PRODUCT MONOGRAPH

# OPSUMIT®

macitentan

10 mg film-coated tablet

Endothelin Receptor Antagonist

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 corrected simple 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 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. 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:** The development of testicular tubular atrophy in male animals was observed after treatment with macitentan (*See Toxicology, Reproductive toxicity*). Decreases in sperm count have been observed in patients taking ERAs. OPSUMIT®, like other ERAs, may have an adverse effect on spermatogenesis in men.

**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 |
| 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*). The incidence of elevated aminotransferases of >8 x ULN was 2.1% on OPSUMIT® 10 mg versus 0.4% in the placebo group.

***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*).

***Long-term safety:*** 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 as described above.

**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)

Vascular disorders:
flushing

Respiratory, thoracic and mediastinal disorders:
nasal congestion

General disorders and administration site conditions:
edema/fluid retention

## DRUG INTERACTIONS

***In vitro* studies**

The metabolism of OPSUMIT® to its active metabolite is catalyzed mainly by CYP3A4, with minor contributions from CYP2C8, CYP2C9 and CYP2C19.

OPSUMIT® and its active metabolite do not have relevant inhibitory or inducing effects on CYP enzymes.

OPSUMIT® and its active metabolite are not substrates of the multi-drug resistance protein (P-gp, MDR-1) or organic anion transporting polypeptides (OATP1B1 and OATP1B3).

OPSUMIT® and its active metabolite are not inhibitors of hepatic or renal drug transporters at clinically relevant concentrations, including the multi-drug resistance protein (P gp, MDR-1), the multidrug and toxin extrusion transporters (MATE1 and MATE2-K), the bile salt export pump (BSEP), the sodium-dependent co-transporting polypeptide (NTCP), and the organic anion transporting polypeptides (OATP1B1 and OATP1B3).

**Drug-Drug Interactions**

*Warfarin*: Level of Evidence - Clinical trial. In healthy volunteers receiving 25 mg warfarin, daily doses of OPSUMIT® 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 OPSUMIT®. No dose adjustment is warranted.

*Sildenafil*: Level of Evidence - Clinical trial. At steady-state in healthy volunteers, the exposure to sildenafil 20 mg t.i.d. was increased by 15% during concomitant administration of OPSUMIT® 10 mg once daily. Sildenafil, a CYP3A4 substrate, did not affect the pharmacokinetics of OPSUMIT®, while there was a 15% reduction in the exposure to the active metabolite of OPSUMIT®. These changes are not considered clinically relevant. In a placebo-controlled trial in patients with PAH, the efficacy and safety of OPSUMIT® 10 mg in combination with sildenafil were demonstrated. No dose adjustment is warranted.

*Strong CYP3A4 inhibitors (ketoconazole)*: Level of Evidence - Clinical trial. In the presence of ketoconazole 400 mg daily, a strong CYP3A4 inhibitor, exposure to OPSUMIT® increased approximately 2-fold in healthy volunteers. Exposure to the active metabolite of OPSUMIT® was reduced by 26%. The clinical significance of these changes is not known. Caution should be exercised when OPSUMIT® is administered concomitantly with strong CYP3A4 inhibitors (e.g., itraconazole, ketoconazole, voriconazole, clarithromycin, telithromycin, nefazodone, ritonavir, and saquinavir).

*Fluconazole*: In the presence of fluconazole 400 mg daily, a moderate dual inhibitor of CYP3A4 and CYP2C9, exposure to OPSUMIT® may increase approximately 3.8-fold based on physiologically based pharmacokinetic (PBPK) modelling. However, there was no clinically relevant change in exposure to the active metabolite of OPSUMIT®. Caution should be exercised when OPSUMIT® is administered concomitantly with moderate dual inhibitors of CYP3A4 and CYP2C9 (e.g., fluconazole and amiodarone).

Caution should also be exercised when OPSUMIT® is administered concomitantly with both a moderate CYP3A4 inhibitor (e.g., ciprofloxacin, cyclosporine, diltiazem, erythromycin, verapamil) and moderate CYP2C9 inhibitor (e.g., miconazole, piperine).

*Cyclosporin A*: Level of Evidence - Clinical trial. 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 OPSUMIT® and its active metabolite to a clinically relevant extent. No dose

adjustment is warranted.

*Rifampicin*: Level of Evidence - Clinical trial. In healthy volunteers, concomitant treatment with rifampicin 600 mg daily, a potent inducer of CYP3A4, reduced the steady-state exposure (AUC) to OPSUMIT® by 79% but did not affect the exposure to the active metabolite. Reduced efficacy of OPSUMIT® in the presence of a potent inducer of CYP3A4, such as rifampicin, should be considered. The combination of OPSUMIT® with strong CYP3A4 inducers should be avoided.

*Hormonal contraceptives*: Level of Evidence - Theoretical. OPSUMIT® 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.

*Breast cancer resistance protein substrate drugs*: Level of Evidence - Clinical trial. OPSUMIT® 10 mg once daily did not affect the pharmacokinetics of oral riociguat or rosuvastatin (riociguat 1mg; rosuvastatin 10 mg). No dose adjustment is warranted.

**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. The film-coated tablets must be swallowed whole, with water, and must not be chewed, divided or crushed.

## 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.

## ACTION AND CLINICAL PHARMACOLOGY

Pharmacotherapeutic group: Anti-hypertensives, anti-hypertensives for pulmonary arterial hypertension, ATC code: C02KX04.

**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 has four primary metabolic pathways. Oxidative depropylation of the sulfamide yields a pharmacologically active metabolite. This reaction is dependent on the cytochrome P450 system, mainly CYP3A4 with minor contributions from CYP2C8, CYP2C9 and CYP2C19. The active metabolite circulates in human plasma and may contribute to the 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.

**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.

## INCOMPATIBILITIES

Not applicable.

## SHELF LIFE

See expiry date on the outer pack.

## STORAGE AND STABILITY

Do not store above 30ºC.
Keep out of the reach and sight of children.

## 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 both sides. 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:

- 30 film-coated tablets PVC/ PE/PVDC white opaque film aluminum foil blisters in carton

# PART II: SCIENTIFIC INFORMATION

## PHARMACEUTICAL INFORMATION

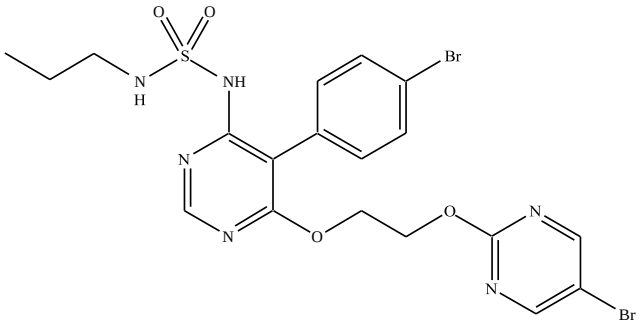
### Drug Substance

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.

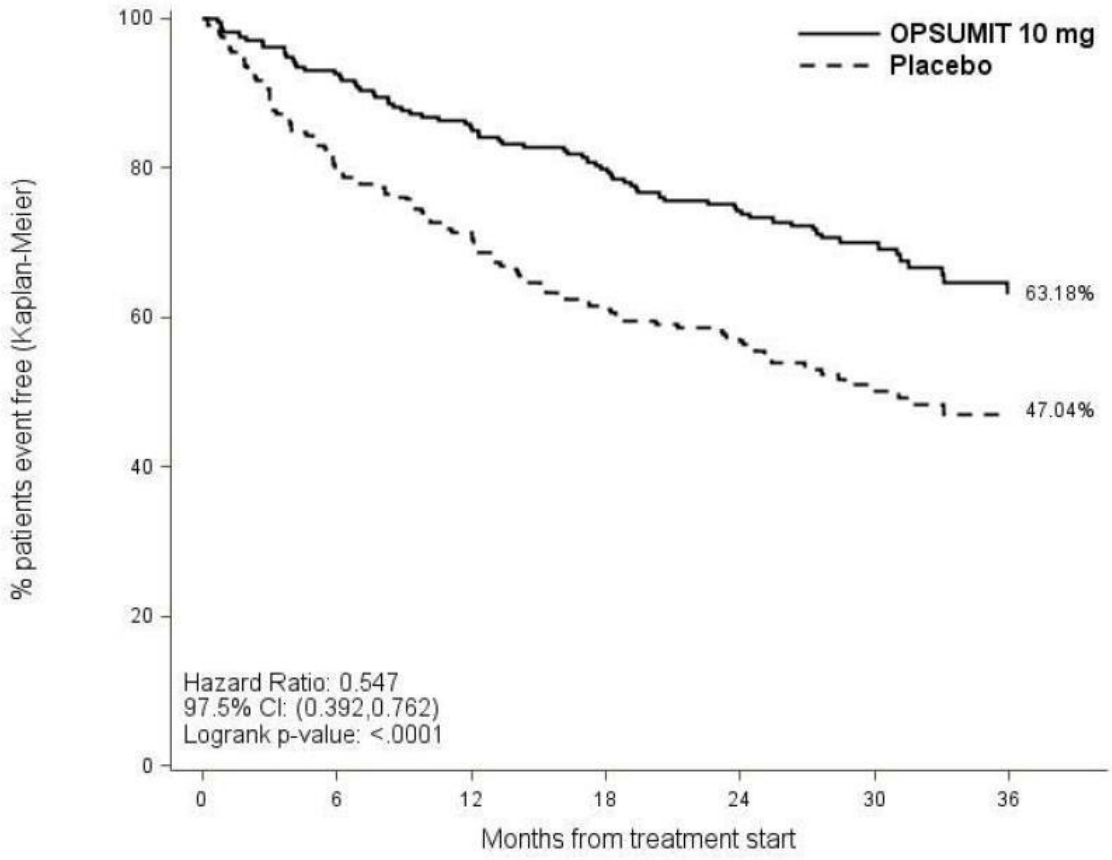
Efficacy was evaluated up to the end of double-blind treatment (EOT). The EOT either coincided with end of study (EOS) for patients who completed the study as scheduled or occurred earlier in case of premature discontinuation of study drug. For those patients who stopped treatment prior to EOS, PAH therapy, 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).

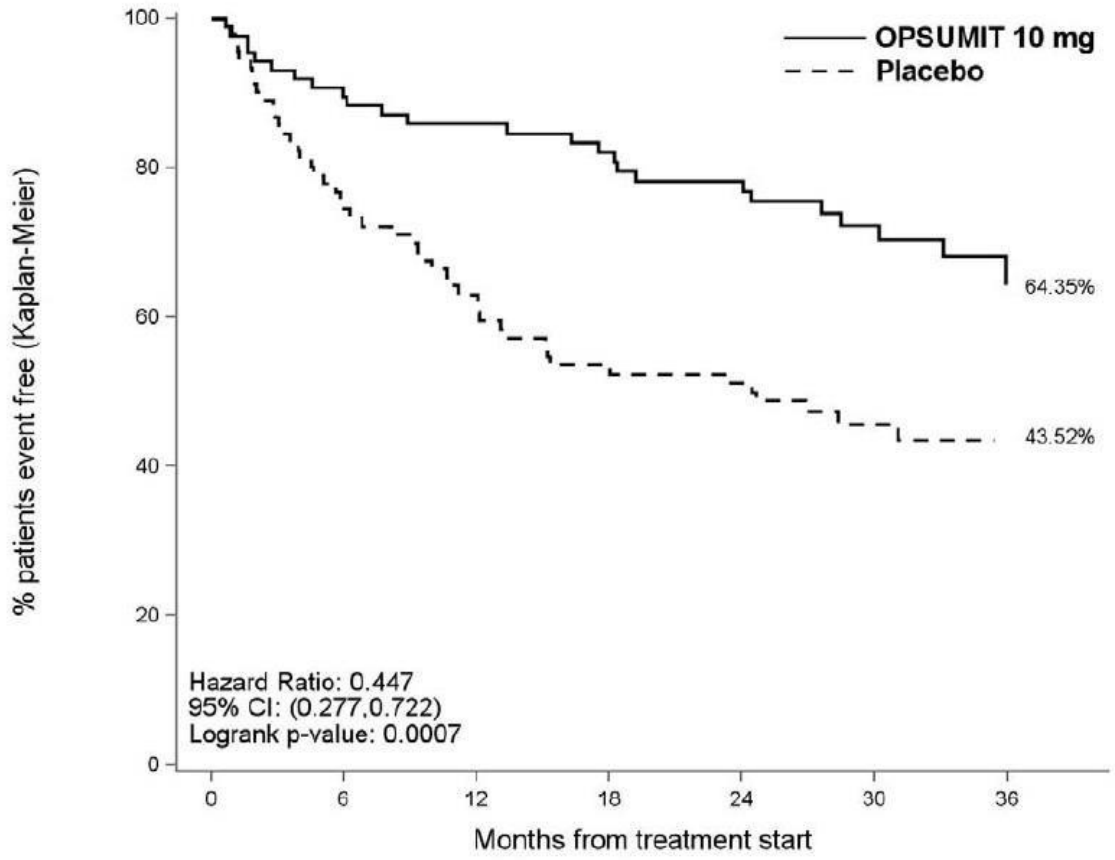
Consistent efficacy of OPSUMIT® 10 mg on the primary endpoint was seen across subgroups of age, sex, race, geographical region, etiology, by monotherapy or in combination with another PAH therapy, 6MWD, and WHO FC.

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).

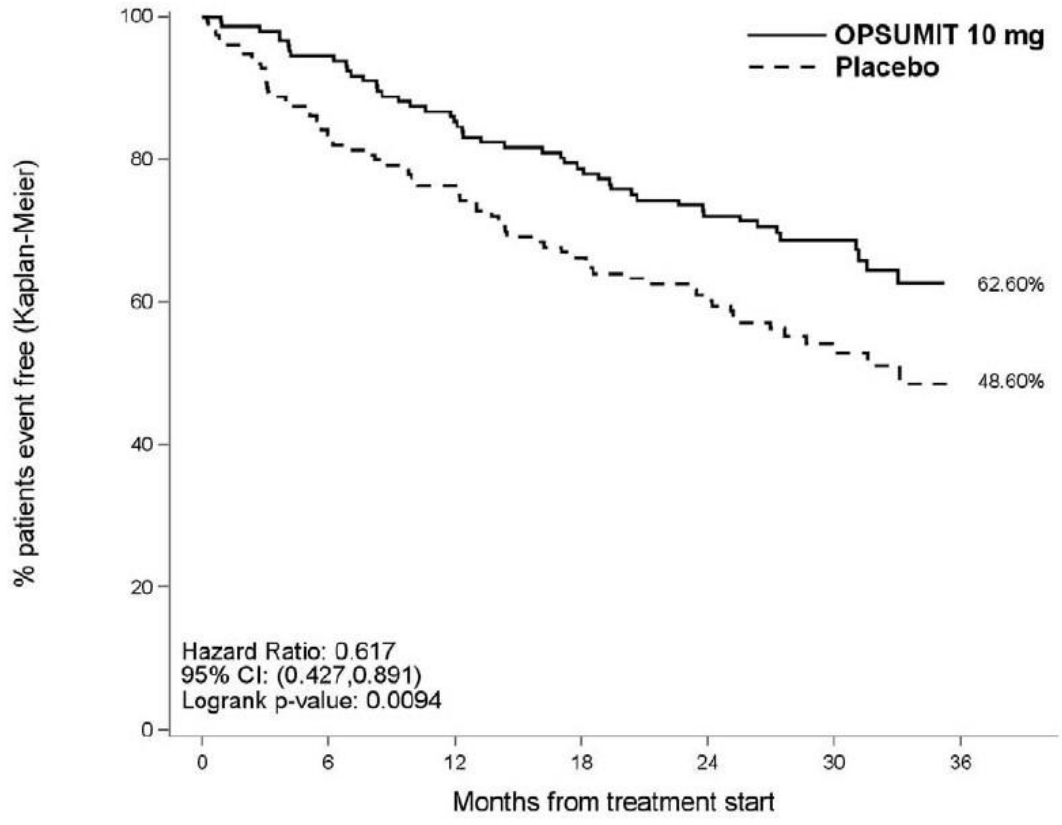
**Figure 2: Kaplan-Meier Estimates of Primary Endpoint Events up to EOT; Monotherapy at Baseline in SERAPHIN***




| 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 |

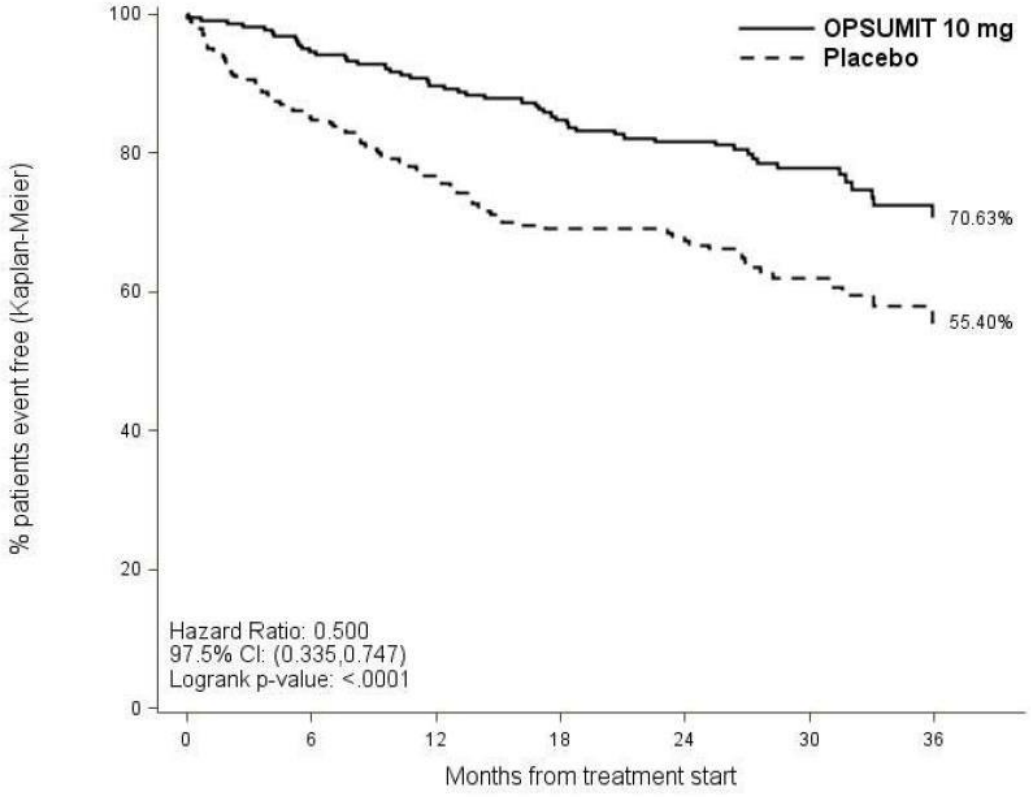
*At baseline, patients were treated with a stable dose of either phosphodiesterase inhibitors and/or inhaled/oral prostanoids.

†**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).

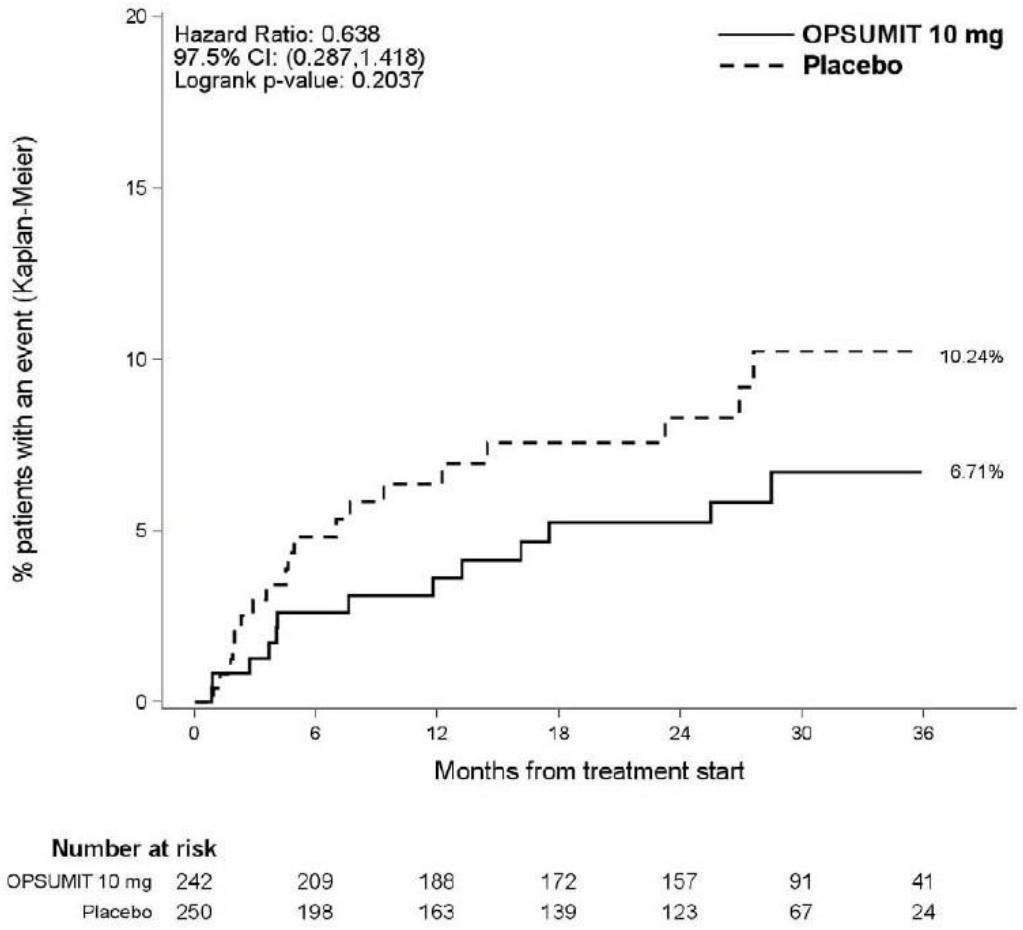
**Figure 4:** **Kaplan-Meier Estimates of Death due to PAH or Hospitalization for PAH up to EOT in SERAPHIN**




| 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.

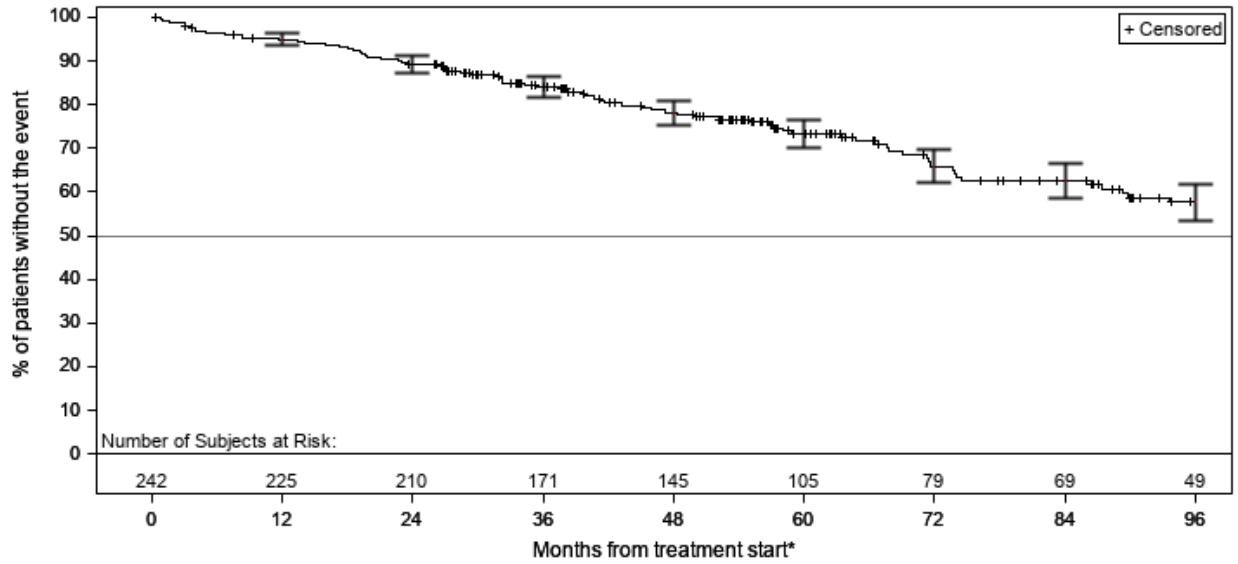
Treatment with OPSUMIT® 10 mg led to a 74% higher chance of WHO FC improvement relative to placebo (risk ratio 1.74; 97.5% CI 1.10–2.74; p=0.0063). Treatment with OPSUMIT® 10 mg led to an improvement of at least one WHO FC at Month 6 in 22% of patients compared to 13% of patients treated with placebo.

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 variables 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.

Long-term treatment of PAH
In long-term follow-up of patients who were treated with macitentan 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. Without a control group, these data must be interpreted cautiously.

**Figure 6: Kaplan-Meier estimates of time to death (all-cause) in SERAPHIN and its long-term OL extension from treatment start up to study closure, 10 mg DB/OL, Safety analysis set**




Note: 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 +- standard error.
*Treatment start corresponds to the start of double-blind macitentan 10 mg in AC-055-302

## 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.

## PRODUCT REGISTRANT

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