HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use OPSUMIT safely and effectively. See full prescribing information for OPSUMIT.

OPSUMIT® (macitentan) tablets, for oral use
Initial U.S. Approval: 2013

WARNING: EMBRYO-FETAL TOXICITY

See full prescribing information for complete boxed warning

- **Do not administer OPSUMIT to a pregnant female because it may cause fetal harm (4.1, 5.1, 8.1).**
- **Females of reproductive potential: exclude pregnancy before start of treatment, monthly during treatment, and 1 month after stopping treatment. Prevent pregnancy during treatment and for one month after treatment by using acceptable methods of contraception (2.2, 8.6).**
- **For all female patients, OPSUMIT is available only through a restricted program called the OPSUMIT Risk Evaluation and Mitigation Strategy (REMS) (5.2).**

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

- Warnings and Precautions (5.4) 03/2017

----------INDICATIONS AND USAGE----------

OPSUMIT is an endothelin receptor antagonist (ERA) indicated for the treatment of pulmonary arterial hypertension (PAH, WHO Group I) to delay disease progression. Disease progression included: death, initiation of intravenous (IV) or subcutaneous prostanoids, or clinical worsening of PAH (decreased 6-minute walk distance, worsened PAH symptoms and need for additional PAH treatment). OPSUMIT also reduced hospitalization for PAH (1.1).

----------DOSAGE AND ADMINISTRATION----------

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

----------DOSAGE FORMS AND STRENGTHS----------

- Tablet: 10 mg (3)

----------CONTRAINDICATIONS----------

- Pregnancy (4.1)

----------WARNINGS AND PRECAUTIONS----------

- ERAs cause hepatotoxicity and liver failure. Obtain baseline liver enzymes and monitor as clinically indicated (5.3).
- Fluid retention may require intervention (5.4).
- Decreases in hemoglobin (5.5).
- Pulmonary edema in patients with pulmonary veno-occlusive disease. If confirmed, discontinue treatment (5.6).
- Decreases in sperm count have been observed in patients taking ERAs (5.7).

----------ADVERSE REACTIONS----------

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

To report SUSPECTED ADVERSE REACTIONS, contact Actelion at 1-866-228-3546 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------DRUG INTERACTIONS----------

Strong CYP3A4 inducers (rifampin) reduce exposure to macitentan: avoid co-administration with OPSUMIT (7.1, 12.3).
Strong CYP3A4 inhibitors (ketoconazole, ritonavir) increase exposure to macitentan: avoid co-administration with OPSUMIT (7.2, 12.3).

----------USE IN SPECIFIC POPULATIONS----------

Nursing mothers: discontinue OPSUMIT or breastfeeding (8.3).

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide

Revised: 03/2017

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the Full Prescribing Information are not listed.

FULL PRESCRIBING INFORMATION

WARNING: EMBRYO-FETAL TOXICITY

- **Do not administer OPSUMIT to a pregnant female because it may cause fetal harm *[see Contraindications (4.1), Warnings and Precautions (5.1), Use in Specific Populations (8.1)]*.**
- **Females of reproductive potential: Exclude pregnancy before the start of treatment, monthly during treatment, and 1 month after stopping treatment. Prevent pregnancy during treatment and for one month after stopping treatment by using acceptable methods of contraception *[see Use in Specific Populations (8.6)]*.**
- **For all female patients, OPSUMIT is available only through a restricted program called the OPSUMIT Risk Evaluation and Mitigation Strategy (REMS) *[see Warnings and Precautions (5.2)]*.**

1 INDICATIONS AND USAGE

1.1 Pulmonary Arterial Hypertension

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

Effectiveness was established in a long-term study in PAH patients with predominantly WHO Functional Class II-III symptoms treated for an average of 2 years. Patients were treated with OPSUMIT monotherapy or in combination with phosphodiesterase-5 inhibitors or inhaled prostanoids. Patients had idiopathic and heritable PAH (57%), PAH caused by connective tissue disorders (31%), and PAH caused by congenital heart disease with repaired shunts (8%) *[see Clinical Studies (14.1)]*.

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dosage

The recommended dosage of OPSUMIT is 10 mg once daily for oral administration. Doses higher than 10 mg once daily have not been studied in patients with PAH and are not recommended.

2.2 Pregnancy Testing in Females of Reproductive Potential

Initiate treatment with OPSUMIT in females of reproductive potential only after a negative pregnancy test. Obtain monthly pregnancy test during treatment *[see Use in Specific Populations (8.6)]*.

3 DOSAGE FORMS AND STRENGTHS

Tablets: 10 mg, bi-convex film-coated, round, white, and debossed with "10" on one side.

4 CONTRAINDICATIONS

4.1 Pregnancy

OPSUMIT may cause fetal harm when administered to a pregnant woman. OPSUMIT is contraindicated in females who are pregnant. OPSUMIT was consistently shown to have teratogenic effects when administered to animals. If OPSUMIT is used during pregnancy, apprise the patient of the potential hazard to a fetus *[see Warnings and Precautions (5.1) and Use in Specific Populations (8.1)]*.

5 WARNINGS AND PRECAUTIONS

5.1 Embryo-fetal Toxicity

OPSUMIT may cause fetal harm when administered during pregnancy and is contraindicated for use in females who are pregnant. In females of reproductive potential, exclude pregnancy prior to initiation of therapy, ensure use of acceptable contraceptive methods and obtain monthly pregnancy tests *[see Dosage and Administration (2.2) and Use in Specific Populations (8.1, 8.6)]*.

OPSUMIT is available for females through the OPSUMIT REMS Program, a restricted distribution program *[see Warnings and Precautions (5.2)]*.

5.2 OPSUMIT REMS Program

For all females, OPSUMIT is available only through a restricted program called the OPSUMIT REMS Program, because of the risk of embryo-fetal toxicity *[see Contraindications (4.1), Warnings and Precautions (5.1), and Use in Specific Populations (8.1, 8.6)]*.

Notable requirements of the OPSUMIT REMS Program include the following:

- Prescribers must be certified with the program by enrolling and completing training.
- All females, regardless of reproductive potential, must enroll in the OPSUMIT REMS Program prior to initiating OPSUMIT. Male patients are not enrolled in the REMS.
- Females of reproductive potential must comply with the pregnancy testing and contraception requirements *[see Use in Specific Populations (8.6)]*.
- Pharmacies must be certified with the program and must only dispense to patients who are authorized to receive OPSUMIT.

Further information is available at www.OPSUMITREMS.com or 1-866-228-3546. Information on OPSUMIT certified pharmacies or wholesale distributors is available through Actelion Pathways at 1-866-228-3546.

5.3 Hepatotoxicity

ERAs have caused elevations of aminotransferases, hepatotoxicity, and liver failure. The incidence of elevated aminotransferases in the study of OPSUMIT in PAH is shown in Table 1.

Table 1 Incidence of Elevated Aminotransferases in the SERAPHIN Study

	OPSUMIT 10 mg (N=242)	**Placebo (N=249)**
>3 x ULN	3.4%	4.5%
>8 x ULN	2.1%	0.4%

In the placebo-controlled study of OPSUMIT, discontinuations for hepatic adverse events were 3.3% in the OPSUMIT 10 mg group vs. 1.6% for placebo.

Obtain liver enzyme tests prior to initiation of OPSUMIT and repeat during treatment as clinically indicated *[see Adverse Reactions (6.2)]*.

Advise patients to report symptoms suggesting hepatic injury (nausea, vomiting, right upper quadrant pain, fatigue, anorexia, jaundice, dark urine, fever, or itching). If clinically relevant aminotransferase elevations occur, or if elevations are accompanied by an increase in bilirubin >2 x ULN, or by clinical symptoms of hepatotoxicity, discontinue OPSUMIT. Consider re-initiation of OPSUMIT when hepatic enzyme levels normalize in patients who have not experienced clinical symptoms of hepatotoxicity.

5.4 Fluid Retention

Peripheral edema and fluid retention are known clinical consequences of PAH and known effects of ERAs. In the placebo-controlled study of OPSUMIT in PAH, the incidence of edema was 21.9% in the OPSUMIT 10 mg group and 20.5% in the placebo group.

Patients with underlying left ventricular dysfunction may be at particular risk for developing significant fluid retention after initiation of ERA treatment. In a small study of OPSUMIT in patients with pulmonary hypertension because of left ventricular dysfunction, more patients in the OPSUMIT group developed significant fluid retention and had more hospitalizations because of worsening heart failure compared to those randomized to placebo. Postmarketing cases of edema and fluid retention occurring within weeks of starting OPSUMIT, some requiring intervention with a diuretic or hospitalization for decompensated heart failure, have been reported *[see Adverse Reactions (6.2)]*.

Monitor for signs of fluid retention after OPSUMIT initiation. If clinically significant fluid retention develops, evaluate the patient to determine the cause, such as OPSUMIT or underlying heart failure, and the possible need to discontinue OPSUMIT.

5.5 Hemoglobin Decrease

Decreases in hemoglobin concentration and hematocrit have occurred following administration of other ERAs and were observed in clinical studies with OPSUMIT. These decreases occurred early and stabilized thereafter. In the placebo-controlled study of OPSUMIT in PAH, OPSUMIT 10 mg caused a mean decrease in hemoglobin from baseline to up to 18 months of about 1.0 g/dL compared to no change in the placebo group. A decrease in hemoglobin to below 10.0 g/dL was reported in 8.7% of the OPSUMIT 10 mg group and in 3.4% of the placebo group.

Decreases in hemoglobin seldom require transfusion. Initiation of OPSUMIT is not recommended in patients with severe anemia. Measure hemoglobin prior to initiation of treatment and repeat during treatment as clinically indicated *[see Adverse Reactions (6.1)]*.

5.6 Pulmonary Edema with Pulmonary Veno-occlusive Disease (PVOD)

Should signs of pulmonary edema occur, consider the possibility of associated PVOD. If confirmed, discontinue OPSUMIT.

5.7 Decreased Sperm Counts

Other ERAs have caused adverse effects on spermatogenesis. Counsel men about potential effects on fertility *[see Use in Specific Populations (8.6) and Nonclinical Toxicology (13.1)]*.

6 ADVERSE REACTIONS

Clinically significant adverse reactions that appear in other sections of the labeling include:

- Embryo-fetal Toxicity *[see Warnings and Precautions (5.1)]*
- Hepatotoxicity *[see Warnings and Precautions (5.3)]*
- Fluid Retention *[see Warnings and Precautions (5.4)]*
- Decrease in Hemoglobin *[see Warnings and Precautions (5.5)]*

6.1 Clinical Trial Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

Safety data for OPSUMIT were obtained primarily from one placebo-controlled clinical study in 742 patients with PAH (SERAPHIN study) *[see Clinical Studies (14)]*. The exposure to OPSUMIT in this trial was up to 3.6 years with a median exposure of about 2 years (N=542 for 1 year; N=429 for 2 years; and N=98 for more than 3 years). The overall incidence of treatment discontinuations because of adverse events was similar across OPSUMIT 10 mg and placebo treatment groups (approximately 11%).

Table 2 presents adverse reactions more frequent on OPSUMIT than on placebo by ≥3%.

Table 2 Adverse Reactions

Adverse Reaction	**OPSUMIT 10 mg (N=242)** (%)	**Placebo (N=249)** (%)
Anemia	13	3
Nasopharyngitis/pharyngitis	20	13
Bronchitis	12	6
Headache	14	9
Influenza	6	2
Urinary tract infection	9	6

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