PRODUCT MONOGRAPH

[Pr]**OPSUMIT®** macitentan

10 mg film-coated tablet

Professed Standard

Endothelin Receptor Antagonist

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Date of Revision:
November 18, 2015

Submission Control No: 186896

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[Pr]OPSUMIT™
macitentan

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Nonmedicinal Ingredients
Oral	10 mg film-coated tablet	lactose monohydrate, magnesium stearate, microcrystalline cellulose, polysorbate 80, povidone, and sodium starch glycolate Type A, polyvinyl alcohol, soya lecithin, talc, titanium dioxide, and xanthan gum

INDICATIONS AND CLINICAL USE

OPSUMIT® (macitentan) is indicated for the long-term treatment of pulmonary arterial hypertension (PAH, WHO Group l) to reduce morbidity in patients of WHO Functional Class II or III whose PAH is either idiopathic or heritable, or associated with connective tissue disease or congenital heart disease.

OPSUMIT is effective when used as monotherapy or in combination with phosphodiesterase-5 inhíbitors.

Geriatrics (≥ 65 years of age): Of the total number of subjects in the clinical study of OPSUMIT for PAH, 14% were ≥65 years of age.

Pediatrics (<18 years of age): The safety and efficacy of OPSUMIT in children and adolescents <18 years of age has not yet been established.

CONTRAINDICATIONS

OPSUMIT (macitentan) is contraindicated in:

- Patients who are hypersensitive to this drug or to any ingredient in the formulation or component of the container. For a complete listing, see the Dosage Forms, Composition and Packaging section of the Product Monograph.
- Women who are or may become pregnant. (*see Warnings and Precautions, Special Populations, Pregnant Women*).
- Nursing women (*see Warnings and Precautions, Special Populations, Nursing Women).*

WARNINGS AND PRECAUTIONS

Hepatic/Biliary/Pancreatic

Elevations of liver aminotransferases (AST, ALT) have been associated with PAH and with other endothelin receptor antagonists (ERAs). In a long-term double blind, placebo controlled Phase III outcome study of OPSUMIT, the incidence of an increase in ALT of >3 times the upper limit of normal (ULN) was 3.4% in the 10 mg group compared to 1.6% in the placebo group. However, OPSUMIT 10 mg was not associated with increased incidences of treatment emergent elevations of AST and/or ALT >3 x ULN versus placebo (3.4% in the 10 mg group compared to 4.5% in the placebo group). OPSUMIT is not to be initiated in patients with elevated aminotransferases (>3 x ULN) at baseline and is not recommended in patients with moderate to severe hepatic impairment (*see Dosage and Administration, Patients with Hepatic Impairment)*.

Liver enzyme tests should be obtained prior to initiation of OPSUMIT. Subsequently, monthly testing during the first year of treatment is recommended. They may then be repeated less frequently during treatment as clinically indicated (*see Monitoring and Laboratory Tests*).

If unexplained clinically relevant aminotransferase elevations occur, or if elevations are accompanied by an increase in bilirubin >2 x ULN, or by clinical symptoms of liver injury (e.g. jaundice), OPSUMIT treatment should be discontinued. Re-initiation of OPSUMIT may be considered following the return of hepatic enzyme levels to within the normal range in patients who have not experienced clinical symptoms of liver injury (*see Adverse Reactions).*

Hematologic

As with other ERAs, treatment with OPSUMIT has been associated with a decrease in hemoglobin concentration. OPSUMIT related decreases in hemoglobin concentration occurred early, were not progressive, stabilised before 12 weeks of treatment and remained stable during chronic treatment. Cases of anemia requiring transfusion have been reported with OPSUMIT and other ERAs. Initiation of OPSUMIT is not recommended in patients with severe anemia.

It is recommended that hemoglobin concentrations are measured prior to initiation of treatment, again after one month, and periodically thereafter as clinically indicated (see Monitoring and Laboratory Tests and Adverse Reactions).

Renal

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

Pulmonary Veno-Occlusive Disease

Cases of pulmonary edema have been reported with vasodilators (mainly prostacyclins) when used in patients with pulmonary veno-occlusive disease. Consequently, if signs of pulmonary edema occur when OPSUMIT is administered in patients with PAH, the possibility of pulmonary veno-occlusive disease should be considered.

Special Populations

Pregnant Women: PAH is a contraindication to pregnancy, due to a high mortality risk to both mother and fetus. There are limited data from the use of OPSUMIT in pregnant women. The potential risk for humans is still unknown. In animal studies, macitentan was teratogenic in rabbits and rats causing cardiovascular and mandibular arch fusion abnormalities at all dose levels tested. Women receiving OPSUMIT must be advised of the risk of harm to the fetus. OPSUMIT is contraindicated during pregnancy (*see Contraindications*).

OPSUMIT treatment should only be initiated in women of child-bearing potential when the absence of pregnancy has been verified, appropriate advice on contraception provided, and reliable contraception is practiced. Women should not become pregnant for 1 month after discontinuation of OPSUMIT. Monthly pregnancy tests during treatment with OPSUMIT are recommended to allow the early detection of pregnancy.

Nursing Women: It is not known whether macitentan is excreted into human breast milk. In rats, macitentan and its metabolites were excreted into milk during lactation. Breast-feeding is contraindicated during treatment with OPSUMIT.

Male Fertility: In a randomized, placebo-controlled study in healthy subjects , administration of macitentan 10 mg for >12 weeks was not associated with a clinically relevant reduction in mean sperm count. Changes in sperm morphology and motility observed were within the range of the variability of the measurements.

In repeated-dose toxicity studies, pathologic changes in testes (tubular dilatation, tubular degeneration and/or tubular atrophy; and/or hypospermatogenesis) occurred in rats or dogs at >18-fold human exposure (*see Toxicology, Reproductive toxicity).*

Pediatrics (<18 years of age): The safety and efficacy of OPSUMIT in children and adolescents <18 years of age have not yet been established.

Geriatrics (≥ 65 years of age): Of the total number of subjects in the clinical study of OPSUMIT for pulmonary arterial hypertension, 14% were ≥65 years of age. There is limited clinical experience in patients >75 years of age, and therefore macitentan should be used with caution in this population (*see Dosage and Administration, Geriatrics*).

Monitoring and Laboratory Tests

Hematologic: It is recommended that hemoglobin concentrations are measured prior to initiation

of treatment, again after one month, and periodically thereafter as clinically indicated (*see Warnings and Precautions, Hematologic and Adverse Reactions*).

Hepatic/Biliary/Pancreatic: Liver enzyme tests should be obtained prior to initiation of OPSUMIT and subsequently at monthly intervals during the first year of treatment. They may then be repeated less frequently during treatment as clinically indicated (*see Warnings and Precautions, Hepatic/Biliary/Pancreatic*).

ADVERSE REACTIONS

Adverse Drug Reaction Overview

The most common adverse reactions (>3% compared to placebo) are nasopharyngitis, headache, anemia, bronchitis, urinary tract infection, pharyngitis and influenza.

Clinical Trial Adverse Drug Reactions

> *Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates*.

Safety data for OPSUMIT were obtained from 1 long-term placebo-controlled clinical study in 742 patients with PAH. Doses of 3 mg and 10 mg OPSUMIT were administered once daily. Safety data for the recommended dose of OPSUMIT 10 mg are presented. The exposure to OPSUMIT in this trial was up to 3.6 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 due to adverse events (AEs) was 11% (26/242 patients) for OPSUMIT 10 mg and 12% (31/249 patients) for placebo. The overall incidence of patients with a serious AE was 45% (109/242 patients) for OPSUMIT 10 mg and 55% (137/249 patients) for placebo.

The majority of AEs were mild to moderate in intensity. Table 1 presents treatment-emergent AEs reported by >3% of patients in the OPSUMIT 10 mg group and more frequently than on placebo by >3%.

Table 1: Treatment-emergent Adverse Reactions Reported by >3% of Patients on OPSUMIT and more frequent than on Placebo by >3%

System Organ Class / Adverse Events (AEs)	OPSUMIT 10 mg (N=242) (%)	Placebo (N=249) (%)
Blood and Lymphatic System Disorders		
Anemia	13	3
Infections and Infestations		
Nasopharyngitis	14	10
Bronchitis	12	6
Urinary tract infection	9	6

System Organ Class / Adverse Events (AEs)	OPSUMIT 10 mg (N=242) (%)	Placebo (N=249) (%)
Pharyngitis	6	3
Influenza	6	2
Nervous System Disorders		
Headache	14	9

Hypotension has been associated with the use of ERAs. In a long-term double-blind study in patients with PAH, hypotension as an AE was reported for 7.0% and 4.4% of patients on macitentan 10 mg and placebo, respectively. This corresponded to 3.5 events/100 patient-years on macitentan 10 mg compared to 2.7 events/ 100 patient-years on placebo.

Edema/ fluid retention has been associated with the use of ERAs and is also a clinical manifestation of right heart failure and underlying PAH disease. In a long-term double-blind study in patients with PAH, the incidence of edema AEs in macitentan 10 mg and placebo treatment groups was 21.9%, and 20.5%, respectively. This corresponded to 11.0 events/100 patient-years on macitentan 10 mg compared to 12.5 events/100 patient-years on placebo.

Less Common Clinical Trial Adverse Events (<3% and >1 patient in the 10 mg macitentan treatment group and more frequent than placebo)

Blood and Lymphatic System Disorders: anemia, eosinophilia, hemorrhagic, leukopenia, lymphadenitis, polycythemia
Cardiac Disorders: atrial flutter, atrial tachycardia, atrioventricular block first degree, bundle branch block right, pericardial effusion, supraventricular tachycardia
Ear and Labyrinth Disorders: vertigo
Eye Disorders: cataract, conjunctivitis, lacrimation increased, vision blurred
Gastrointestinal Disorders: abdominal pain, colitis, constipation, diverticulum intestinal, food poisoning, gastritis erosive, hemorrhoids, irritable bowel syndrome, periodontitis, toothache
General Disorders and Administration Site Conditions: influenza like-illness, non-cardiac chest pain, sudden death
Hepatobiliary Disorders: cholelithiasis, hyperbilirubinemia
Immune System Disorders: drug hypersensitivity
Infections and Infestations: ear infection, furuncle, gastroenteritis viral, infection parasitic, lower respiratory infection, oral herpes, overgrowth bacterial, strongyloidiasis, tonsillitis, tooth abscess, tracheitis
Injury, Poisoning and Procedural Complications: arthropod sting, contusion, laceration
Investigations: alanine aminotransferase increased, blood creatinine increased, blood urea increased, hematocrit decreased, hemoglobin decreased, platelet count decreased, red blood cell count decreased, weight decreased, white blood cell count decreased
Metabolism and Nutrition Disorders: hyperkalemia, hyponatremia
Musculoskeletal and Connective Tissue Disorders: arthritis, costochondritis, myofascial pain syndrome, muscle spasms, osteoarthritis, osteochondrosis, plantar fasciitis, systemic sclerosis
Neoplasms Benign, Malignant and Unspecified (including cysts and polyps): uterine leiomyoma
Nervous System Disorders: dizziness exertional, migraine, neuralgia, sciatica

Psychiatric Disorders: anxiety, decreased activity
Reproductive System and Breast Disorders: amenorrhea, gynecomastia, menorrhagia, metrorrhagia, ovarian cyst, uterine cervical erosion
Respiratory, Thoracic and Mediastinal Disorders: bronchial hyperreactivity, chronic obstructive pulmonary disease, dysphonia, dyspnoea exertional, hydrothorax, hypoxia, nasal congestion, oropharyngeal pain, productive cough, respiratory failure, rhinitis allergic, rhinorrhea
Skin and Subcutaneous Tissue Disorders: dermatitis allergic, eczema, erythema, photosensitivity reaction, pruritis, swelling face urticaria
Vascular Disorders: flushing, hematoma, hot flush, orthostatic hypotension, thrombophlebitis, varicose vein

Abnormal Hematologic and Clinical Chemistry Findings

Liver aminotransferases: The incidence of aminotransferase elevations (ALT/AST) >3 x ULN was 3.4% on OPSUMIT 10 mg and 4.5% on placebo in a double-blind study in patients with PAH. Elevations >5 x ULN occurred in 2.5% of patients on OPSUMIT 10 mg versus 2% of patients on placebo (*see Warnings and Precautions, Hepatic/Biliary/Pancreatic*).

Hemoglobin: In a double-blind study in patients with PAH, OPSUMIT 10 mg was associated with a mean decrease in hemoglobin versus placebo of 1.0 g/dL. A decrease in hemoglobin concentration to below 10 g/dL was reported in 8.7% of patients treated with OPSUMIT 10 mg and 3.4% of placebo-treated patients (*see Warnings and Precautions, Hematologic*).

Post-Market Adverse Drug Reactions
In addition to adverse events identified from clinical studies, the following adverse events were identified during post-approval use of OPSUMIT. Because these events have been reported voluntarily from a population of unknown size, estimates of frequency cannot be made.

Immune system disorders:
hypersensitivity reactions (angioedema, pruritus and rash)

Respiratory, thoracic and mediastinal disorders:
nasal congestion

General disorders and administration site conditions:
edema/fluid retention

DRUG INTERACTIONS

Overview

Macitentan clearance is mediated by several human P450 enzymes including CYP3A4 and CYP2C9 with minor contributions of CYP2C8 and CYP2C19.

At clinically relevant concentrations, macitentan and its active metabolite do not have relevant inhibitory or inducing effects on CYP enzymes.

Macitentan is neither a substrate nor an inhibitor of the multi-drug resistance protein (P-gp, MDR-1). At clinically relevant concentrations, the active metabolite of macitentan is not an inhibitor of P-gp. At clinically relevant concentrations, macitentan and its active metabolite are neither substrates nor inhibitors of the organic anion transporting polypeptides OATP1B1 and OATP1B3.

At clinically relevant concentrations, macitentan and its active metabolite are not inhibitors of the uptake transporters OCT1, OCT2, OAT1, OAT, and the drug efflux pumps BCRP, MATE-1, and MATE2-K.

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).

Drug-Drug Interactions

Table 2: Established or Potential Drug-Drug Interactions

Drug interaction	Level of Evidence	Effect	Clinical comment
Sildenafil	CT	At steady-state in healthy volunteers, the exposure to sildenafil 20 mg t.i.d. was increased by 15% during concomitant administration of macitentan 10 mg once daily. Sildenafil, a CYP3A4 substrate, did not affect the pharmacokinetics of macitentan, while there was a 15% reduction in the exposure to the active metabolite of macitentan. These changes are not considered clinically relevant. In a placebo-controlled trial in patients with PAH, the efficacy and safety of macitentan 10 mg in combination with sildenafil were demonstrated.	No dose adjustment is warranted.
Hormonal contraceptives	T	Macitentan 10 mg once daily did not affect the pharmacokinetics of an oral contraceptive (norethisterone 1 mg and ethinyl estradiol 35 µg).	No dose adjustment is warranted.

Drug interaction	Level of Evidence	Effect	Clinical comment
Warfarin	CT	In healthy volunteers receiving 25 mg warfarin, daily doses of macitentan did not have a clinically relevant effect on the pharmacokinetics of S-warfarin (CYP2C9 substrate) or R-warfarin (CYP3A4 substrate). The pharmacodynamic effect of warfarin on International Normalized Ratio (INR) was not affected by macitentan.	No dose adjustment is warranted.
Strong CYP3A4 inhibitors (ketoconazole)	CT	In the presence of ketoconazole 400 mg daily, a strong CYP3A4 inhibitor, exposure to macitentan increased approximately 2-fold in healthy volunteers. Exposure to the active metabolite of macitentan was reduced by 26%. The clinical significance of these changes is not known.	Caution should be exercised when macitentan is administered concomitantly with strong CYP3A4 inhibitors.
Cyclosporin A	CT	In healthy volunteers, 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.	No dose adjustment is warranted.
Rifampicin	CT	In healthy volunteers, concomitant treatment with rifampicin 600 mg daily, a potent inducer of CYP3A4, reduced the steady-state exposure (AUC) 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.

Drug-Food Interactions

The exposure to macitentan and its active metabolite is unchanged in the presence of food and, therefore, macitentan can be given with or without food.

Drug-Herb Interactions

Interactions with herbal products have not been established.

Drug-Laboratory Interactions

Interactions with laboratory tests have not been established.

DOSAGE AND ADMINISTRATION

Recommended Dose and Dosage Adjustment

The recommended dose of OPSUMIT is 10 mg once daily.

Patients with Hepatic Impairment

There is no clinical experience with the use of OPSUMIT in PAH patients with moderate or severe hepatic impairment. Therefore, use of OPSUMIT in this patient population is not recommended (*see Warnings and Precautions, Hepatic/Biliary/Pancreatic).* No dose adjustment is required in patients with mild hepatic impairment.

Patients with Renal Impairment

Patients with moderate or severe renal impairment may run a higher risk of experiencing hypotension and anemia during treatment with macitentan. Therefore monitoring of blood pressure and hemoglobin should be considered. There is no experience with the use of OPSUMIT in patients undergoing dialysis, and therefore OPSUMIT is not recommended in this population (*see Warnings and Precautions, Renal*).

Geriatrics

No dose adjustment is required in patients ≥65 years of age.

There is limited clinical experience in patients >75 years of age, and therefore macitentan should be used with caution in this population (*see Warnings and Precautions, Special Populations, Geriatrics (≥65 years of age)*).

Pediatrics (<18 years of age)

The safety and efficacy of OPSUMIT in children and adolescents <18 years of age have not yet been established.

Missed Dose

If a dose of OPSUMIT is missed, the tablet should be taken as soon as it is remembered.

Administration

OPSUMIT is to be taken orally at a dose of 10 mg once daily, with or without food.

OVERDOSAGE

There is currently no experience with overdosage of OPSUMIT. In a clinical study in healthy subjects where macitentan was administered as a single dose of up to and including 600 mg, AEs of headache, nausea and vomiting were observed. In the event of an overdose, standard supportive measures should be taken, as required. Due to the high degree of protein binding of macitentan, dialysis is unlikely to be effective.

For management of a suspected drug overdose, contact your regional Poison Control Centre.

ACTION AND CLINICAL PHARMACOLOGY

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 orally active, dual ET_A and ET_B receptor antagonist that prevents the binding of ET-1 to its receptors. Macitentan displays high affinity to and sustained occupancy of the ET receptors in human pulmonary arterial smooth muscle cells and has physicochemical properties favoring penetration into lung tissue. In animal studies, penetration of macitentan in lung tissues was higher in rats with induced pulmonary hypertension compared to normal rats.

In models of pulmonary hypertension, macitentan selectively decreased mean pulmonary arterial pressure without affecting systemic blood pressure, decreased pulmonary arterial hypertrophy and right ventricular remodeling, and significantly increased survival compared to vehicle-treated rats.

Pharmacodynamics

In healthy subjects, macitentan dose-dependently increased plasma ET-1 concentrations at single and multiple doses.

Cardiac Electrophysiology: In a randomized, placebo-controlled four-way crossover study with a positive control in healthy subjects, repeated doses of 10 mg and 30 mg macitentan had no significant effect on the QTc interval.

Pharmacokinetics

The pharmacokinetics of macitentan and its active metabolite have mainly been documented in healthy subjects. 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. Trough plasma concentrations of macitentan in PAH patients were not influenced by the severity of the disease.

After repeated administration of doses of ≤30 mg, the pharmacokinetics of macitentan are dose proportional.

Absorption: Maximum plasma concentrations of macitentan are achieved about 8 hours after administration. Thereafter, plasma concentrations of macitentan and its active metabolite decreased slowly, with an apparent elimination half-life of approximately 16 hours and 48 hours, respectively.

In healthy subjects, the exposure to macitentan and its active metabolite is unchanged in the presence of food and, therefore, macitentan may be taken with or without food.

Distribution: Macitentan and its active metabolite ACT-132577 are well distributed into tissues as indicated by an apparent volume of distribution (Vss/F) of approximately 50 L and 40 L, respectively. Macitentan and its active metabolite are highly bound to plasma proteins (>99%) primarily to albumin and to a lesser extent to alpha1-acid glycoprotein.

Metabolism: Macitentan primarily undergoes oxidative depropylation of the sulfamide to form a pharmacologically active metabolite. This reaction is dependent on the cytochrome P450 system, mainly CYP3A4 with a minor contribution of CYP2C19. Very small amounts of the active metabolite are also formed by CYP2C8 and CYP2C9. The active metabolite circulates in human plasma and may contribute to the overall pharmacological effect.
Excretion: Macitentan is excreted only after extensive metabolism. The major excretion route is via urine, accounting for about 50% of the dose.

Special Populations and Conditions

Age/Race/Gender: There is no clinically relevant effect of age, gender or race on the pharmacokinetics of macitentan and its active metabolite.

Hepatic Insufficiency: Exposure to macitentan was decreased by 21%, 34%, and 6% and for the active metabolite by 20%, 25%, and 25% in subjects with mild, moderate, or severe hepatic impairment, respectively. This decrease is not considered clinically relevant.

Renal Insufficiency: Exposure to macitentan and its active metabolite was increased by 1.3- and 1.6-fold, respectively, in patients with severe renal impairment. This increase is not considered clinically relevant.

STORAGE AND STABILITY

Store at 15ºC – 30ºC.

DOSAGE FORMS, COMPOSITION AND PACKAGING

OPSUMIT is available as 10 mg film-coated tablets for oral administration. Each bi-convex film-coated tablet is round, white, and debossed with "10" on one side. The tablets include the following inactive ingredients: lactose monohydrate, magnesium stearate, microcrystalline

cellulose, polysorbate 80, povidone, and sodium starch glycolate Type A. The tablets are film-coated with a coating material containing polyvinyl alcohol, soya lecithin, talc, titanium dioxide, and xanthan gum.

OPSUMIT tablets are supplied as follows:

- 15 or 30 count film-coated tablets PVC/ PE/PVDC aluminum foil blisters in carton

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

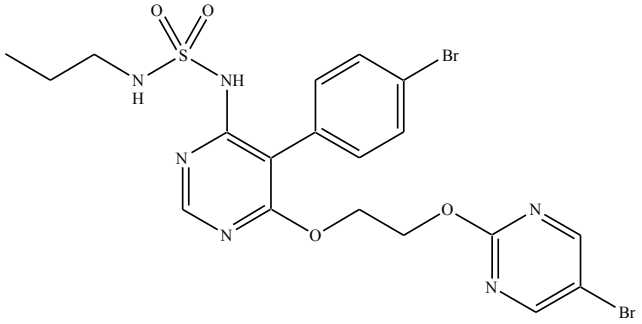
Drug Substance

Proper name: macitentan

Chemical name: N-[5-(4-Bromophenyl)-6-[2-[(5-bromo-2-pyrimidinyl)oxy]ethoxy]-4-pyrimidinyl]-N'-propylsulfamide

Molecular formula and molecular mass: $C_{19}H_{20}Br_2N_6O_4S$, 588.27

Structural formula:



Physicochemical properties: 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.

CLINICAL TRIALS

Pulmonary Arterial Hypertension: A multicenter, double blind, placebo controlled, parallel group, event driven, Phase 3 outcome study (AC-055-302/SERAPHIN) was conducted in 742 patients with symptomatic pulmonary arterial hypertension (PAH) who were randomized to three treatment groups [placebo (N=250), 3 mg macitentan (N=250) or 10 mg OPSUMIT (N=242) once daily. At baseline, the majority of enrolled patients (64%) were treated with a stable dose of specific therapy for PAH, either oral phosphodiesterase inhibitors (61%) and/or inhaled/oral prostanoids (6%). The primary study endpoint was the time to first occurrence of a morbidity or mortality event up to end of double-blind treatment (EOT), defined as death, or atrial septostomy, or lung transplantation, or initiation of intravenous (i.v.) or subcutaneous (s.c.) prostanoids, or other worsening of PAH. Other worsening of PAH was defined as the concurrent presence of all of the three following components: a sustained decrease in 6-minute walk distance (6MWD) of at least 15% from baseline; worsening of PAH symptoms (worsening of WHO FC or right heart failure); and need for new treatment for PAH. All events were confirmed by an independent adjudication committee, blinded to treatment allocation.

The median treatment duration was 101, 116 weeks and 118 weeks in the placebo, macitentan 3 mg and 10 mg groups, respectively, up to a maximum of 188 weeks on macitentan.

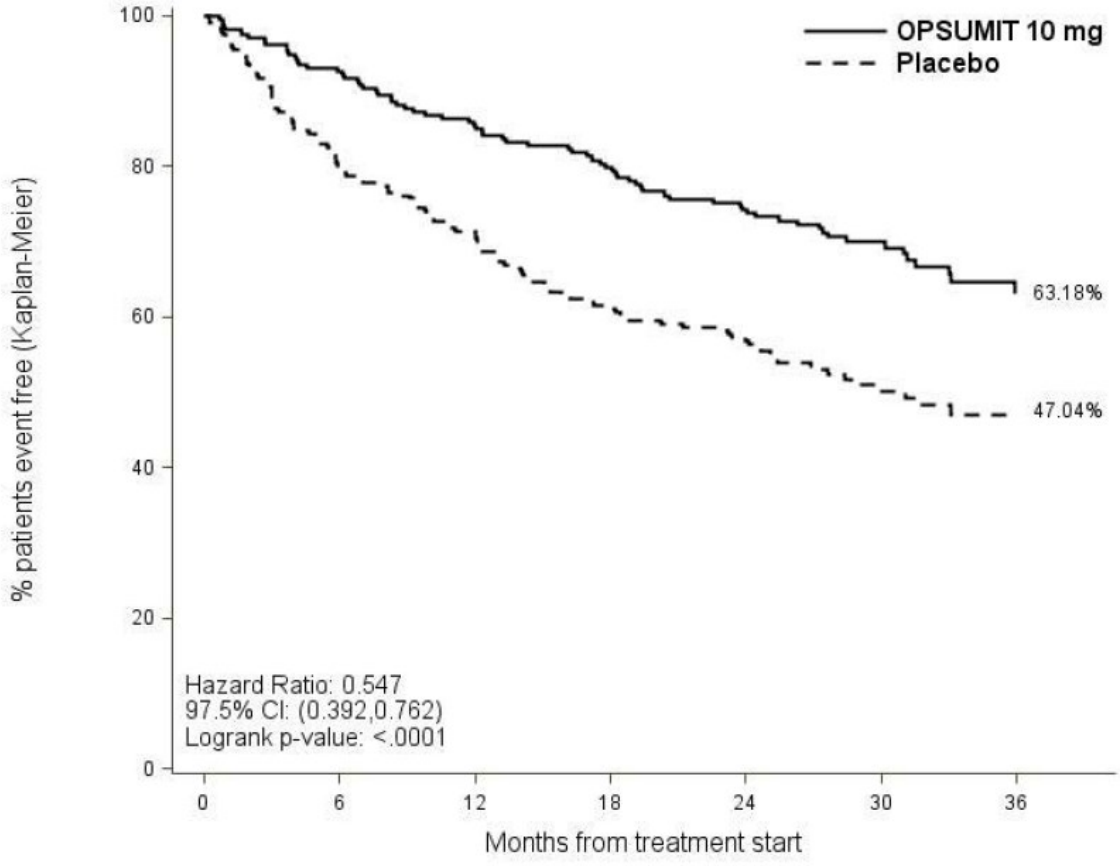
Efficacy was evaluated up to the end of double-blind treatment (EOT). The EOT either coincided with end of study (EOS) for patients who completed the study as scheduled or occurred earlier in case of premature discontinuation of study drug. For those patients who stopped treatment prior to EOS, PAH therapy, including OPSUMIT 10 mg, may have been initiated. All patients were followed up to EOS for vital status. The ascertainment rate for vital status at the EOS was greater than 95%.

The mean age of all patients was 46 years (range 12-85 years) with the majority of subjects being Caucasian (55%) and female (77%). Approximately 52%, 46%, and 2% of patients were in WHO FC II, III, and IV, respectively.

Idiopathic or heritable PAH was the most common etiology in the study population (57%) followed by PAH due to connective tissue disorders (31%), PAH associated with congenital heart disease with shunts (8%) and PAH associated with other etiologies [drugs and toxins (3%) and HIV (1%)].

Outcome Endpoints: Treatment with OPSUMIT 10 mg resulted in a 45% relative risk reduction (HR 0.55, 97.5% CI 0.39 0.76; logrank $p<0.0001$) in the occurrence of a primary endpoint event up to EOT compared to placebo. The proportion of patients without an event at 3 years was 63.2% in OPSUMIT 10 mg compared to 47.0% in placebo, corresponding to an absolute risk reduction of 16.2% at 3 years (Figure 1). The beneficial effect of OPSUMIT 10 mg was primarily attributable to a reduction in other PAH worsening events (the concurrent presence of sustained deterioration in 6MWD and worsening of PAH symptoms and need for new PAH treatment). The treatment effect was established early and sustained for a median treatment duration of 2 years.

Figure 1: Kaplan-Meier Estimates of Primary Endpoint Events up to EOT in SERAPHIN*



Number at risk							
OPSUMIT 10 mg	242	208	187	171	155	91	41
Placebo	250	188	160	135	122	64	23

***Note: The treatment response on the primary endpoint was almost entirely attributable to an effect on morbidity.**

During treatment, 46.4% and 31.4% of the patients in the placebo and OPSUMIT 10 mg dose group, respectively, experienced a primary endpoint event, with worsening of PAH reported as the most common first event in the placebo (37.2%) and OPSUMIT 10 mg (24.4%) treatment groups. Other events reported that contributed to the primary endpoint included death (6.8% placebo, 6.6% OPSUMIT 10 mg,) and i.v./s.c. prostanoid initiation (2.4% placebo, 0.4% OPSUMIT 10 mg).

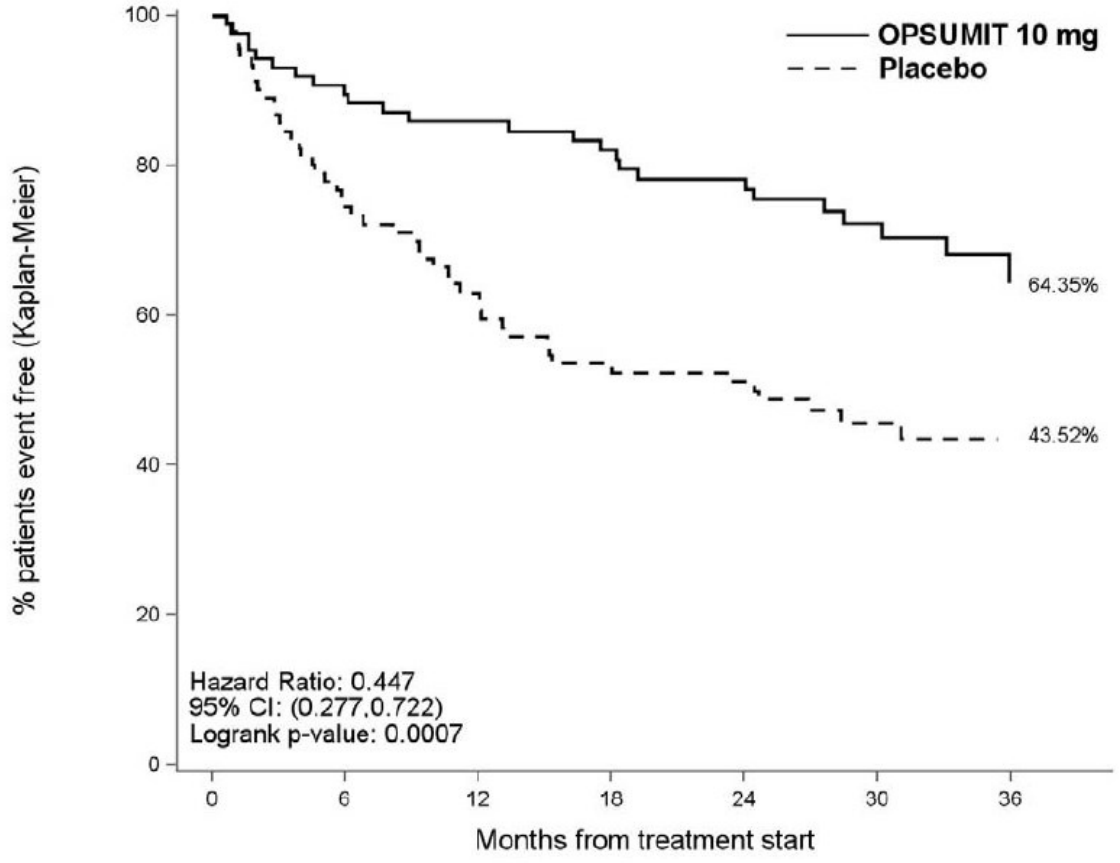
Consistent efficacy of OPSUMIT 10 mg on the primary endpoint was seen across subgroups of age, sex, race, geographical region, etiology, by monotherapy or in combination with another PAH therapy, 6MWD, and WHO FC.

Treatment with OPSUMIT 10 mg in monotherapy resulted in a 55% relative risk reduction (HR 0.45, 95% CI 0.28-0.72; logrank p=0.0007) in the occurrence of a primary endpoint event

compared to placebo. The proportion of patients without an event at 3 years was 64.4% in OPSUMIT 10 mg compared to 43.5% in placebo, corresponding to an absolute risk reduction of 20.9% (Figure 2).

Treatment with OPSUMIT 10 mg in combination with another PAH therapy resulted in a 38% relative risk reduction (HR 0.62, 95% CI 0.43 0.89; logrank p=0.0094) in the occurrence of a primary endpoint event. The proportion of patients without an event at 3 years was 62.6% in OPSUMIT 10 mg compared to 48.6% in placebo, corresponding to an absolute risk reduction of 14.0% (Figure 3).

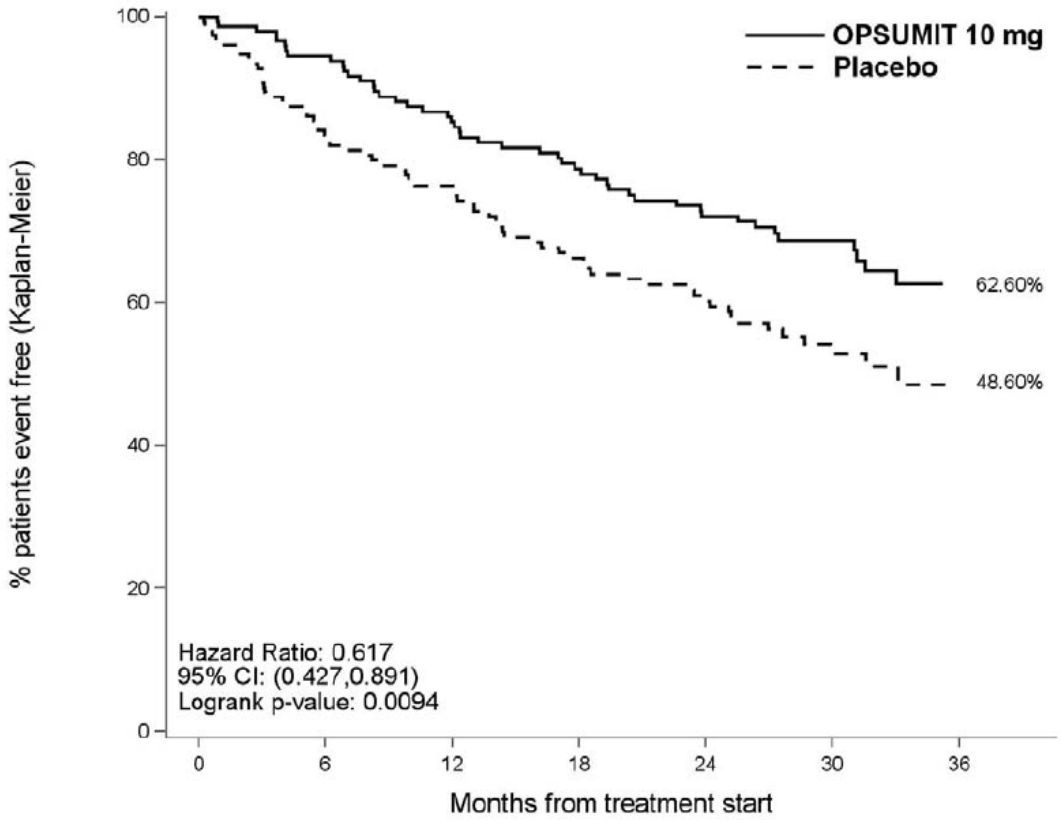
Figure 2: Kaplan-Meier Estimates of Primary Endpoint Events up to EOT; Monotherapy at Baseline in SERAPHIN*



Number at risk							
OPSUMIT 10 mg	88	74	68	64	58	38	17
Placebo	96	66	54	45	42	24	13

***Note: The treatment response on the primary endpoint was almost entirely attributable to an effect on morbidity.**

Figure 3: **Kaplan-Meier Estimates of Primary Endpoint Events up to EOT; Combination PAH Therapy* at Baseline in SERAPHIN†**



Number at risk							
OPSUMIT 10 mg	154	134	119	107	97	53	24
Placebo	154	122	106	90	80	40	10

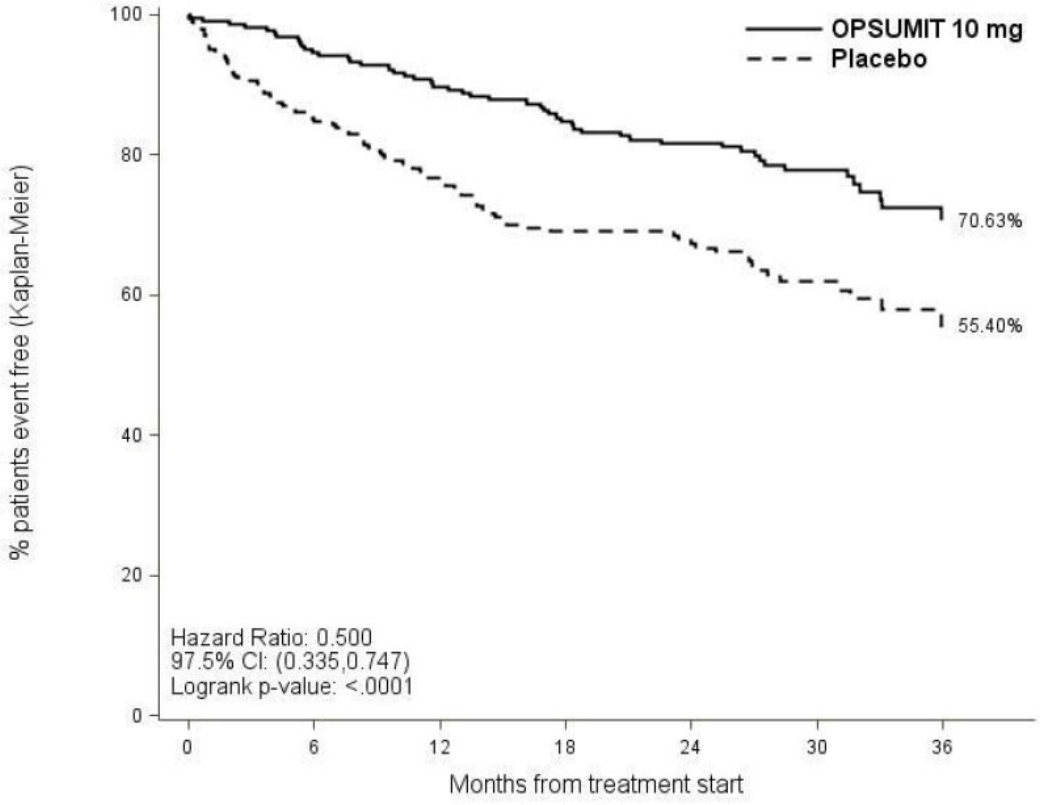
*At baseline, patients were treated with a stable dose of either phosphodiesterase inhibitors and/or inhaled/oral prostanoids.

†**Note: The treatment effect in the primary endpoint was almost entirely attributable to an effect on morbidity.**

Treatment with OPSUMIT 10 mg resulted in a 50% relative risk reduction (HR 0.50, 97.5% CI 0.34-0.75; logrank p<0.0001) in the occurrence of PAH related death or hospitalization for PAH, up to EOT compared to placebo. The proportion of patients without a PAH related death or hospitalization for PAH at 3 years was 70.6% in OPSUMIT 10 mg compared to 55.4% in placebo, corresponding to an absolute risk reduction of 15.2% (Figure 4).

Treatment with OPSUMIT 10 mg resulted in fewer PAH related hospitalizations per year (0.3 and 0.7 with OPSUMIT 10 mg and placebo, respectively) and for all causes (0.5 and 1.0 with OPSUMIT 10 mg and placebo, respectively).

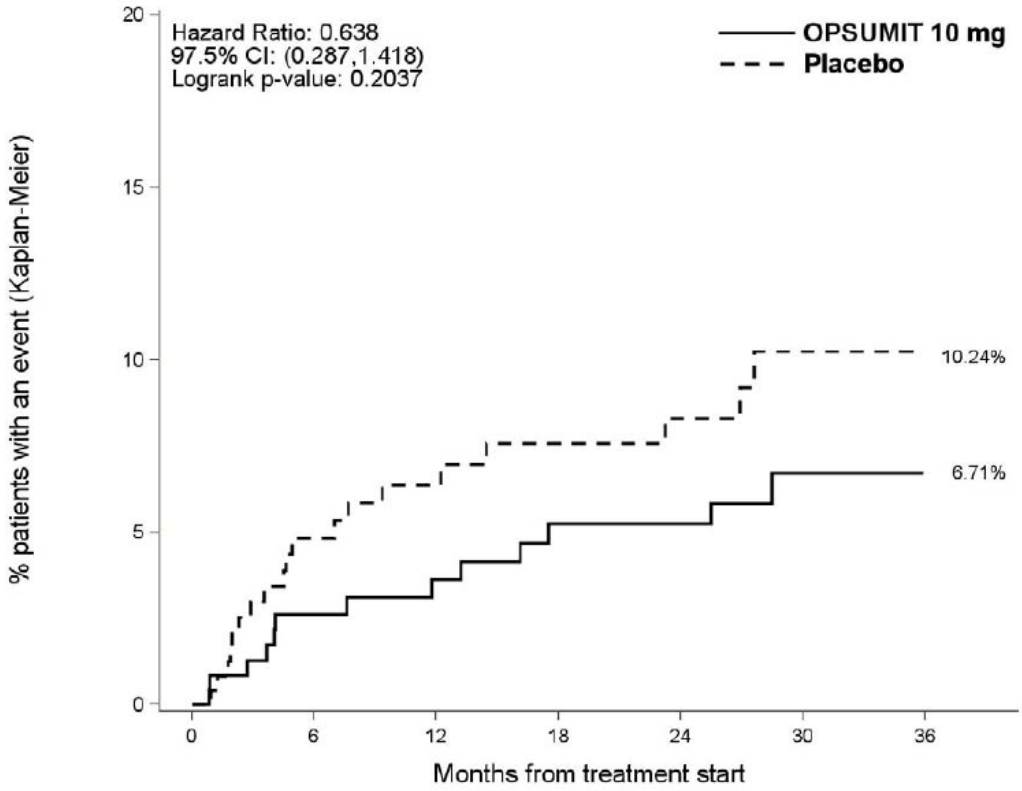
Figure 4: Kaplan-Meier Estimates of Death due to PAH or Hospitalization for PAH up to EOT in SERAPHIN



Number at risk							
OPSUMIT 10 mg	242	203	183	166	152	86	39
Placebo	250	188	155	132	119	62	22

Treatment with OPSUMIT 10 mg resulted in a 36% relative risk reduction (HR 0.64, 97.5% CI 0.29-1.42; logrank p=0.2037) in the occurrence of death of all causes up to EOT. The proportion of deaths of all causes at 3 years was 10.2% in placebo compared to 6.7% in OPSUMIT 10 mg, corresponding to an absolute risk reduction of 3.5% (Figure 5). The relative risk reduction for death up to EOS was 23%.(HR 0.77, 97.5% CI 0.46-1.28; logrank p=0.2509). The proportion of deaths of all causes at 3 years was 19.3% in the placebo group compared to 17.1% in the OPSUMIT 10 mg, corresponding to an absolute risk reduction of 2.2%.

Figure 5: Kaplan-Meier Estimates of Death of all Causes up EOT in SERAPHIN



Symptomatic and Functional Endpoints: Exercise ability was evaluated as a secondary endpoint. Treatment with OPSUMIT 10 mg at Month 6 resulted in a placebo-corrected mean increase in 6MWD of 22 meters (97.5% CI 3-41; p=0.0078). Evaluation of 6MWD by functional class resulted in a placebo corrected mean increase from baseline to Month 6 in FC III/IV patients of 37 meters (97.5% CI 5- 69; p=0.0088) and in FC I/II of 12 meters (97.5% CI -8-33; p=0.1762).The increase in 6MWD achieved with OPSUMIT was maintained for the duration of the study.

Treatment with OPSUMIT 10 mg led to a 74% higher chance of WHO FC improvement relative to placebo (risk ratio 1.74; 97.5% CI 1.10–2.74; p=0.0063). Treatment with OPSUMIT 10 mg led to an improvement of at least one WHO FC at Month 6 in 22% of patients compared to 13% of patients treated with placebo.

OPSUMIT 10 mg improved quality of life assessed by the SF-36 questionnaire. Improvements compared to placebo were observed in 7 out of 8 domains at Month 6 including physical functioning, role-physical, bodily pain, vitality, social functioning, role emotional, and mental health domains of the SF 36 questionnaire (SF-36).

Hemodynamic Endpoints: Hemodynamic parameters were assessed in a subset of patients (placebo, N=67, OPSUMIT 10 mg, N=57) after 6 months of treatment. Patients treated with OPSUMIT 10 mg achieved a median reduction of 36.5% (CI 21.7-49.2%) in pulmonary vascular resistance and an increase of 0.58 L/min/m^2 (CI 0.28-0.93 L/min/m^2) in cardiac index compared to placebo.

DETAILED PHARMACOLOGY

Steady-state conditions of macitentan and its active metabolite are achieved after 3 days and 7 days, respectively. Peak plasma concentrations of macitentan were reached 8 hours after administration and the AUC_{0-24} and C_{max} of macitentan were dose-proportional over the tested dose range (1 to 30 mg o.d.). As anticipated from the observed $t_{1/2}$ of 16 hours and 48 hours for macitentan and its active metabolite, respectively, the accumulation of macitentan was minimal (approximately 1.5-fold) whereas that of the active metabolite was about 8.5-fold. Macitentan and its circulating metabolites are highly bound (≥ 99%) to plasma proteins, mainly albumin, in all species, including man.

TOXICOLOGY

Acute toxicity studies:
Macitentan had a low order of acute toxicity in rodents. No deaths occurred following a single oral dose of 2000 mg/kg in mice and rats.

Repeated-dose toxicity studies:
No adverse effects were observed in repeated-dose oral toxicity studies in rats or dogs with treatment durations ≤ 26 or 39 weeks at exposures of 2- to 6-fold the human exposure at 10 mg/day.

Prolonged coagulation test times (PT and APTT) leading to hemorrhage and death occurred at a very high dose level (1500 mg/kg/day) in male rats. As exposure at this dose was 137-fold the human exposure, this finding is considered of limited relevance for humans.

Generally mild to moderate decreases in red blood cell parameters (red blood cell count,

hemoglobin, hematocrit) that occurred in rats or dogs were reversible.

In dogs, macitentan decreased blood pressure at exposures similar to the therapeutic human exposure. Intimal thickening of coronary arteries, considered secondary to hemodynamic changes, was observed in dogs at 17-fold the human exposure after 4 to 39 weeks of treatment. Treatment-related coronary intimal thickening of coronary arteries was not observed in dogs at 4-fold (males) to 9-fold (females) human exposure.

Increased incidences of arteritis/peri-arteritis of coronary arteries occurred in dogs at ≥ 17-fold human exposure. Due to the species-specific sensitivity and the safety margin, this finding is considered of limited relevance for humans.

There were no adverse liver findings in long-term studies conducted in B6C3F1 mice, rats, and dogs at exposures of 12- to 116-fold the human exposure. The relevance of increased aminotransferase activities and liver cell necrosis observed in CD-1 mice at ≥ 5 mg/kg/day is not known in view of the inconsistency of these findings across studies.

Liver cell hypertrophy in mice, rats and dogs and associated thyroid follicular cell hypertrophy in rats, represent adaptive changes related to hepatic enzyme induction.

Pathologic changes in testes (tubular dilatation, degeneration and/or atrophy; and/or hypospermatogensis) occurred in rats or dogs at >18-fold human exposure.

Carcinogenicity:
Carcinogenicity studies of 2 years duration did not reveal any carcinogenic potential at exposures 18-fold and 116-fold the human exposure in rats and mice, respectively.

Mutagenicity:
Macitentan was not genotoxic in a standard battery of *in vitro* and *in vivo* assays. Macitentan was not phototoxic *in* vivo.

Reproductive toxicity:
Macitentan was teratogenic in rabbits and rats at all dose levels tested. In both species there were cardiovascular abnormalities and mandibular arch fusion abnormalities.

Macitentan was fetotoxic in rabbits at a dose 218-fold the human exposure.

Administration of macitentan to female rats from late pregnancy through lactation caused reduced pup survival and impairment of the reproductive capability of the offspring at maternal exposures 5-fold the human exposure.

Treatment of juvenile rats from postnatal Day 4 to Day 114 led to reduced body weight gain and testicular tubular atrophy at exposures 6-fold the human exposure.

Treatment with macitentan also caused a reduction in the numbers of implantation sites and live embryos. Although at an exposure 3-fold the human exposure, macitentan had no effects on

sperm count or motility, the incidence of sperm misshapen or with abnormally curved hook was increased.

Testicular tubular dilatation was not observed in repeated-dose toxicity studies at exposures 8- and 6-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. In mice treated for 2 years with macitentan, uterine weight was increased and there was an increase in the mean severity and incidence of uterine endometrial cysts at exposures 9-fold and 90-fold the human exposure, respectively.

REFERENCES

1. Pulido T, Adzerikho I, Channick RN, Delcroix M, Galiè N, Ghofrani H-A, et al. Macitentan and Morbidity and Mortality in Pulmonary Arterial Hypertension. N Engl J Med. 2013;369(9):809-818.

PART III: CONSUMER INFORMATION

[PR]OPSUMIT®Macitentan tablets

This leaflet is part III of a three-part "Product Monograph" published when OPSUMIT was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about OPSUMIT. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

What the medication is used for:
OPSUMIT is a prescription medicine used to treat people with certain types of pulmonary arterial hypertension (PAH).

What it does:
PAH is high blood pressure in the blood vessels that lead blood from the heart to the lungs. OPSUMIT lowers high blood pressure in your lungs and lets your heart pump blood better.

OPSUMIT may lower the chance of your disease getting worse.

OPSUMIT can be taken alone or with some other PAH medications prescribed by your doctor.

When it should not be used:
Do not take OPSUMIT if you:

- are allergic (hypersensitive) to macitentan or any of the other ingredients of OPSUMIT (*see "What the nonmedicinal ingredients are")*.
- are pregnant, if you are planning to become pregnant, or if you could become pregnant because you are not using reliable birth control (contraception).
- are breastfeeding. It is not known if OPSUMIT can pass through your milk and harm your baby. Therefore, breastfeeding is not recommended.

What the medicinal ingredient is:
macitentan

What the nonmedicinal ingredients are:
lactose monohydrate, magnesium stearate, microcrystalline cellulose, polysorbate 80, polyvinyl alcohol, povidone, and sodium starch glycolate Type A, soya lecithin, talc, titanium dioxide, and xanthan gum

What dosage forms it comes in:
10 mg tablet

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

- Serious birth defects.
- Anemia (a reduced number of red blood cells)

BEFORE you use OPSUMIT talk to your doctor or pharmacist if:

- You are or are planning on becoming pregnant.
- OPSUMIT can cause serious birth defects if taken during pregnancy.
- Do not take OPSUMIT if you are pregnant. Talk to your doctor if you become pregnant while on treatment.
- Females who are able to get pregnant must take a pregnancy test before starting OPSUMIT. Monthly pregnancy tests during treatment with OPSUMIT are recommended to allow the early detection of pregnancy.
- Do not get pregnant while you are taking OPSUMIT. Talk with your doctor or gynecologist (a doctor who specializes in female reproduction) to find out about how to prevent pregnancy.
- Do not have unprotected sex. Tell your doctor right away if you have unprotected sex. Tell your doctor right away if you think your birth control has failed.
- If you become pregnant, call your doctor right away. Stop taking OPSUMIT.

INTERACTIONS WITH THIS MEDICATION

Drugs that may interact with OPSUMIT include:

- Rifampicin, an antibiotic.

PROPER USE OF THIS MEDICATION

Usual dose:

- Take one tablet once daily with or without food.
- Take OPSUMIT exactly as your doctor tells you to take it.
- It will be easier to remember to take OPSUMIT if you take it at the same time each day.
- Do not split, crush, or chew OPSUMIT tablets.
- If you take more than the prescribed dose of OPSUMIT, call your doctor right away.
- Do not stop taking OPSUMIT unless your doctor tells you to.

Tests during treatment:
Some patients taking OPSUMIT were found to have abnormal liver function values (increase in liver enzymes) and some patients developed anemia (reduction in red blood cells). Because these findings may not cause symptoms you can feel or observe yourself, your doctor will do regular blood tests to assess any changes in your liver function and hemoglobin level.

Liver function:
This blood test will be done:

- every month during the first year of treatment or more frequently, if needed.

If you develop abnormal liver function, your doctor may decide to stop treatment with OPSUMIT. When your blood test results for liver function return to normal, your doctor may decide to restart treatment with OPSUMIT.

Anemia:
This blood test will be done:

- at one month after treatment start and as decided by doctor thereafter .

If you develop anemia, your doctor may decide to perform further tests to investigate the cause.

Your regular blood tests, both for liver function and anemia, are an important part of your treatment.

Overdose:

In case of drug overdose, contact a health care practitioner, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

Missed Dose:
If you miss a dose of OPSUMIT, take your tablet as soon as you remember. Do not take 2 doses at the same time. If it is almost time for your next dose, skip the missed dose. Just take the next dose at your regular time.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

OPSUMIT can cause serious side effects, including:

- Serious birth defects. See "Warnings and Precautions".
- Low red blood cell levels (anemia).
- Liver problem.

Most common side effects include:

- Stuffy nose (nasopharyngitis)
- Headache
- Sore throat (pharyngitis)
- Flu (influenza)

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Symptom / effect		Talk with your doctor or pharmacist		Stop taking drug and call your doctor or pharmacist
		Only if severe	In all cases	
Very Common	Low red blood cell levels (anemia)	✓		
	Irritation of the airways (bronchitis)	✓		
Common	Urinary tract infection	✓		
Known	Allergic reaction (symptoms include swelling in the mouth, tongue, face and throat, itching, rash)			✓
Rare	Yellowing of the skin or eyes (jaundice) or other symptoms that indicate liver damage such as nausea, vomiting, fever, abdominal pain or unusual tiredness		✓	

This is not a complete list of side effects. For any unexpected effects while taking OPSUMIT, contact your doctor or pharmacist.

HOW TO STORE IT

Store OPSUMIT tablets at room temperature between 15°C and 30°C.

Keep OPSUMIT out of the reach and sight of children.

REPORTING SUSPECTED SIDE EFFECTS

You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways:

- **Report online at www.healthcanada.gc.ca/medeffect**
- **Call toll-free at 1-866-234-2345**
- **Complete a Canada Vigilance Reporting Form and:**
  - **Fax toll-free to 1-866-678-6789, or**
  - **Mail to: Canada Vigilance Program**
    Health Canada
    Postal Locator 0701E
    Ottawa, Ontario
    K1A 0K9

Postage paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available on the MedEffect™ Canada Web site at www.healthcanada.gc.ca/medeffect.

NOTE: Should you require information related to the management of side effects, contact your health professional. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

This document plus the full product monograph, prepared for health professionals can be found at:
http://www.actelion.com
Or by contacting the sponsor, Actelion Pharmaceuticals Canada Inc., at:
1-866-531-4885

This leaflet was prepared by Actelion Pharmaceuticals Canada Inc.

Last revised: November 18, 2015