To be sold by retail on the prescription of Cardiologist only

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Macitentan Tablets 10mg

Macitent® मसिटेंट

MACITENTAN TABLETS 10mg
Composition
Each film coated tablet contains:
Macitentan……..10mg
Colours: Titanium dioxide IP

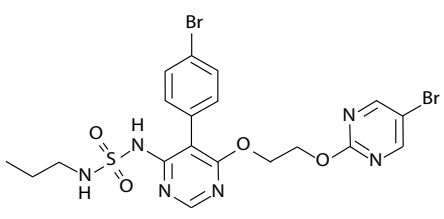
WARNING

WARNING: EMBRYO-FETAL TOXICITY

Do not administer Macitentan to a pregnant female because it may cause fetal harm.

Females of reproductive potential: Exclude pregnancy before the start of treatment, monthly during treatment, and 1 month after stopping treatment. Prevent pregnancy during treatment and for one month after stopping treatment by using acceptable methods of contraception.

DRUG DESCRIPTION
Macitentan is an endothelin receptor antagonist (ERA). 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 $C_{19}H_{20}Br_2N_6O_4S$ and a molecular weight of 588.27. Macitentan is achiral and has the following structural formula:



Macitentan is a crystalline powder that is insoluble in water. In the solid state macitentan is very stable, is not hygroscopic, and is not light sensitive.

DOSAGE FORM AND STRENGTHS
Macitentan is available as a 10 mg film-coated tablet for once daily oral administration.

INDICATIONS

Pulmonary Arterial Hypertension
Macitentan is an endothelin receptor antagonist (ERA) indicated for the treatment of pulmonary arterial hypertension (PAH, WHO Group I) to delay disease progression. Disease progression included: death, initiation of intravenous (IV) or subcutaneous prostanoids, or clinical worsening of PAH (decreased 6-minute walk distance, worsened PAH symptoms and need for additional PAH treatment). Macitentan also reduced hospitalization for PAH.

DOSAGE AND METHOD OF ADMINISTRATION
Treatment should only be initiated and monitored by a physician experienced in the treatment of PAH
Macitentan is to be taken orally at a dose of 10 mg once daily, with or without food. Doses higher than 10 mg once daily have not been studied in patients with PAH and are not recommended. The film-coated tablets are not breakable and are to be swallowed whole, with water.
Macitentan should be taken every day at about the same time. If the patient misses a dose of Macitentan, 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.

Pregnancy Testing in Females of Reproductive Potential
Initiate treatment with macitentan in females of reproductive potential only after a negative pregnancy test. Obtain monthly pregnancy test during treatment

Elderly
No dose adjustment is required in patients over the age of 65 years. There is limited clinical experience in patients over the age of 75 years. Therefore macitentan should be used with caution in this population.

Hepatic impairment
Based on pharmacokinetic (PK) data, no dose adjustment is required in patients with mild, moderate or severe hepatic impairment. However, there is no clinical experience with the use of macitentan in PAH patients with moderate or severe hepatic impairment. Macitentan must not be initiated in patients with severe hepatic impairment, or clinically significant elevated hepatic aminotransferases (greater than 3 times the Upper Limit of Normal (> 3 × ULN).

Renal impairment
Based on PK data, no dose adjustment is required in patients with renal impairment. There is no clinical experience with the use of macitentan in PAH patients with severe renal impairment. The use of macitentan is not recommended in patients undergoing dialysis.

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

USE IN SPECIAL POPULATIONS

Pregnancy
Pregnancy Category X

Risk Summary

Macitentan may cause fetal harm when administered to a pregnant woman and is contraindicated during pregnancy. Macitentan was teratogenic in rabbits and rats at all doses tested. A no-effect dose was not established in either species. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, advise the patient of the potential hazard to a fetus.

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.

Nursing Mothers
It is not known whether macitentan is present in human milk. Macitentan and its metabolites were present in the milk of lactating rats. Because many drugs are present in human milk and because of the potential for serious adverse reactions from macitentan in nursing infants, nursing mothers should discontinue nursing or discontinue macitentan.

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

Geriatric Use
No overall differences in safety or effectiveness were observed between elderly patients and younger patients.

Females and Males of Reproductive Potential
Females

Pregnancy Testing: Female patients of reproductive potential must have a negative pregnancy test prior to starting treatment with macitentan and monthly pregnancy tests during treatment with macitentan. Advice patients to contact their health care provider if they become pregnant or suspect they may be pregnant. Perform a pregnancy test if pregnancy is suspected for any reason. For positive pregnancy tests, counsel patients on the potential risk to 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 ch sen 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 counselling by another healthcare provider trained in contraceptive counselling.

Males

Testicular effects: Like other endothelin receptor antagonists, macitentan may have an adverse effect on spermatogenesis.

CONTRAINDICATIONS
- Hypersensitivity to the active substance or to any of the excipients
- Macitentan is contraindicated in females who are pregnant. If macitentan is used during pregnancy, apprise the patient of the potential hazard to a fetus
- Women of childbearing potential who are not using reliable contraception
- Breastfeeding
- Patients with severe hepatic impairment (with or without cirrhosis)
- Baseline values of hepatic aminotransferases (aspartate aminotransferases (AST) and/or alanine aminotransferases (ALT) > 3 × ULN)

WARNINGS AND PRECAUTIONS

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

Decreased Sperm Counts
Other ERAs have caused adverse effects on spermatogenesis. Counsel men about potential effects on fertility.

Hepatotoxicity
Endothelin receptor antagonists (ERAs) have caused elevations of aminotransferases, hepatotoxicity, and liver failure. Macitentan is not to be initiated in patients with severe hepatic impairment or elevated aminotransferases (> 3 × ULN), and is not recommended in patients with moderate hepatic impairment. Liver enzyme tests should be obtained prior to initiation of macitentan.

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 x 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.

Patients with underlying left ventricular dysfunction may be at particular risk for developing significant fluid retention after initiation of ERA treatment. 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.

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.

Pulmonary Edema with Pulmonary Veno-occlusive Disease (PVOD)
Cases of pulmonary oedema have been reported with vasodilators (mainly prostacyclins) when used in patients with pulmonary veno-occlusive disease. Consequently, if signs of pulmonary oedema occur when macitentan is administered in patients with PAH, the possibility of pulmonary veno-occlusive disease should be considered. If confirmed, discontinue macitentan.

Haemoglobin Decrease
As with other ERAs, treatment with macitentan has been associated with a decrease in haemoglobin concentration. Cases of anaemia requiring blood cell transfusion have been reported with macitentan and other ERAs. Initiation of macitentan is not recommended in patients with severe anaemia. It is recommended that haemoglobin concentrations be measured prior to initiation of treatment and tests repeated during treatment as clinically indicated.

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.

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).

Renal impairment
Patients with renal impairment may run a higher risk of experiencing hypotension and anaemia during treatment with macitentan. Therefore, monitoring of blood pressure and haemoglobin should be considered. There is no clinical experience with the use of macitentan in PAH patients with severe renal impairment. Caution is recommended in this population. There is no experience with the use of macitentan in patients undergoing dialysis, therefore macitentan is not recommended in this population.

Elderly
There is limited clinical experience with macitentan in patients over the age of 75 years, therefore macitentan should be used with caution in this population.

Excipients
Macitentan tablets contain lactose. Patients with rare hereditary problems of galactose intolerance, Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.
Macitentan tablets contain lecithin derived from soya. If a patient is hypersensitive to soya, macitentan must not be used.

DRUG INTERATIONS

In vitro studies

The cytochrome P450 enzymes CYP3A4, CYP2C8, CYP2C9, and CYP2C19 are involved in the metabolism of macitentan and formation of its metabolites. Macitentan and its active metabolite do not have clinically relevant inhibitory or inducing effects on cytochrome P450 enzymes.

Macitentan and its active metabolite are not inhibitors of hepatic or renal uptake transporters at clinically relevant concentrations, including the organic anion transporting polypeptides (OATP1B1 and OATP1B3). Macitentan and its active metabolite are not relevant substrates of OATP1B1 and OATP1B3, but enter the liver by passive diffusion.

Macitentan and its active metabolite are not inhibitors of hepatic or renal efflux pumps at clinically relevant concentrations, including the multi-drug resistance protein (P-gp, MDR-1) and multidrug and toxin extrusion transporters (MATE1 and MATE2-K). Macitentan inhibits the breast cancer resistance protein (BCRP) at clinically relevant intestinal concentrations. Macitentan is not a substrate for P-gp/MDR-1.

At clinically relevant concentrations, macitentan and its active metabolite do not interact with proteins involved in hepatic bile salt transport, i.e., the bile salt export pump (BSEP) and the sodium-dependent taurocholate co-transporting polypeptide (NTCP).

In vivo studies

Interaction studies have only been performed in adults.

Warfarin: Macitentan given as multiple doses of 10 mg once daily had no effect on exposure to S-warfarin (CYP2C9 substrate) or R-warfarin (CYP3A4 substrate) after a single dose of 25 mg warfarin. The pharmacodynamic effect of warfarin on International Normalized Ratio (INR) was not affected by macitentan. The pharmacokinetics of macitentan and its active metabolite were not affected by warfarin.

Sildenafil: At steady-state, the exposure to sildenafil 20 mg t.i.d. was increased by 15% during concomitant administration of macitentan 10 mg once daily. Sildenafil, a CYP3A4 substrate, did not affect the pharmacokinetics of macitentan, while there was a 15% reduction in the exposure to the active metabolite of macitentan. These changes are not considered clinically relevant.

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.

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
Cyclosporine A: Concomitant treatment with cyclosporine A 100 mg b.i.d., a combined CYP3A4 and OATP inhibitor, did not alter the steady-state exposure to macitentan and its active metabolite to a clinically relevant extent.
Hormonal contraceptives: Macitentan 10 mg once daily did not affect the pharmacokinetics of an oral contraceptive (norethisterone 1 mg and ethinyl estradiol 35 µg).

UNDESIRABLE EFFECTS
Clinically significant adverse reactions that appear in other sections of the labeling include:
- Embryo-fetal Toxicity
- Hepatotoxicity
- Fluid Retention
- Decrease in Hemoglobin

Clinical Trial Experience

Tabulated list of adverse reactions
Adverse reactions associated with macitentan obtained from clinical study are tabulated below.
Frequencies are defined as: very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1,000 to < 1/100); rare (≥ 1/10,000 to < 1/1,000); very rare (< 1/10,000).

System organ class	Frequency	Adverse reaction
Infections and infestations	Very Common	Nasopharyngitis
	Very Common	Bronchitis
	Common	Pharyngitis
	Common	Influenza
	Common	Urinary tract infection
Blood and lymphatic system disorders	Very Common	Anaemia
Immune system disorders	Uncommon	Hypersensitivity reactions (e.g., angioedema, pruritus, rash)
Nervous system disorders	Very Common	Headache
Vascular disorders	Common	Hypotension
Respiratory, thoracic and mediastinal disorders	Common	Nasal congestion
General disorders and administration site conditions	Very common	Oedema, fluid retention

Post-marketing Experience
The following adverse reactions have been identified during postapproval 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)

Respiratory, thoracic and mediastinal disorders: nasal congestion

Hepatobiliary 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

OVERDOSE

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.

PHARMACODYNAMIC AND PHARMACODYNAMIC PROPERTIES

Mechanism of Action
Endothelin (ET)-1 and its receptors (ETA and ETB) mediate a variety of deleterious effects, such as vasoconstriction, fibrosis, proliferation, hypertrophy, and inflammation. In disease conditions such as PAH, the local ET system is upregulated and is involved in vascular hypertrophy and in organ damage.

Macitentan is an endothelin receptor antagonist that prevents 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*.

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 22-49) in pulmonary vascular resistance and an increase of 0.6 L/min/m2 (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.

Pharmacokinetics
The pharmacokinetics of macitentan and its active metabolite have been studied primarily in healthy subjects. The pharmacokinetics of macitentan is 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 a minor contribution of 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 faeces.

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.

INCOMPATABILITES
Not applicable

PACKAGING INFORMATION
Macitentan tablets are 10mg white colored, round shaped, biconvex, film coated tablets, debossed with "M" on one side and "10" on other side and are Supplied as 10's Blister pack (Material description: Base foil- White opaque, 250 mic PVC/25 mic PE/90GSM PVDC: Lid foil - 0.025 mm plain foil 7 GSM aluminium lid foil).

STORAGE
Store below 30°C

Keep away from infants and small children

Manufactured by:
MSN Laboratories Private Limited,
Formulation Division,
Unit-II, Sy.No. 1277, 1319 to 1324,
Nandigama (Village & Mandal),
Rangareddy (District),
Telangana - 509 228, India.

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