

PRODUCT MONOGRAPH
INCLUDING PATIENT MEDICATION INFORMATION

PrOPSUMIT[®]

Macitentan Tablets

Film-coated Tablets
10 mg

Oral Administration

Professed Standard

Endothelin Receptor Antagonist

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RECENT MAJOR LABEL CHANGES

7 Warnings and Precautions, Fertility

11/2022

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PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

OPSUMIT[®] (macitentan) is indicated for:

- the long-term treatment of pulmonary arterial hypertension (PAH, WHO Group I) 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 inhibitors.

1.1 Pediatrics

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

1.2 Geriatrics

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.

2 CONTRAINDICATIONS

OPSUMIT[®] (macitentan) is contraindicated in:

- patients who are hypersensitive to this drug or to any ingredient in the formulation, including any non-medicinal ingredient, or component of the container. For a complete listing, see [6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING](#).
- Women who are or may become pregnant (see [7.1.1 Pregnant Women](#)).
- Nursing women (see [7.1.2 Breast-feeding](#)).

4 DOSAGE AND ADMINISTRATION

4.2 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 [7 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 [7 WARNINGS AND PRECAUTIONS, Renal](#)).

Geriatrics (≥65 years of age)

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 [7.1.4 Geriatrics](#)).

Pediatrics (<18 years of age)

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

4.4 Administration

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

4.5 Missed Dose

If a dose of OPSUMIT® is missed, the tablet should be taken as soon as it is remembered. Otherwise, advise the patient to skip the dose and take the next dose at the regular time. The patient should be advised not to take 2 doses on the same day to make up for a missed dose.

5 OVERDOSAGE

There is currently no experience with overdose of OPSUMIT®. In a clinical study in healthy subjects where macitentan was administered as a single dose 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 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.

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Table 1: Dosage Forms, Strengths, Composition and Packaging.

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

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 both sides.

OPSUMIT® tablets are supplied as follows:

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

7 WARNINGS AND PRECAUTIONS

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 [7 WARNINGS AND PRECAUTIONS, Monitoring and Laboratory Tests](#) and [8 ADVERSE REACTIONS](#)).

Hepatic/Biliary/Pancreatic

Elevations of liver aminotransferases (AST, ALT) have been associated with PAH and with 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. The incidence of elevated aminotransferases of >8 x ULN was 2.1% in the macitentan 10 mg group compared to 0.4% in the placebo group. Post-market cases of liver injury have been reported with OPSUMIT[®] use (see [8.5 Post-Market Adverse Reactions, Gastrointestinal Disorders](#)). 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 [4.2 Recommended Dose and Dosage Adjustment, 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 [7 WARNINGS AND PRECAUTIONS, 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 [8 ADVERSE REACTIONS](#)).

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 [7 WARNINGS AND PRECAUTIONS, Hematologic](#) and [8 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 [7 WARNINGS AND PRECAUTIONS, Hepatic/Biliary/Pancreatic](#)).

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.

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.

Reproductive Health: Female and Male Potential

Fertility

. Based on findings in animals, OPSUMIT[®] may impair fertility in males of reproductive potential. Decreases in sperm cell count have been observed in patients taking ERAs. OPSUMIT[®], like other ERAs, may have an adverse effect on spermatogenesis in men. It is not known whether the effects on fertility would be reversible. Counsel men about potential effects on fertility.

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 [16 NON-CLINICAL TOXICOLOGY](#), **Reproductive toxicity**).

7.1 Special Populations

7.1.1 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 [2 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.

7.1.2 Breast-feeding

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[®] (see [2 CONTRAINDICATIONS](#)).

7.1.3 Pediatrics

Pediatrics (<18 years of age): The safety and efficacy of OPSUMIT[®] in children and adolescents <18 years of age has not been established (see [10 CLINICAL PHARMACOLOGY](#), **Pediatrics**).

7.1.4 Geriatrics

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 [4 DOSAGE AND ADMINISTRATION](#)).

8 ADVERSE REACTIONS

8.1 Adverse Reaction Overview

The most common adverse reactions (>3% compared to placebo) are nasopharyngitis (14%), headache (14%), anemia (13%), bronchitis (12%), urinary tract infection (9%), pharyngitis (6%) and influenza (6%).

8.2 Clinical Trial Adverse 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 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 2 presents treatment-emergent AEs reported by >3% of patients in the OPSUMIT[®] 10 mg group and more frequently than on placebo by >3%.

Table 2: 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
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.

Open-Label Extension Study

Of the 742 patients who participated in the pivotal SERAPHIN double-blind study, 550 patients entered a long-term open-label extension study (182 patients who continued on OPSUMIT® 10 mg and 368 patients who received placebo or macitentan 3 mg and crossed over to OPSUMIT® 10 mg).

Long-term follow up of patients treated with OPSUMIT® 10 mg in the double-blind / open-label extension studies (N=242) for a median exposure of 4.6 years and a maximum exposure of 11.8 years showed a safety profile that was consistent with that described above for the double-blind, placebo-controlled phase.

8.3 Less Common Clinical Trial Adverse Reactions

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

8.4 Abnormal Laboratory Findings: Hematologic, Clinical Chemistry and Other Quantitative Data

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 [7 WARNINGS AND PRECAUTIONS, Hematologic](#)).

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. The incidence of elevated aminotransferases of >8 x ULN was 2.1% on OPSUMIT® 10 mg versus 0.4% in the placebo group (see [7 WARNINGS AND PRECAUTIONS, Hepatic/Biliary/Pancreatic](#)).

Elevations of liver aminotransferases (ALT, AST) and liver injury have been reported with OPSUMIT® 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.

8.5 Post-Market Adverse 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.

Gastrointestinal Disorders: elevations of liver aminotransferases (ALT, AST), liver injury

General Disorders and Administration Site Conditions: edema/fluid retention

Immune System Disorders: hypersensitivity reactions (angioedema, pruritus and rash)

Respiratory, Thoracic and Mediastinal disorders: nasal congestion

9 DRUG INTERACTIONS

9.2 Drug Interactions Overview

The metabolism of macitentan to its active metabolite is catalyzed mainly by CYP3A4, with minor contributions from CYP2C8, CYP2C9 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).

9.4 Drug-Drug Interactions

The drugs listed in this table are based on either drug interaction case reports or studies, or potential interactions due to the expected magnitude and seriousness of the interaction (i.e., those identified as contraindicated).

Table 3: Established or Potential Drug-Drug Interactions

Proper / Common name	Source of Evidence	Effect	Clinical comment
Sildenafil	CT	At steady-state in healthy volunteers, the exposure to sildenafil 20 mg three times daily 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.

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. The pharmacokinetics of macitentan and its active metabolite were not affected by warfarin.	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 (e.g., itraconazole, ketoconazole, voriconazole, clarithromycin, nefazodone, ritonavir, saquinavir).
Moderate Dual or Combined CYP3A4 and CYP2C9 Inhibitors (fluconazole)	T	In the presence of fluconazole 400 mg daily, a moderate dual inhibitor of CYP3A4 and CYP2C9, exposure to macitentan may increase approximately 3.8 fold or higher in CYP2C9 poor metabolisers, as assessed in physiologically based pharmacokinetic modelling. However, there were no clinically relevant changes in exposure to the active metabolite of macitentan, and the clinical significance of these findings is not known. The uncertainties of such modelling should be considered.	Caution should be exercised when macitentan is administered concomitantly with dual inhibitors and moderate dual inhibitors of CYP3A4 and CYP2C9 (e.g., fluconazole, amiodarone). Caution should also be exercised when macitentan is administered concomitantly with both a moderate CYP3A4 inhibitor (e.g., ciprofloxacin, cyclosporine, diltiazem, erythromycin, verapamil) and CYP2C9 inhibitor (e.g., miconazole).

Cyclosporin A	CT	In healthy volunteers, concomitant treatment with cyclosporine A 100 mg twice daily, a combined CYP3A4 and OATP inhibitor, did not alter the steady-state exposure to macitentan and its active metabolite to a clinically relevant extent.	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.
Breast cancer resistance protein substrate drugs		Macitentan 10 mg once daily did not affect the pharmacokinetics of oral rosuvastatin 10 mg.	No dose adjustment is warranted.
Riociguat		Macitentan 10 mg once daily did not affect the pharmacokinetics of oral riociguat 1 mg.	No dose adjustment is warranted.

Legend: C = Case Study; CT = Clinical Trial; T = Theoretical

9.5 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.

9.6 Drug-Herb Interactions

Interactions with herbal products have not been established.

9.7 Drug-Laboratory Test Interactions

Interactions with laboratory tests have not been established.

10 CLINICAL PHARMACOLOGY

10.1 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 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.

10.2 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.

10.3 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 (V_{ss}/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 has four primary metabolic pathways. 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.

Other metabolic pathways yield products without pharmacological activity. For these pathways, CYP2C9 plays a predominant role with minor contributions from CYP2C8, CYP2C19 and CYP3A4.

Elimination: Macitentan is excreted only after extensive metabolism. The major excretion route is via urine, accounting for about 50% of the dose.

Special Populations and Conditions

Pediatrics: The pharmacokinetics of macitentan and its metabolite ACT-132577 were assessed in 16 pediatric patients (5 were 6 to 11 years old and 11 were adolescents 12 to 17 years old) with pulmonary arterial hypertension. Pediatric patients in the ≥ 25 kg and < 50 kg body weight subgroup were administered 7.5 mg once daily dose of macitentan (8 patients). A dose of 10 mg once daily of macitentan was administered to pediatric patients with a body weight of ≥ 50 kg (8 patients).

Macitentan exposure, based on C_{max} and AUC_T was in a similar range regardless of weight and age. Compared to adult data from 20 patients treated with macitentan 10 mg once daily in Study AC-055-303 (SERAPHIN PK substudy), macitentan exposure appeared to be marginally lower in children as compared to adults while there were no indications of differences in exposure to its metabolite ACT-132577 in children.

The safety and efficacy of OPSUMIT® in children and adolescents <18 years of age has not been established; therefore, Health Canada has not authorized an indication for pediatric use.

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.

11 STORAGE, STABILITY AND DISPOSAL

Store at room temperature (15 to 30°C).
Keep out of reach and sight of children.

12 SPECIAL HANDLING INSTRUCTIONS

This information is not available for this drug product.

PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

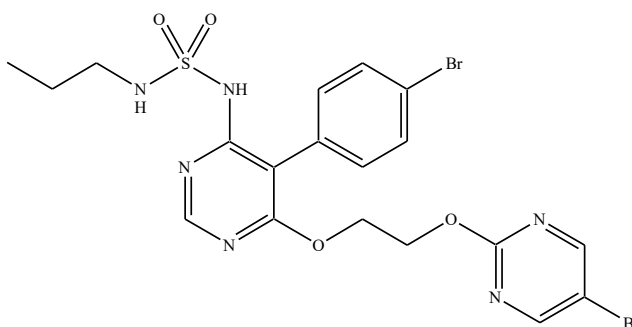
Drug Substance

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: C₁₉H₂₀Br₂N₆O₄S, 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.

14 CLINICAL TRIALS

14.1 Clinical Trials by Indication

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.

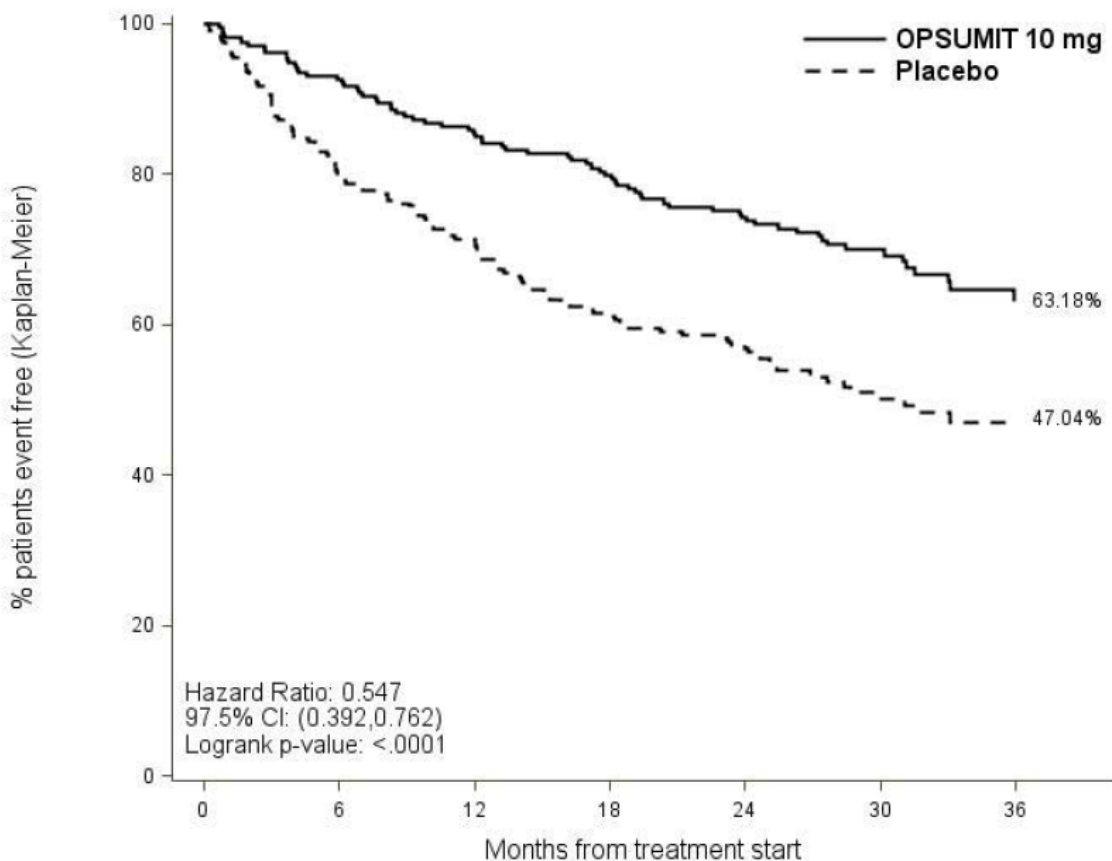
Idiopathic or heritable PAH was the most common etiology in the study population (57%) followed by PAH due to connective tissue disorders (31%), PAH associated with congenital heart disease with shunts (8%) and PAH associated with other etiologies [drugs and toxins (3%) and HIV (1%)].

Study Results

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		0	6	12	18	24	30	36
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).

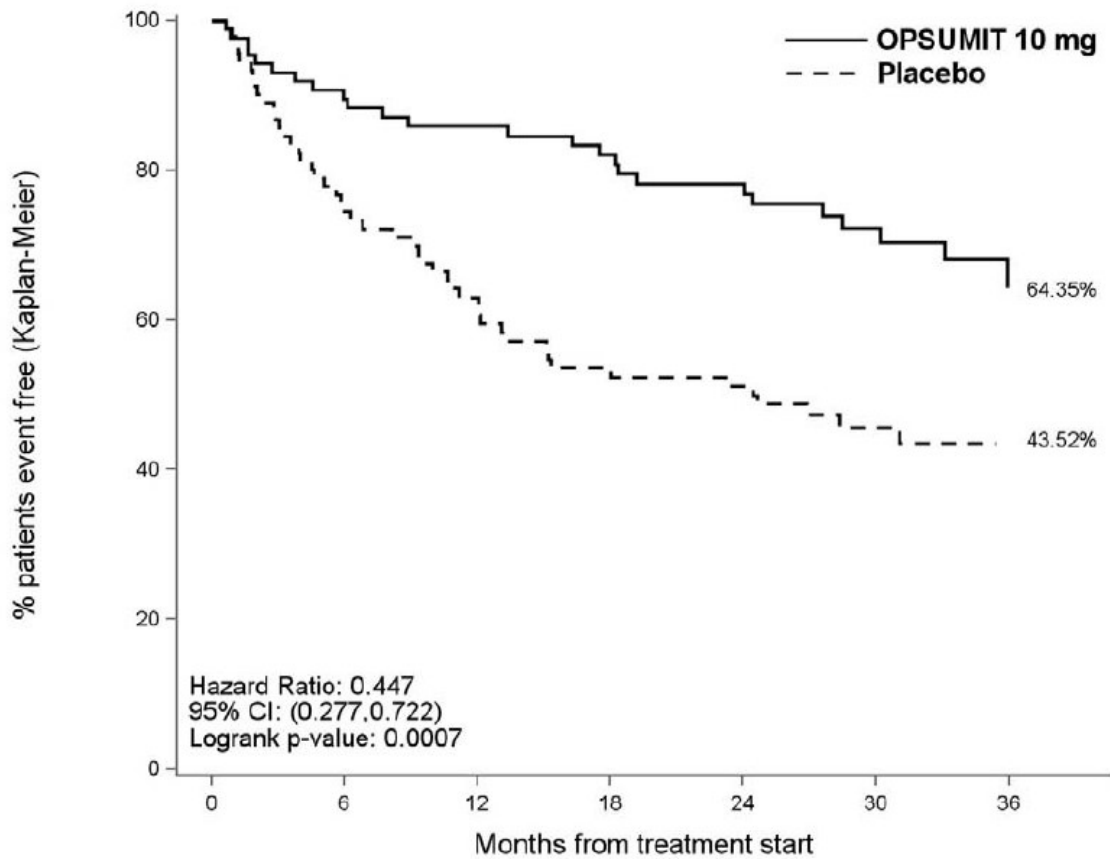
Consistent efficacy of OPSUMIT[®] 10 mg on the primary endpoint was seen across subgroups of age, sex, race, geographical region, etiology, by monotherapy or in combination with another PAH therapy, 6MWD, and WHO FC.

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).

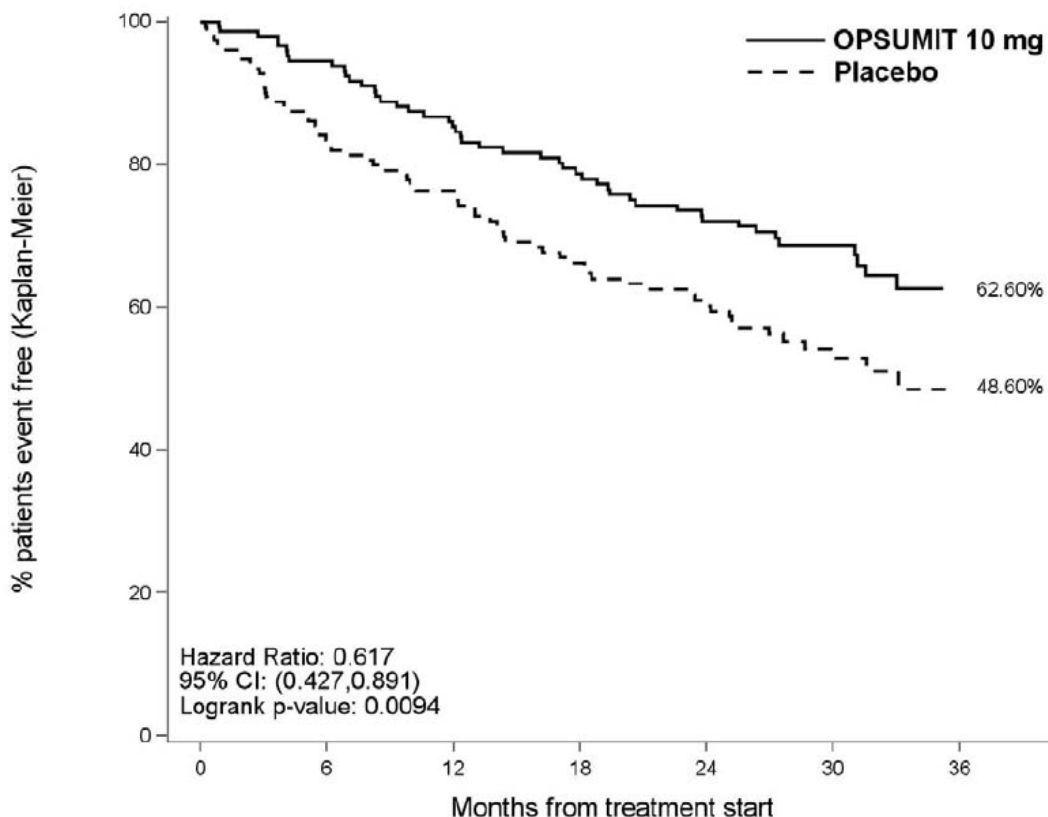
Figure 2: Kaplan-Meier Estimates of Primary Endpoint Events up to EOT; Monotherapy at Baseline in SERAPHIN*



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

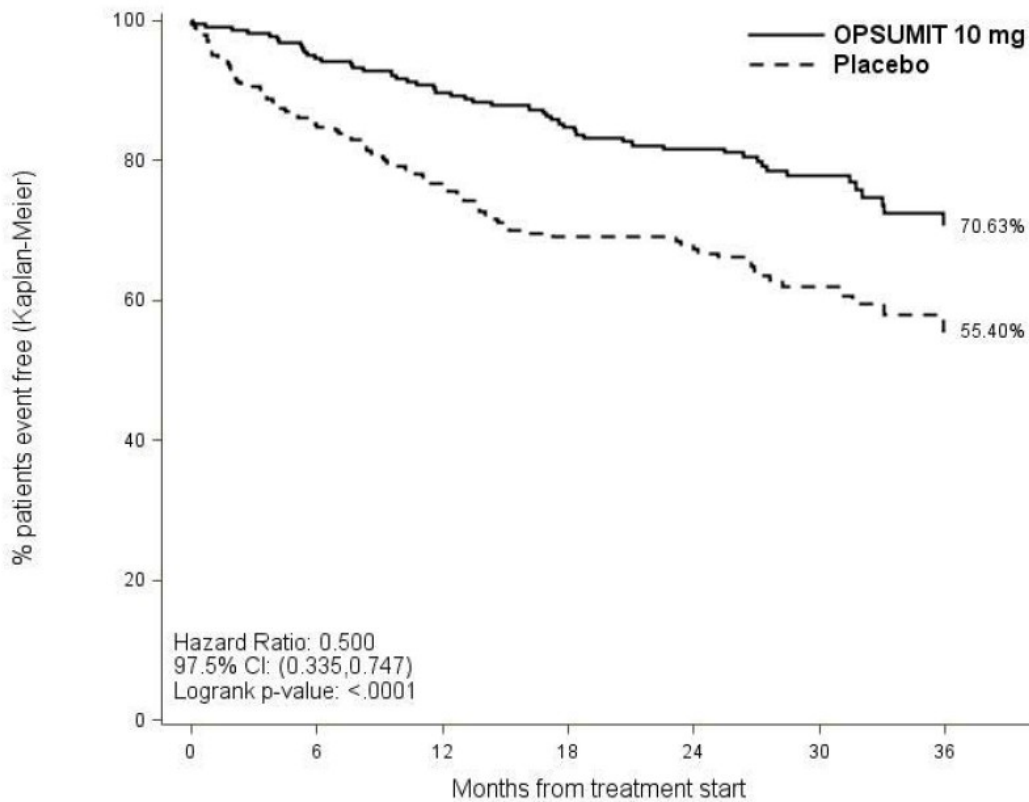
*At baseline, patients were treated with a stable dose of either phosphodiesterase inhibitors and/or inhaled/oral prostanoids.

†**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).

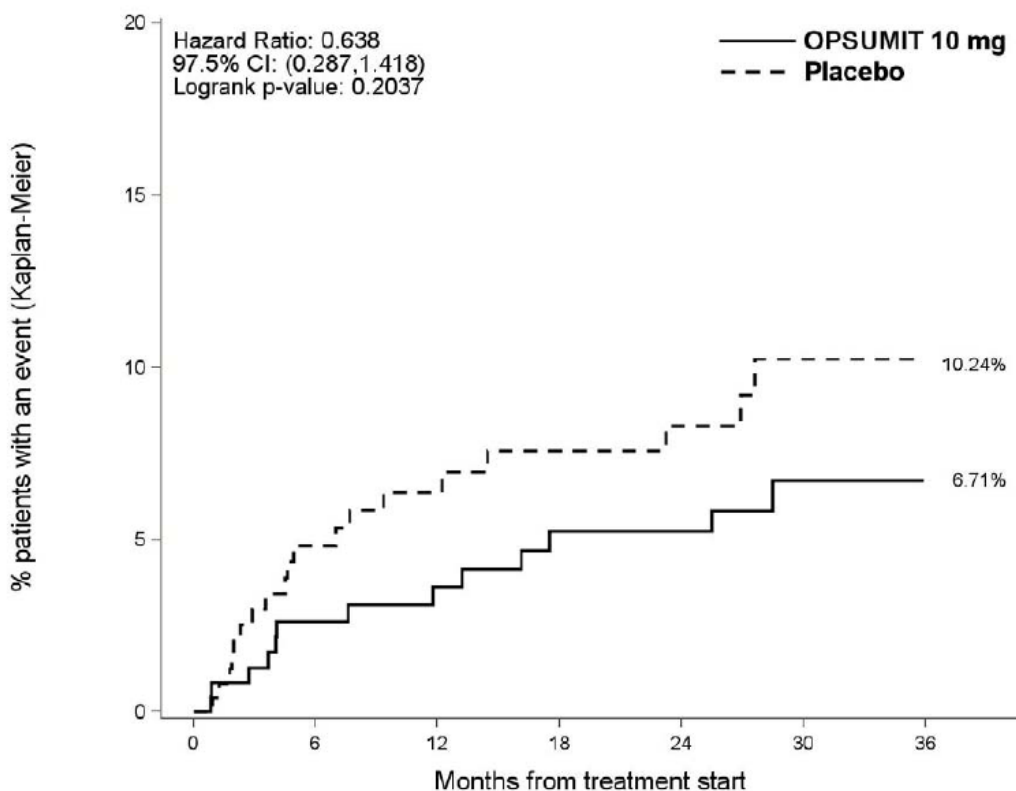
Figure 4: Kaplan-Meier Estimates of Death due to PAH or Hospitalization for PAH up to EOT in SERAPHIN



Number at risk		0	6	12	18	24	30	36
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



Number at risk		0	6	12	18	24	30	36
OPSUMIT 10 mg	242	209	188	172	157	91	41	
Placebo	250	198	163	139	123	67	24	

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).

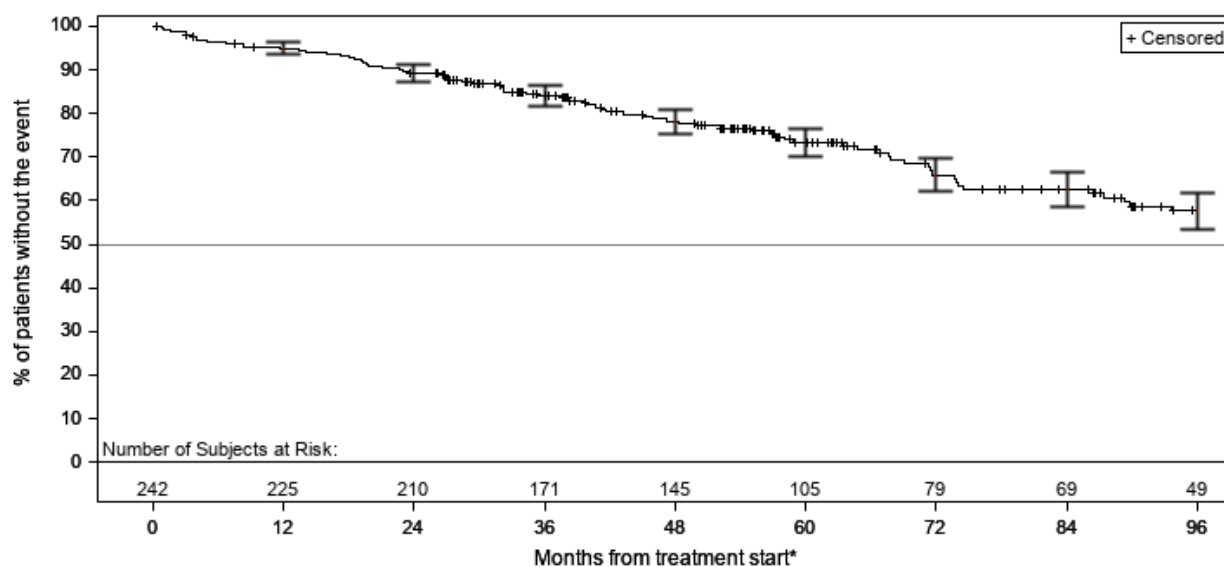
Hemodynamic Endpoints

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/m² (CI 0.28-0.93 L/min/m²) in cardiac index compared to placebo.

Long-Term Treatment of PAH

In long-term follow-up of patients who were treated with OPSUMIT® 10 mg in the double-blind / open-label extension studies (N=242), Kaplan-Meier estimates of survival at 1, 2, 3, 4, 5, 6, 7, 8 and 9 years were 95%, 89%, 84%, 78%, 73%, 66%, 63%, 58% and 53% respectively (Figure 6). The median follow-up time was 5.9 years. These uncontrolled observations do not allow comparison with a group not given OPSUMIT® and cannot be used to determine the long term-effect of OPSUMIT® on mortality.

Figure 6: Kaplan-Meier estimates of time to death (all-causes) in long-term follow-up of OPSUMIT® treatment



Survival curves are presented up to the time when more than 10% of the subjects are still at risk.

Error bars show Kaplan-Meier estimate \pm standard error.

*Treatment start corresponds to the start of double-blind macitentan 10 mg in AC-055-302.

15 MICROBIOLOGY

This information is not available for this drug product.

16 NON-CLINICAL TOXICOLOGY

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 AUC₀₋₂₄ 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.

General 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 hypospermatogenesis) 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.

PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

Pr **OPSUMIT[®]**

Macitentan Tablets

Read this carefully before you start taking **OPSUMIT[®]** and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **OPSUMIT[®]**.

What is OPSUMIT[®] used for?

OPSUMIT[®] is used in adults to treat certain types of pulmonary arterial hypertension (PAH), which is high blood pressure in the blood vessels leading to your lungs. It can be taken on its own or with other PAH medications as prescribed by your healthcare professional.

How does OPSUMIT[®] work?

OPSUMIT[®] is an endothelin receptor antagonist (ERA). It works by lowering high blood pressure in your lungs. This makes it easier for your heart to pump blood through the pulmonary arteries and can help lower the chance of your disease getting worse.

What are the ingredients in OPSUMIT[®]?

Medicinal ingredient: Macitentan.

Non-medicinal ingredients: Lactose monohydrate, magnesium stearate, microcrystalline cellulose, polysorbate 80, polyvinyl alcohol, povidone, sodium starch glycolate Type A, soya lecithin, talc, titanium dioxide, and xanthan gum.

OPSUMIT[®] comes in the following dosage forms:

Tablets: 10 mg of macitentan.

Do not use OPSUMIT[®] if:

- you are allergic to macitentan or any of the other ingredients in **OPSUMIT[®]**.
- you are pregnant, think you are pregnant, plan to become pregnant, or could become pregnant because you are not using reliable birth control. **OPSUMIT[®]** can cause serious birth defects if taken during pregnancy. If you think you are pregnant or get pregnant while taking **OPSUMIT[®]**, tell your healthcare professional right away.
- you are breastfeeding or plan to breastfeed. It is not known if **OPSUMIT[®]** can pass through your breast milk and harm your baby.

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take OPSUMIT[®]. Talk about any health conditions or problems you may have, including if you:

- have low red blood cell levels (anemia).
- have liver problems.
- have kidney problems.
- have pulmonary veno-occlusive disease (PVOD), a condition where your blood vessels are blocked.

- are on dialysis

Other warnings you should know about:**Pregnancy:**

- Do not take OPSUMIT[®] if you are pregnant. Talk to your healthcare professional if you become pregnant while on treatment.
- If you are able to get pregnant, you 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 have unprotected sex. Tell your healthcare professional right away if you have unprotected sex, or if you think your birth control has failed.
- You should NOT get pregnant while you are taking OPSUMIT[®] or within 1 month after stopping your treatment. Talk with your healthcare professional or gynecologist (a healthcare professional who specializes in female reproduction) to find out about how to prevent pregnancy.
- If you become pregnant while taking OPSUMIT[®] or within 1 month after stopping your treatment, call your healthcare professional right away.

Fertility in Men:

- Decreases in sperm count have been observed with OPSUMIT[®] and related drugs. Speak with your healthcare professional if you plan on fathering a child.

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 healthcare professional will do regular blood tests to assess any changes in your liver function and hemoglobin level.

Liver Function:

This blood test will be done:

- prior to initiation of OPSUMIT[®],
- every month during the first year of treatment or more frequently, if needed.

If you develop abnormal liver function, your healthcare professional may decide to stop treatment with OPSUMIT[®].

When your blood test results for liver function return to normal, your healthcare professional may decide to restart treatment with OPSUMIT[®].

Anemia:

This blood test will be done:

- prior to initiation of OPSUMIT[®],
- at one month after treatment start and as decided by healthcare professional thereafter.

If you develop anemia, your healthcare professional 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.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

The following may interact with OPSUMIT®:

- rifampicin, clarithromycin, ciprofloxacin, erythromycin (antibiotics used to treat infection).
- ritonavir, saquinavir (used to treat HIV infection).
- nefazodone (used to treat depression).
- ketoconazole, itraconazole, fluconazole, miconazole, voriconazole (medicine used against fungal infection).
- amiodarone (medicine used to control heartbeat).
- cyclosporine (used to prevent organ rejection after transplant).
- diltiazem, verapamil (used to treat high blood pressure of specific heart problems).

How to take OPSUMIT®:

- Always take OPSUMIT® exactly as your healthcare professional tells you to. Check with your healthcare professional if you are not sure. Do not stop taking OPSUMIT® unless your healthcare professional tells you to
- Swallow the tablets whole. Do NOT break, crush, or chew the tablets.
- OPSUMIT® can be taken with or without food.
- Try to take OPSUMIT® at the same time each day.

Usual Dose:

The recommended dose of OPSUMIT® is one tablet once a day.

Overdose:

If you think you, or a person you are caring for, have taken too much OPSUMIT®, contact a healthcare professional, 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.

What are possible side effects from using OPSUMIT®?

These are not all the possible side effects you may feel when taking OPSUMIT®. If you experience any side effects not listed here, tell your healthcare professional.

Side effects may include:

- Stuffy nose and congestion (nasopharyngitis);
- Headache;
- Sore throat (pharyngitis);
- Flu (influenza).

Serious side effects and what to do about them			
Symptom / effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
VERY COMMON			
Anemia (decreased number of red blood cells): fatigue, loss of energy, irregular heartbeats, pale complexion, shortness of breath, weakness	✓		
Bronchitis (irritation of the airways): coughing, mucus production, fatigue, shortness of breath, slight fever and chills, chest discomfort	✓		
Edema: unusual swelling of the arms, hands, legs, feet and ankles, face or airway passages	✓		
COMMON			
Hypotension (low blood pressure): dizziness, fainting, light-headedness, blurred vision, nausea, vomiting, fatigue (may occur when you go from lying or sitting to standing up)	✓		
Urinary tract infection (infection in urinary system including kidneys, ureters, bladder and urethra): pain or burning sensation while urinating, frequent urination, blood in urine, pain in the pelvis, strong smelling urine, cloudy urine	✓		
RARE			
Liver problems: yellowing of your skin and eyes (jaundice), right upper stomach area pain or swelling, fever, nausea or vomiting, unusual dark urine, unusual tiredness		✓	
UNKNOWN FREQUENCY			

Allergic reaction: fever, skin rash, hives, itching, swelling, shortness of breath, wheezing, runny nose, itchy, or watery eyes			✓
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If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, tell your healthcare professional.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (<https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.html>) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your healthcare professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:

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

Keep out of reach and sight of children.

If you want more information about OPSUMIT®:

- Talk to your healthcare professional
- Find the full Product Monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website (<https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html>); the manufacturer’s website www.janssen.com/canada, or by calling 1-800-567-3331 or 1-800-387-8781.

This leaflet was prepared by Janssen Inc., Toronto Ontario, M3C 1L9

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