at clinically relevant plasma concentrations.

Effect of other drugs on macitentan

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

PBPK modeling and simulations based analysis showed that a moderate dual inhibitor of CYP3A4 and CYP2C9 such as fluconazole (400 mg once daily) is predicted to increase macitentan exposure approximately 4-fold without relevant effect on the exposure to its active metabolite.

Effect of macitentan on other drugs
Warfarin: Macitentan once daily dosing did not alter the exposure to R- and S-warfarin or their effect on international normalized ratio (INR).
Sildenafil: At steady-state, the exposure to sildenafil 20 mg t.i.d. increased by 15% during concomitant administration of macitentan 10 mg once daily. This change is not considered clinically relevant.
Hormonal contraceptives: Macitentan 10 mg once daily did not affect the pharmacokinetics of an oral contraceptive (norethisterone 1 mg and ethinyl estradiol 35 µg).
BCRP Substrate drugs: Macitentan 10 mg once daily did not affect the pharmacokinetics of concomitant use of a BCRP substrate drug (riociguat 1 mg and rosuvastatin 10 mg).

5.3 Preclinical safety data

Nonclinical Toxicology Carcinogenesis, Mutagenesis, Impairment of Fertility
Carcinogenesis
Carcinogenicity studies of 2 years' duration did not reveal any carcinogenic potential at exposures 75-fold and 140-fold the human exposure (based on AUC) in male and female mice, respectively, and 8.3- and 42-fold in male and female rats, respectively.
Mutagenesis
Macitentan was not genotoxic in a standard battery of in vitro and in vivo assays that included a bacterial reverse mutation assay, an assay for gene mutations in mouse lymphoma cells, a chromosome aberration test in human lymphocytes, and an in vivo micronucleus test in rats.
Impairment of Fertility
Treatment of juvenile rats from postnatal Day 4 to Day 114 led to reduced body weight gain and testicular tubular atrophy at exposures 7-fold the human exposure. Fertility was not affected.
Reversible testicular tubular dilatation was observed in chronic toxicity studies at exposures greater than 7-fold and 23-fold the human exposure in rats and dogs, respectively. After 2 years of treatment, tubular atrophy was seen in rats at 4-fold the human exposure. Macitentan did not affect male or female fertility at exposures ranging from 19- to 44-fold the human exposure, respectively, and had no effect on sperm count, motility, and morphology in male rats. No testicular findings were noted in mice after treatment up to 2 years.
Animal Toxicology
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.
There were no adverse liver findings in long-term studies conducted in mice, rats, and dogs at exposures of 12- to 116-fold the human exposure.

6. Pharmaceutical Particulars

6.1 List of Excipients

Lactose Monohydrate (Pharmatose 200M), Sodium Starch Glycolate Type A (Primojel), Povidone (Kollidon 30), Polysorbate 80 (Crillet 4), Purified water, Sodium Stearyl Fumarate and Opadry AMB White.
Opadry AMB White Composition: Polyvinyl Alcohol, Soya Lecithin, Talc, Titanium dioxide, and Xanthan gum.
HOW SUPPLIED
PLATERO (Macitentan Tablets 10mg)
Each film-coated tablet contains Macitentan 10mg
White colored, round, biconvex, film coated tablets debossed with "HM" on one side and "21" on other side.

6.2 Incompatibilities

Not applicable

6.3 Shelf-Life

24 months

6.4 Special Precautions for storage

Store below 30°C

6.5 Nature and Content of container

3×10’s Blister pack

6.6 Special precautions for disposal and other handling

Not applicable

7. Marketing Authorization Holder

Hetero Labs Limited,
7-2-A2, Hetero Corporate,
Industrial Estates,
Sanath Nagar, Hyderabad-500 018.
Telangana state, India

8. Marketing Authorization Number

CTD12370

9. Date of first authorization/renewal of the authorization

2026 July 18

10. Date of revision of the text

2026 July 18