Reason for issue	NA

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use MACITENTAN TABLETS safely and effectively. See full prescribing information for MACITENTAN TABLETS.
MACITENTAN tablets, for oral use
Initial U.S. Approval: 2013

WARNING: EMBRYO-FETAL TOXICITY
See full prescribing information for complete boxed warning.
- **Based on animal data, macitentan may cause fetal harm if used during pregnancy (4.1, 5.1, 8.1).**
- **Females of reproductive potential: exclude pregnancy before start of treatment. Prevent pregnancy prior to initiation of treatment, during treatment and for one month after treatment by using effective methods of contraception (2.2, 8.3).**
- **When pregnancy is detected, discontinue macitentan as soon as possible (5.1).**

----------RECENT MAJOR CHANGES----------

Boxed Warning	4/2025
Dosage and Administration (2.2)	4/2025
Warnings and Precautions (5.1)	4/2025
Warnings and Precautions (5.2)	Removal 4/2025

----------INDICATIONS AND USAGE----------
Macitentan tablets are endothelin receptor antagonist (ERA) indicated for the treatment of pulmonary arterial hypertension (PAH, WHO Group I) in adults to reduce the risks of disease progression and hospitalization for PAH (1.1).

----------DOSAGE AND ADMINISTRATION----------
- 10 mg once daily. Doses higher than 10 mg once daily have not been studied in patients with PAH and are not recommended (2.1).

----------DOSAGE FORMS AND STRENGTHS----------
- Tablet: 10 mg (3)

----------CONTRAINDICATIONS----------
- Pregnancy (4.1)
- Hypersensitivity (4.2)

----------WARNINGS AND PRECAUTIONS----------
- ERAs cause hepatotoxicity and liver failure. Obtain baseline liver enzymes and monitor as clinically indicated (5.2).
- Fluid retention may require intervention (5.3).
- Decreases in hemoglobin (5.4).
- Pulmonary edema in patients with pulmonary veno-occlusive disease. If confirmed, discontinue treatment (5.5).
- Decreases in sperm count have been observed in patients taking ERAs (5.6).

----------ADVERSE REACTIONS----------
Most common adverse reactions (more frequent than placebo by ≥ 3%) are anemia, nasopharyngitis/pharyngitis, bronchitis, headache, influenza, and urinary tract infection (6.1).

To report SUSPECTED ADVERSE REACTIONS, contact Sun Pharmaceutical Industries Inc. at 1-800-818-4555 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------DRUG INTERACTIONS----------
- Strong CYP3A4 inducers (rifampin) reduce exposure to macitentan: avoid co-administration with macitentan (7.1, 12.3).
- Strong CYP3A4 inhibitors (ketoconazole, ritonavir) increase exposure to macitentan: avoid co-administration with macitentan (7.2, 12.3).
- Moderate dual CYP3A4 and CYP2C9 inhibitors (fluconazole, amiodarone) or use of combined CYP3A4 and CYP2C9 inhibitors may increase exposure to macitentan: avoid co-administration with macitentan (7.3, 12.3).

----------USE IN SPECIFIC POPULATIONS----------
- Lactation: Advise not to breastfeed. (8.2)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 06/2025

FULL PRESCRIBING INFORMATION: CONTENTS*
WARNING: EMBRYO-FETAL TOXICITY

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*Sections or subsections omitted from the full prescribing information are not listed.

2D

MACITENTAN TABLETS
11002578

FULL PRESCRIBING INFORMATION

WARNING: EMBRYO-FETAL TOXICITY
Macitentan tablets are contraindicated for use during pregnancy because it may cause fetal harm based on animal data *[see Contraindications (4.1), Warnings and Precautions (5.1), Use in Specific Populations (8.1)]*.

Therefore, for females of reproductive potential, exclude pregnancy before the start of treatment with macitentan. Advise use of effective contraception before the initiation of treatment, during treatment, and for one month after stopping treatment with macitentan *[see Dosage and Administration (2.2), Use in Specific Populations (8.3)]*. When pregnancy is detected, discontinue macitentan as soon as possible *[see Warnings and Precautions (5.1)]*.

1 INDICATIONS AND USAGE
1.1 Pulmonary Arterial Hypertension
Macitentan tablets are an endothelin receptor antagonist (ERA) indicated for the treatment of pulmonary arterial hypertension (PAH, WHO Group I) in adults 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%) *[see Clinical Studies (14.1)]*.

2 DOSAGE AND ADMINISTRATION
2.1 Recommended Dosage
The recommended dosage of macitentan tablets 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.

2.2 Pregnancy Testing in Females of Reproductive Potential
Exclude pregnancy before initiating treatment with macitentan tablets in females of reproductive potential *[see Boxed Warning, Contraindications (4.1), Warnings and Precautions (5.1), and Use in Specific Populations (8.3)]*.

3 DOSAGE FORMS AND STRENGTHS
Tablets: 10 mg, white to off-white, round biconvex film-coated tablet debossed with "**M1**" on one side and plain on other side.

4 CONTRAINDICATIONS
4.1 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 *[see Warnings and Precautions (5.1) and Use in Specific Populations (8.1)]*.

4.2 Hypersensitivity
Macitentan is contraindicated in patients with a history of a hypersensitivity reaction to macitentan or any component of the product *[see Adverse Reactions (6.2)]*.

5 WARNINGS AND PRECAUTIONS
5.1 Embryo-fetal Toxicity
Based on data from animal reproduction studies, macitentan may cause fetal harm when administered to a pregnant patient and is contraindicated during pregnancy. The available human data for ERAs do not establish the presence or absence of major birth defects related to the use of macitentan. Advise patients who can become pregnant of the potential risk to a fetus. Obtain a pregnancy test prior to initiation of therapy with macitentan. Advise patients who can become pregnant to use effective contraceptive methods prior to initiation of treatment, during treatment, and for one month after discontinuation of treatment with macitentan. When pregnancy is detected, discontinue use as soon as possible *[see Dosage and Administration (2.2), Contraindications (4.1), and Use in Specific Populations (8.1, 8.3)]*.

5.2 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 Table 1.

Table 1 Incidence of Elevated Aminotransferases in the SERAPHIN Study

	Macitentan 10 mg (N = 242)	Placebo (N = 249)
> 3 times ULN	3.4%	4.5%
> 8 times 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 *[see Adverse Reactions (6.2)]*.

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 times ULN, or by clinical symptoms of hepatotoxicity, discontinue macitentan. Consider re-initiation of macitentan when hepatic enzyme levels normalize in patients who have not experienced clinical symptoms of hepatotoxicity.

5.3 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. Postmarketing 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 *[see Adverse Reactions (6.2)]*.

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.

5.4 Hemoglobin Decrease
Decreases in hemoglobin concentration and hematocrit 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 hemoglobin from baseline to up to 18 months of about 1 g/dL compared to no change in the placebo group. A decrease in hemoglobin to below 10 g/dL was reported in 8.7% of the macitentan 10 mg group and in 3.4% of the placebo group. Decreases in hemoglobin seldom require transfusion. Initiation of macitentan is not recommended in patients with severe anemia. Measure hemoglobin prior to initiation of treatment and repeat during treatment as clinically indicated *[see Adverse Reactions (6.1)]*.

5.5 Pulmonary Edema with Pulmonary Veno-occlusive Disease (PVOD)
Should signs of pulmonary edema occur, consider the possibility of associated PVOD. If confirmed, discontinue macitentan.

5.6 Decreased Sperm Counts
Macitentan, like other ERAs, may have an adverse effect on spermatogenesis. Counsel men about potential effects on fertility *[see Use in Specific Populations (8.3) and Nonclinical Toxicology (13.1)]*.

6 ADVERSE REACTIONS
Clinically significant adverse reactions that appear in other sections of the labeling include:
- Embryo-fetal Toxicity *[see Warnings and Precautions (5.1)]*
- Hepatotoxicity *[see Warnings and Precautions (5.2)]*
- Fluid Retention *[see Warnings and Precautions (5.3)]*
- Decrease in Hemoglobin *[see Warnings and Precautions (5.4)]*

6.1 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) *[see Clinical Studies (14.1)]*. 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 presents adverse reactions more frequent on macitentan than on placebo by ≥ 3%.

Table 2 Adverse Reactions

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

6.2 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 *[see Warnings and Precautions (5.2)]*.

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 *[see Warnings and Precautions (5.3)]*.

Cardiac disorders: symptomatic hypotension

7 DRUG INTERACTIONS
7.1 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 *[see Clinical Pharmacology (12.3)]*.

7.2 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 *[see Clinical Pharmacology (12.3)]*. Use other PAH treatment options when strong CYP3A4 inhibitors are needed as part of HIV treatment *[see Clinical Pharmacology (12.3)]*.

7.3 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) modeling. Avoid concomitant use of macitentan with moderate dual inhibitors of CYP3A4 and CYP2C9 (such as fluconazole and amiodarone) *[see Clinical Pharmacology (12.3)]*.

Concomitant treatment of both a moderate CYP3A4 inhibitor and moderate CYP2C9 inhibitor with macitentan should also be avoided *[see Clinical Pharmacology (12.3)]*.

8 USE IN SPECIFIC POPULATIONS
8.1 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 *[see Clinical Considerations]*. Available data from postmarketing reports and published literature over decades of use with ERAs in the same class as macitentan have not identified an increased risk of major birth defects; however, these data are limited. Methodological limitations of these postmarketing reports and published literature include lack of a control group; limited information regarding dose, duration, and timing of drug exposure; and missing data. These limitations preclude establishing a reliable estimate of the risk of adverse fetal and neonatal outcomes with maternal ERA use. 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 *[see Contraindications (4.1)]*.

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 to 4% and 15 to 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 labor.

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.

8.2 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.

8.3 Females and Males of Reproductive Potential
Based on data from animal reproductive toxicity studies, macitentan can cause fetal harm, including birth defects and fetal death, when administered to a pregnant patient and is contraindicated during pregnancy *[see Contraindications (4.1), and Use in Specific Populations (8.1)]*.

Pregnancy Testing
Verify that patients who can become pregnant are not pregnant prior to initiating macitentan. The patient should contact their 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 should discuss the risks to the pregnancy, and the fetus.

Contraception
Patients who can become pregnant who are using macitentan tablets should use an effective method of contraception prior to initiation of treatment, during treatment, and for one month after discontinuation of treatment with macitentan tablets to prevent pregnancy *[see Warnings and Precautions (5.1)]*.

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 *[see Warnings and Precautions (5.6), Adverse Reactions (6.1), and Nonclinical Toxicology (13.1)]*.

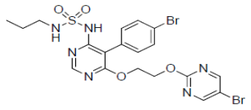
8.4 Pediatric Use
The safety and effectiveness of macitentan in pediatric patients have not been established for the treatment of PAH.

Pediatric information describing a clinical study in which efficacy was not demonstrated is approved for Actelion Pharmaceuticals US, Inc.'s Opsumit (macitentan) tablets. However, due to Actelion Pharmaceuticals US, Inc.'s marketing exclusivity rights, this drug product is not labeled with that information.

8.5 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.

10 OVERDOSAGE
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.

11 DESCRIPTION
Macitentan is an endothelin receptor antagonist. The chemical name of macitentan is N-[5-(4-Bromophenyl)-6-[2-[(5-bromo-2-pyrimidinyl)oxy]ethoxy]-4-pyrimidinyl]-N'-propylsulfamide. It has a molecular formula of $C_{19}H_{20}Br_2N_8O_4S$ and a molecular weight of 588.27. Macitentan is achiral and has the following structural formula:



Macitentan is a white to off-white crystalline powder with pinkish shade. It is freely soluble in dimethylsulphoxide and N,N-dimethylformamide, soluble in dichloromethane and ethyl acetate, insoluble in water. In the solid state macitentan is very stable, is not hygroscopic, and is not light sensitive.

Macitentan tablets are available as a 10 mg film-coated tablet for once daily oral administration. The tablets include the following inactive ingredients: crospovidone, magnesium stearate, mannitol, microcrystalline cellulose, polysorbate 80 and povidone. The tablets are film-coated with a coating material containing polyvinyl alcohol, soya lecithin, talc, titanium dioxide, and xanthan gum.

12 CLINICAL PHARMACOLOGY
12.1 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 ETA and ETB 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.

12.2 Pharmacodynamics
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 to 49) in pulmonary vascular resistance and an increase of 0.6 L/min/m^2 (95% CI 0.3 to 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.

12.3 Pharmacokinetics
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 to 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), sodium-taurocholate 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.

300 mm
40 mm
400 mm

Prepared By	Reviewed By	Approved By				
Packaging Development	Quality Assurance	Packaging Development	Production	Marketing/ Customer	Regulatory Affairs	Quality Assurance

Gopi Shah

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Date: 2025.10.08 19:32:21 +05'30'

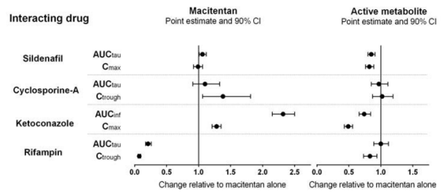
Reason for Issue	NA

In Vivo Studies

Effect of other drugs on macitentan

The effect of other drugs on macitentan and its active metabolite are studied in healthy subjects and are shown in Figure 1 below.

Figure 1



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 *[see Drug Interactions (7.2)]*.

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 *[see Drug Interactions (7.3)]*.

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).

13 NONCLINICAL TOXICOLOGY

13.1 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.

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.

13.2 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.

14 CLINICAL STUDIES

14.1 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 6 minute 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 to 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).

Figure 2 Kaplan-Meier Estimates of the Occurrence of the Primary Endpoint Event in the SERAPHIN Study

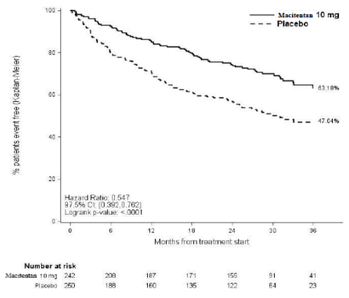


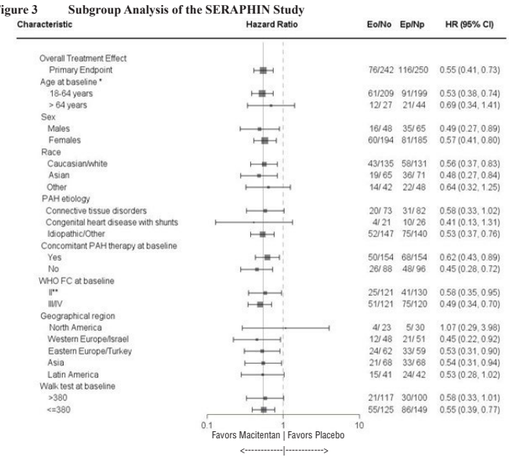
Table 3 Summary of Primary Endpoint Events

	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.

Figure 3 Subgroup Analysis of the SERAPHIN Study



*there were 6 patients in Macitentan and 7 in placebo that were under 18 years

**includes 1 patient in Macitentan with WHO FC I at baseline

Eo = Number of events macitentan 10 mg; No = Number of patients randomized to macitentan 10 mg

Ep = Number of events placebo; Np = Number of patients randomized to placebo

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 to 0.75; logrank p < 0.0001) (Table 4 and Figure 4).

Figure 4 Kaplan-Meier Estimates of the Occurrence of Death due to PAH or Hospitalization for PAH in SERAPHIN

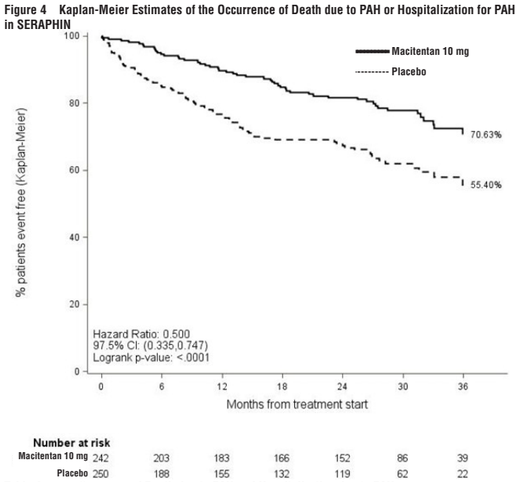


Table 4 Summary of Death due to PAH and Hospitalization due to PAH

	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)	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 to 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 term-effect of macitentan on mortality.

16 HOW SUPPLIED/STORAGE AND HANDLING

Macitentan tablets are 10 mg white to off-white, round biconvex film-coated tablet debossed with "**M1**" on one side and plain on other side.

15 count (5x3 unit-dose) PVC/PE/PVDC aluminium foil child resistant blisters in carton (NDC 47335-070-15)

30 count white high-density polyethylene bottle with child-resistant closure in carton, (NDC 47335-070-30)

Store at 20° C to 25° C (68° F to 77° F). Excursions are permitted between 15° C and 30° C (59° F and 86° F). [See USP Controlled Room Temperature].

This package is child-resistant. **Keep out of reach of children.**

17 PATIENT COUNSELING INFORMATION

Advise patient to read FDA-approved patient labeling (Medication Guide).

Embryo-Fetal Toxicity

Counsel female patients of reproductive potential about the need to use effective methods of contraception prior to initiation of treatment with macitentan tablets, during treatment and for one month after treatment discontinuation. Females of reproductive potential should have a negative pregnancy test prior to treatment with macitentan tablets *[see Contraindications (4.1), and Use in Specific Populations (8.1, 8.3)]*.

Patients should be instructed to contact their physician if they suspect they may be pregnant. Patients should seek additional contraceptive advice from a gynecologist or similar expert as needed.

Educate and counsel females of reproductive potential on the use of emergency contraception in the event of unprotected sex or contraceptive failure.

Advise pre-pubertal females to report any changes in their reproductive status immediately to her prescriber.

Review the Medication Guide with female patients.

Lactation

Advise women not to breastfeed during treatment with macitentan tablets *[see Use in Specific Populations (8.2)]*.

Hepatotoxicity

Some members of this pharmacological class are hepatotoxic. Educate patients on signs of hepatotoxicity. Advise patients that they should contact their doctor if they have unexplained nausea, vomiting, right upper quadrant pain, fatigue, anorexia, jaundice, dark urine, fever, or itching *[see Warnings and Precautions (5.2)]*.

Fluid Retention

Educate patients on signs of fluid retention. Advise patients that they should contact their doctor if they have unusual weight increase or swelling of the ankles or legs *[see Warnings and Precautions (5.3)]*.

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June 2025 FDA-09

Medication Guide
Macitentan [ma" si ten' tan]
Tablets
Rx only

Read this Medication Guide for macitentan tablets before you start taking macitentan tablets and each time you get a refill. There may be new information. This Medication Guide does not take the place of talking with your healthcare provider about your medical condition or your treatment.

What is the most important information I should know about macitentan tablets?

- **Serious birth defects.**

Macitentan tablets can cause serious birth defects if taken during pregnancy.

- **Females should not be pregnant when they start taking macitentan tablets or become pregnant during treatment with macitentan tablets.**
- Females who are able to get pregnant should have a negative pregnancy test before beginning treatment with macitentan tablets. Talk to your healthcare provider about your menstrual cycle. Your healthcare provider will decide when to do the pregnancy test and will order a pregnancy test for you depending on your menstrual cycle.
  - Females who are able to get pregnant are females who:
    - have entered puberty, even if they have not started their menstrual period, **and**
    - have a uterus, **and**
    - have not gone through menopause. Menopause means that you have not had a menstrual period for at least 12 months for natural reasons, or that you have had your ovaries removed.
  - Females who are not able to get pregnant are females who:
    - have not yet entered puberty, **or**
    - do not have a uterus, **or**
    - have gone through menopause. Menopause means that you have not had a menstrual period for at least 12 months for natural reasons, or that you have had your ovaries removed, **or**
    - are infertile for other medical reasons and this infertility is permanent and cannot be reversed.

Females who are able to get pregnant should use effective birth control before starting treatment with macitentan tablets, during treatment, and for one month after stopping macitentan tablets because the medicine may still be in the body.

- Talk with your healthcare provider or gynecologist (a doctor who specializes in female reproduction) to find out about options for acceptable birth control that you may use to prevent pregnancy during treatment with macitentan tablets.
- If you decide that you want to change the form of birth control that you use, talk with your healthcare provider or gynecologist to be sure that you choose another acceptable form of birth control.
- **Do not have unprotected sex. Talk to your healthcare provider or pharmacist right away if you have unprotected sex or if you think your birth control has failed. Your healthcare provider may talk with you about using emergency birth control.**
- **Tell your healthcare provider right away if you miss a menstrual period or think you may be pregnant.**

If you are the parent or caregiver of a female child who started taking macitentan tablets before reaching puberty, you should check your child regularly to see if she is developing signs of puberty. Tell your healthcare provider right away if you notice that she is developing breast buds or any pubic hair. Your healthcare provider should decide if your child has reached puberty. **Your child may reach puberty before having her first menstrual period.**

If you are a female who can get pregnant, you should talk to your healthcare provider to understand the benefits and risks of macitentan tablets.

What are macitentan tablets?

- Macitentan tablets are a prescription medicine used to treat pulmonary arterial hypertension (PAH), which is high blood pressure in the arteries of your lungs.
- Macitentan tablets can improve your ability to exercise, improve some of your symptoms, and help slow down the progression of your disease. Macitentan tablets can also lower your chance of being hospitalized for PAH.
- It is not known if macitentan tablets are safe and effective in children.

Who should not take macitentan tablets?

Do not take macitentan tablets if you are pregnant, plan to become pregnant, or become pregnant during treatment with macitentan tablets. Macitentan tablets can cause serious birth defects (see the Medication Guide section above called "What is the most important information I should know about macitentan tablets?").

Do not take macitentan tablets if you are allergic to macitentan or any of the ingredients in macitentan tablets. See the end of this Medication Guide for a complete list of ingredients in macitentan tablets.

Tell your healthcare provider about all your medical conditions and all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements. Macitentan tablets and other medicines may affect each other causing side effects. Do not start any new medicine until you check with your healthcare provider.

Especially tell your healthcare provider if you take an HIV medicine.

How should I take macitentan tablets?

Macitentan tablets will be mailed to you by a specialty pharmacy. Your healthcare provider will give you complete details.

- Take macitentan tablets exactly as your healthcare provider tells you to take it. Do not stop taking macitentan tablets unless your healthcare provider tells you.
- You can take macitentan tablets with or without food.
- If you take too much macitentan tablets, call your healthcare provider or go to the nearest hospital emergency room right away.
- If you miss a dose of macitentan tablets, take it as soon as you remember that day. Take the next dose at your regular time. Do not take 2 doses at the same time to make up for a missed dose.

What should I avoid while taking macitentan tablets?

- **Do not get pregnant while taking macitentan tablets.** See the serious birth defects section of the Medication Guide above called "What is the most important information I should know about macitentan tablets?" If you miss a menstrual period, or think you might be pregnant, call your healthcare provider right away.
- **It is not known if macitentan passes into your breastmilk. You should not breastfeed if you take macitentan tablets.** Talk to your healthcare provider about the best way to feed your baby if you take macitentan tablets.

What are the possible side effects of macitentan tablets?

Macitentan tablets can cause serious side effects, including:

- **Serious birth defects.** See "What is the most important information I should know about macitentan tablets?"
- Some medicines that are like macitentan tablets can cause liver problems. Your healthcare provider should do blood tests to check your liver before you start taking macitentan tablets. Tell your healthcare provider if you have any of the following symptoms of liver problems while taking macitentan tablets.
  - nausea or vomiting
  - yellowing of your skin or whites of your eyes
  - pain in the upper right stomach
  - dark urine
  - tiredness
  - fever
  - loss of appetite
  - itching
- **Fluid retention** can happen within weeks after starting macitentan tablets. Tell your healthcare provider right away if you have any unusual weight gain or swelling of your ankles or legs. Your healthcare provider will look for the cause of any fluid retention.
- **Low red blood cell levels (anemia) can occur with macitentan tablets treatment, usually during the first weeks after starting therapy. In some cases a blood transfusion may be needed, but this is not common.** Your healthcare provider will do blood tests to check your red blood cells before starting macitentan tablets. Your healthcare provider may also need to do these tests during treatment with macitentan tablets.
- **Decreased sperm count.** Macitentan tablets, and other medicines like macitentan tablets, may cause decreased sperm counts in men who take these medicines. A decreased sperm count may affect the ability to father a child. Tell your healthcare provider if being able to have children is important to you.

The most common side effects of macitentan tablets are:

- Stuffy nose or sore throat
- Irritation of the airways (bronchitis)
- Headache
- Flu
- Urinary tract infection

Tell your healthcare provider if you have any side effect that bothers you or that does not go away. These are not all the possible side effects of macitentan tablets. For more information, ask your healthcare provider or pharmacist.

Call your healthcare provider for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store macitentan tablets?

- Store macitentan tablets at room temperature between 68°F and 77°F (20°C and 25°C).
- **Keep macitentan tablets and all medicines out of the reach of children.**

General information about macitentan tablets

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use macitentan tablets for a condition for which it was not prescribed. Do not give macitentan tablets to other people, even if they have the same symptoms that you have. It may harm them.

This Medication Guide summarizes the most important information about macitentan tablets. If you would like more information, talk with your healthcare provider. You can ask your pharmacist or healthcare provider for information about macitentan tablets that is written for health professionals.

For more information, call 1-800-818-4555.

What are the ingredients in macitentan tablets?

Active ingredient: macitentan

Inactive ingredients: crospovidone, magnesium stearate, mannitol, microcrystalline cellulose, polysorbate 80 and povidone. The tablets are film-coated with a coating material containing polyvinyl alcohol, soya lecithin, talc, titanium dioxide, and xanthan gum.

Manufactured by:
Aizant Drug Research Solutions Pvt. Ltd.
Hyderabad, INDIA

Distributed by:
Sun Pharmaceutical Industries, Inc.
Cranbury, NJ 08512

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PC: 2099

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