INDICATION

OPSUMIT is an endothelin receptor antagonist (ERA) indicated for the treatment of pulmonary arterial hypertension (PAH, WHO Group I) to reduce the risks of disease progression and 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 had idiopathic and heritable PAH (57%), PAH caused by connective tissue disorders (31%), and PAH caused by congenital heart disease with repaired shunts (8%).

IMPORTANT SAFETY INFORMATION

BOXED WARNING: EMBRYO-FETAL TOXICITY

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

Please see Important Safety Information throughout and on pages 10 and 11, and accompanying full Prescribing Information, including BOXED WARNING for embryo-fetal toxicity.

WHO=World Health Organization.
The effect of OPSUMIT® (macitentan) on disease progression in patients with PAH (WHO Group I) was studied in SERAPHIN, a large (N=742), event-driven, multicenter, long-term (average treatment duration 2 years), randomized, double-blind, placebo-controlled phase 3 trial. At study baseline, 36% of patients were not using PAH-specific background therapy and 64% were using background therapy with PDE-5is or inhaled/oral prostanoids.

OPSUMIT 10 mg: n=242
Macitentan 3 mg: n=250
Placebo: n=250

Macitentan 3 mg is not an approved dose.

Trial demographics

• Patients had predominantly WHO FC II (52%) and FC III (46%) symptoms
• Etiologies included IPAH/HPAH (57%), PAH-CTD (31%), PAH-CHD with repaired shunts (8%), PAH associated with drugs and toxins (3%), and PAH-HIV (1%)
• Mean patient age was 46 years, and 77% of patients were female
• 25% of patients were recently diagnosed (<6 months) and 75% were previously diagnosed (≥6 months)

WARNINGS AND PRECAUTIONS

Embryo-fetal Toxicity and OPSUMIT REMS Program

Due to the risk of embryo-fetal toxicity, OPSUMIT is available for females only through a restricted program called the OPSUMIT REMS Program. For females of reproductive potential, exclude pregnancy prior to initiation of therapy, ensure use of acceptable contraceptive methods, and obtain monthly pregnancy tests.

Please see Important Safety Information throughout and on pages 10 and 11, and accompanying full Prescribing Information, including BOXED WARNING for embryo-fetal toxicity.

*OPSUMIT is approved in combination with PDE-5is or inhaled prostanoids, but not oral prostanoids.

FC=functional class; HPAH=heritable PAH; IPAH=idiopathic PAH; PAH-CHD=PAH associated with congenital heart disease; PAH-CTD=PAH associated with connective tissue disorders; PAH-HIV=PAH associated with human immunodeficiency virus; PDE-5i=phosphodiesterase type 5 inhibitor; SERAPHIN=Study with an Endothelin Receptor Antagonist in Pulmonary Arterial Hypertension to Improve Clinical Outcome.
2013 FDA approves OPSUMIT as the first oral once-daily ERA with long-term (average treatment duration 2 years) outcomes data²

Start with OPSUMIT® (macitentan) in monotherapy

Primary endpoint in overall population: OPSUMIT significantly reduced the risk of disease progression by 45% vs placebo¹

The primary endpoint in the SERAPHIN trial was time to the first occurrence of death or a significant morbidity event, defined as atrial septostomy, lung transplantation, initiation of IV or SC prostanoids, or clinical worsening of PAH (decrease in 6MWD of at least 15%, worsened PAH symptoms, and need for additional PAH treatment)¹,²

Summary of primary endpoint events

- **OPSUMIT 10 mg** (n=242), n (%)
- **Placebo** (n=250), n (%)

<table>
<thead>
<tr>
<th>Event</th>
<th>OPSUMIT 10 mg</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients with primary endpoint event¹</td>
<td>76 (31.4)</td>
<td>116 (46.4)</td>
</tr>
<tr>
<td>Component as first event</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Worsening PAH</td>
<td>59 (24.4)</td>
<td>93 (37.2)</td>
</tr>
<tr>
<td>Death</td>
<td>16 (6.6)</td>
<td>17 (6.8)</td>
</tr>
<tr>
<td>Initiation of IV/SC prostanoids</td>
<td>1 (0.4)</td>
<td>0 (2.4)</td>
</tr>
</tbody>
</table>

The beneficial effect of OPSUMIT was primarily attributable to a reduction in clinical worsening events (decrease in 6MWD of at least 15%, worsened PAH symptoms, and need for additional PAH treatment).²

*No patients experienced an event of lung transplantation or atrial septostomy in the placebo or OPSUMIT 10 mg treatment groups.

**Kaplan-Meier estimates of risk of first primary endpoint event in SERAPHIN**¹,²

**WARNINGS AND PRECAUTIONS**

**Embryo-fetal Toxicity and OPSUMIT REMS Program**

- 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.
- Female patients of reproductive potential must comply with the pregnancy testing and contraception requirements.
- Pharmacies must be certified with the program and must only dispense to patients who are authorized to receive OPSUMIT.

Exploratory subgroup analysis: Patients experienced a 38% incremental risk reduction when OPSUMIT was added to stable PAH-specific background therapy²,³

**Kaplan-Meier estimates of risk of first primary endpoint event**²,³

- **38% INCREMENTAL RISK REDUCTION OVER BACKGROUND THERAPY**
- **63%** OPSUMIT + background therapy
- **49%** Placebo + background therapy

**NO. OF EVENTS/NO. OF PATIENTS**

- **OPSUMIT**
  - 50/154
- **Placebo**
  - 68/154

Hepatotoxicity

- ERAs have caused elevations of aminotransferases, hepatotoxicity, and liver failure. The incidence of elevated aminotransferases in the SERAPHIN study >3 x ULN was 3.4% for OPSUMIT vs 4.5% for placebo, and >8 x ULN was 2.1% vs 0.4%, respectively. Discontinuations for hepatic adverse events were 3.3% for OPSUMIT vs 1.6% for placebo.
- Obtain liver enzyme tests prior to initiation of OPSUMIT and repeat during treatment as clinically indicated.
- Advise patients to report symptoms suggesting hepatic injury (nausea, vomiting, right upper quadrant pain, fatigue, anorexia, jaundice, dark urine, fever, or itching).

Please see Important Safety Information throughout and on pages 10 and 11, and accompanying full Prescribing Information, including BOXED WARNING for embryo-fetal toxicity.²

*OPSUMIT is approved in combination with PDE-5is or inhaled prostanoids, but not oral prostanoids.

6MWD = 6-minute walk distance; CI = confidence interval; HR = hazard ratio; IV = intravenous; SC = subcutaneous.
PVR

**Mean PVR at BL for OPSUMIT:**
924 ± 532 dyn•sec/cm²†

**Median reduction in PVR vs placebo:** 37%

Cardiac Index

**Mean cardiac index at BL for OPSUMIT:**
2.55 ± 0.85 L/min/m²†

**Median increase in cardiac index vs placebo:** 0.6 L/min/m²

---

**NO. OF EVENTS/NO. OF PATIENTS**

<table>
<thead>
<tr>
<th></th>
<th>OPSUMIT</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>50% RISK REDUCTION</td>
<td>50/242</td>
<td>84/250</td>
</tr>
<tr>
<td>HR 0.50; 97.5% CI, 0.34-0.75</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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**Summary of death due to PAH and hospitalization due to PAH**

Fifty patients (20.7%) receiving OPSUMIT 10 mg experienced an event of hospitalization for PAH or death due to PAH vs 84 patients (33.6%) receiving placebo. The components were hospitalization for PAH (OPSUMIT, 45 [18.6%]; placebo, 79 [31.6%]) and death due to PAH (OPSUMIT, 5 [2.1%]; placebo, 5 [2.0%]).

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**Analysis of death due to PAH or PAH-related hospitalization**

**Overall Population**

<table>
<thead>
<tr>
<th></th>
<th>OPSUMIT</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>50% Risk Reduction</strong></td>
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<td>84/250</td>
</tr>
<tr>
<td>HR 0.50; 97.5% CI, 0.34-0.75</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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**Subgroup of Patients on Combination Therapy**

<table>
<thead>
<tr>
<th></th>
<th>OPSUMIT</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>35% Incremental Risk Reduction Over Background Therapy</strong></td>
<td>49/154</td>
<td>107/154</td>
</tr>
<tr>
<td>HR 0.65; 95% CI, 0.42-0.99</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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**Exploratory hemodynamic substudy within SERAPHIN**

**Improvement from baseline in key measures of hemodynamics at Month 6 (OPSUMIT: n=57; placebo: n=67)**

**6MWD**

- At Month 6, 6MWD had increased by a mean of 12.5 m in the group receiving OPSUMIT 10 mg (n=242); 6MWD decreased by a mean of 9.4 m in the placebo group (n=249) (placebo-corrected mean increase of 22.0 m; 97.5% CI, 3-41; \( P=0.0078 \)).

**WHO FC**

- At Month 6, 22% of patients in the OPSUMIT 10 mg group (n=242) experienced improvement of at least 1 WHO FC vs 13% of patients in the placebo group (n=249).*

---

**Fluid Retention**

- Peripheral edema and fluid retention are known consequences of PAH and ERAs. In the pivotal PAH study SERAPHIN, edema was reported in 21.9% of the OPSUMIT group vs 20.5% for placebo.

- 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 pulmonary hypertension due to left ventricular dysfunction, more patients in the OPSUMIT group developed significant fluid retention and had more hospitalizations due to worsening heart failure compared 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.

---

**Secondary endpoints in the overall population**

**Significant improvement from baseline in 6MWD at Month 6**

- At Month 6, 6MWD had increased by a mean of 12.5 m in the group receiving OPSUMIT 10 mg (n=242); 6MWD decreased by a mean of 9.4 m in the placebo group (n=249) (placebo-corrected mean increase of 22.0 m; 97.5% CI, 3-41; \( P=0.0078 \)).

**Significant improvement from baseline in WHO FC at Month 6**

- At Month 6, 22% of patients in the OPSUMIT 10 mg group (n=242) experienced improvement of at least 1 WHO FC vs 13% of patients in the placebo group (n=249).*

**Cardiac Index**

- Mean cardiac index at BL for OPSUMIT: 2.55 ± 0.85 L/min/m²

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**Please see Important Safety Information throughout and on pages 10 and 11, and accompanying full Prescribing Information, including BOXED WARNING for embryo-fetal toxicity.**

*Combination therapy: Patients were also using background therapy with PDE-5is (61%) or inhaled/oral prostanoids (6%) at baseline. OPSUMIT is approved in combination with PDE-5is or inhaled prostanoids, but not oral prostanoids.

**Note:**

+ Combination therapy: Patients were also using background therapy with PDE-5is (61%) or inhaled/oral prostanoids (6%) at baseline. OPSUMIT is approved in combination with PDE-5is or inhaled prostanoids, but not oral prostanoids.

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OPSUMIT® (macitentan) has a well-studied safety and tolerability profile

Drug-drug interactions

<table>
<thead>
<tr>
<th>MEDICATION</th>
<th>EFFECT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Strong inducers of CYP3A4 (eg, rifampin)</td>
<td>- Significantly reduce macitentan exposure</td>
</tr>
<tr>
<td>Concomitant use of OPSUMIT with strong CYP3A4 inducers should be avoided</td>
<td></td>
</tr>
<tr>
<td>Strong inhibitors of CYP3A4 (eg, ketoconazole)</td>
<td>- Approximately double macitentan exposure</td>
</tr>
<tr>
<td>Concomitant use of OPSUMIT with strong CYP3A4 inhibitors should be avoided</td>
<td></td>
</tr>
<tr>
<td>Use other PAH treatment options when strong CYP3A4 inhibitors are needed as part of HIV treatment (eg, ritonavir)</td>
<td></td>
</tr>
</tbody>
</table>

Postmarketing experience with OPSUMIT

Because these adverse reactions are reported voluntarily during postapproval use of OPSUMIT from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

- Hypersensitivity reactions (angioedema, pruritus, and rash)
- Nasal congestion
- Elevation of liver aminotransferases (ALT, AST) and liver injury; in most cases alternative causes could be identified
- Hyperkalemia reactions (angioedema, pruritus, and rash)
- Edema/fluid retention. Cases of edema and fluid retention occurred within weeks of starting OPSUMIT, some requiring intervention with a diuretic, fluid management, or hospitalization for decompensated heart failure
- Endothelin receptor antagonists have been associated with elevations of aminotransferases, hepatotoxicity, and cases of liver failure
- Edema/fluid retention. Cases of edema and fluid retention occurred within weeks of starting OPSUMIT, some requiring intervention with a diuretic, fluid management, or hospitalization for decompensated heart failure
- Symptomatic hypotension

Additional adverse events of special interest

- Hypokalemia
- Anemia
- Transient decreases in hemoglobin
- Neutropenia
- Diarrhea
- Feminization in boys
- Siblings
- Abnormal vision
- Abnormal vision

In long-term follow-up of patients who were treated with OPSUMIT 10 mg in the placebo-controlled study (n=242) and the open-label extension study (n=182), Kaplan-Meier estimates of survival at 1, 2, 5, and 7 years were 95%, 89%, 73%, and 63%, respectively. These data are from long-term follow-up and an open-label extension study. 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.

WARRANTS AND PRECAUTIONS (continued)

- Fluid Retention (continued)
  - Monitor for signs of fluid retention after OPSUMIT initiation. If clinically significant fluid retention develops, evaluate the patient to determine the cause and the possible need to discontinue OPSUMIT.
  - Decreases in hemoglobin concentration and hematocrit have occurred following administration of other ERAs and clinical studies with OPSUMIT. These decreases occurred early and stabilized thereafter.
  - In the SERAPHIN study, OPSUMIT caused a mean decrease in hemoglobin from baseline to 18 months of about 1.0 g/dL with no change in the placebo group. A decrease in hemoglobin to below 10.0 g/dL was reported in 8.7% of the OPSUMIT group vs 3.4% for placebo. Decreases in hemoglobin seldom require transfusion.

Please see Important Safety Information throughout and on pages 10 and 11, and accompanying full Prescribing Information, including BOXED WARNING for embryo-fetal toxicity.
OPSUMIT® (macitentan) Important Safety Information

INDICATION
OPSUMIT® (macitentan) is an endothelin receptor antagonist (ERA). It is indicated for the treatment of pulmonary arterial hypertension (PAH), WHO Group II to reduce the risks of disease progression and hospitalization for PAH.

Effectiveness was established in a long-term study in PAH patients with predominantly WHO Functional Class III-IV symptoms treated for an average of 2 years. 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%).

IMPORTANT SAFETY INFORMATION

BOXED WARNING: EMBRYO-FETAL TOXICITY
- Do not administer OPSUMIT to a pregnant female because it may cause fetal harm.
- Females of reproductive potential: Exclude pregnancy before the start of treatment, monthly during treatment, and 1 month after stopping treatment. Prevent pregnancy during treatment and for one month after stopping treatment by using acceptable contraceptive methods. Prevent pregnancy during treatment and for one month after stopping treatment by using acceptable contraceptive methods, and obtain monthly pregnancy tests.
- Prescribers must be certified with the program and must only dispense to patients who are authorized to receive OPSUMIT.
- Pharmacies must be certified with the program and must only dispense to patients who are authorized to receive OPSUMIT.
- All females, regardless of reproductive potential, must undergo pregnancy testing and contraception requirements.
- Prescribers must be certified with the program by enrolling in the OPSUMIT REMS Program prior to initiating OPSUMIT. Male patients are not enrolled in the REMS.
- For all female patients, OPSUMIT is available only through a restricted program called the OPSUMIT REMS Program. For females of reproductive potential, exclude pregnancy prior to initiation of therapy, ensure use of acceptable contraceptive methods, and obtain monthly pregnancy tests.
- Notable requirements of the OPSUMIT REMS Program include:
  - Prescribers must be certified with the program by enrolling in the OPSUMIT REMS Program prior to initiating OPSUMIT.
  - Male patients are not enrolled in the REMS.
  - Prescribers of reproductive potential must comply with the pregnancy testing and contraception requirements.
- Prescribers must be certified with the program and must only dispense to patients who are authorized to receive OPSUMIT.

Hepatotoxicity
- ERAs have caused elevations of aminotransferases, hepatotoxicity, and liver failure. The incidence of elevated aminotransferases in the SERAPHIN study at >3 x ULN was 3.4% for OPSUMIT vs 4.5% for placebo, and >8 x ULN was 2.1% vs 0.6%, respectively.
- Discontinuations for hepatic adverse events were 3.3% for OPSUMIT vs 1.6% for placebo.
- Obtain liver enzyme tests prior to initiation of OPSUMIT and repeat during treatment as clinically indicated.
- 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 aminotрансferase 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.

Fluid Retention
- Peripheral edema and fluid retention are known consequences of PAH and ERAs. In the pivotal PAH study SERAPHIN, edema was reported in 21.9% of the OPSUMIT group vs 20.5% for placebo.
- 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 pulmonary hypertension due to left ventricular dysfunction, more patients in the OPSUMIT group developed significant fluid retention and had more hospitalizations due to worsening heart failure compared 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.
- Monitor for signs of fluid retention after OPSUMIT initiation. If clinically significant fluid retention develops, evaluate the patient to determine the cause and the possible need to discontinue OPSUMIT.

Hemoglobin Decrease
- Decreases in hemoglobin concentration and hematocrit have occurred following administration of other ERAs and in clinical studies with OPSUMIT. These decreases occurred early and stabilized thereafter.
- In the SERAPHIN study, OPSUMIT caused a mean decrease in hemoglobin (from baseline to 18 months) of about 1.0 g/dL in the OPSUMIT group and about 0.1 g/dL in the placebo group. A decrease in hemoglobin to below 10.0 g/dL was reported in 8.7% of the OPSUMIT group vs 3.4% for placebo. Decreases in hemoglobin seldom require transfusion.

CONTRAINDICATIONS
Pregnancy: OPSUMIT may cause fetal harm when administered to a pregnant woman. OPSUMIT is contraindicated in females who are pregnant. If OPSUMIT is used during pregnancy, advise the patient of the potential risk to a fetus.

WARNING: PULMONARY EDEMA WITH PULMONARY VEIN-OCCULSIVE DISEASE (PVOD)
- Should signs of pulmonary edema occur, consider the possibility of associated PVOD. If confirmed, discontinue OPSUMIT.

Decreased Sperm Counts
OPSUMIT, like other ERAs, may have an adverse effect on spermatogenesis. Counsel men about potential effects on fertility.

ADVERSE REACTIONS
Most common adverse reactions (more frequent than placebo by ≥3%) were anemia (13% vs 3%), nasopharyngitis/pharyngitis (20% vs 13%), bronchitis (12% vs 6%), headache (14% vs 9%), influenza (6% vs 2%), and urinary tract infection (9% vs 6%).

DRUG INTERACTIONS
- Strong inducers of CYP3A4 such as rifampicin significantly reduce macitentan exposure. Concomitant use of OPSUMIT with strong CYP3A4 inducers should be avoided.
- Strong inhibitors of CYP3A4 like ketoconazole approximately double macitentan exposure. Many HIV drugs like ritonavir are strong inhibitors of CYP3A4.
- Avoid concomitant use of OPSUMIT with strong CYP3A4 inhibitors. Use other PAH treatment options when strong CYP3A4 inhibitors are needed as part of HIV treatment.

Please see accompanying full Prescribing Information, including BOXED WARNING for embryo-fetal toxicity.
WARNINGS AND PRECAUTIONS (continued)

Hemoglobin Decrease (continued)

• 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.

Pulmonary Edema with Pulmonary Venous-occlusive Disease (PVOD)

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

Decreased Sperm Counts

OPSUMIT, like other ERAs, may have an adverse effect on spermatogenesis. Counsel men about potential effects on fertility.

For patients prescribed OPSUMIT® (macitentan), Actelion is committed to patient access support and financial assistance.

1 OPSUMIT is covered for most insured patients, with broad formulary access: ~95% covered lives nationally as of January 2019.

For commercially insured patients: Actelion Oral PAH Therapy Co-Pay Program†

• Eligible commercially insured patients will have a maximum $5 monthly co-pay for OPSUMIT, up to 13 fills or $20,000 per year
• Contact an Actelion Case Manager for more information

Open to all eligible patients, regardless of coverage: OPSUMIT Voucher Program (OVP)

• Provides a 30-day supply of OPSUMIT free of charge for eligible patients
• Medication shipped in as little as 24 hours after patient consent is confirmed by an Actelion Case Manager and a specialty pharmacy

ADVERSE REACTIONS

Most common adverse reactions (more frequent than placebo by ≥3%) were anemia (13% vs 3%), nasopharyngitis/pharyngitis (20% vs 13%), bronchitis (12% vs 6%), headache (14% vs 9%), influenza (6% vs 2%), and urinary tract infection (9% vs 6%).

DRUG INTERACTIONS

• Strong inducers of CYP3A4 such as rifampin significantly reduce macitentan exposure. Concomitant use of OPSUMIT with strong CYP3A4 inducers should be avoided.
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Please see Important Safety Information throughout and on pages 10 and 11, and accompanying full Prescribing Information, including BOXED WARNING for embryo-fetal toxicity.

*As of January 2019

† 94.5% as of January 2019 in the US for all Commercial and Medicare Part D lives.

‡ Applies to patients who have provided consent to services offered by Actelion Pathways. The Actelion Oral PAH Therapy Co-Pay Program is available for patients who are 18 or older and have commercial health insurance with co-pay/co-insurance exceeding $5 per prescription fill per product. Patients ineligible for the Actelion Oral PAH Therapy Co-Pay Program include those enrolled in Medicare, Medicaid, VA/DOD (Tricare), the Indian Health Service, or any other federal- or state-funded healthcare program, or where prohibited by law. The Actelion Oral PAH Therapy Co-Pay Program is not prescription drug coverage or insurance. Actelion reserves the right to terminate or modify this program at any time or without notice. Other terms and conditions apply.

For all female patients, OPSUMIT is available only through a restricted program called the OPSUMIT Risk Evaluation and Mitigation Strategy (REMS).

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.
**OPSUMIT® (macitentan) milestones from the past, present, and future**

The ongoing commitment of Actelion to advancing the treatment of PAH

<table>
<thead>
<tr>
<th>Year</th>
<th>Event</th>
</tr>
</thead>
<tbody>
<tr>
<td>2008</td>
<td>Recruitment for the SERAPHIN clinical trial begins</td>
</tr>
<tr>
<td>2013</td>
<td>FDA approves OPSUMIT as the first oral once-daily ERA with long-term (average treatment duration 2 years) outcomes data</td>
</tr>
<tr>
<td>2015</td>
<td>ESC/ERS Guidelines recommend OPSUMIT added to sildenafil as an option for sequential combination therapy in PAH (WHO Group I) FC II-III patients</td>
</tr>
<tr>
<td>2017</td>
<td>Open-label extension data add to the understanding of the long-term use of OPSUMIT</td>
</tr>
<tr>
<td>2019</td>
<td>More than 25,000 patients prescribed OPSUMIT in the US since approval in 2013</td>
</tr>
<tr>
<td><strong>Ongoing</strong></td>
<td>Continued commitment to PAH through:</td>
</tr>
<tr>
<td></td>
<td>• Patient support</td>
</tr>
<tr>
<td></td>
<td>• Clinical research including 7 ongoing phase 2 and 3 clinical trials through 2023</td>
</tr>
</tbody>
</table>

**IMPORTANT SAFETY INFORMATION**

**BOXED WARNING: EMBRYO-FETAL TOXICITY**

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

*As of January 2019.*

**References:**
2. OPSUMIT [prescribing information]. South San Francisco, CA: Actelion Pharmaceuticals US, Inc.

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