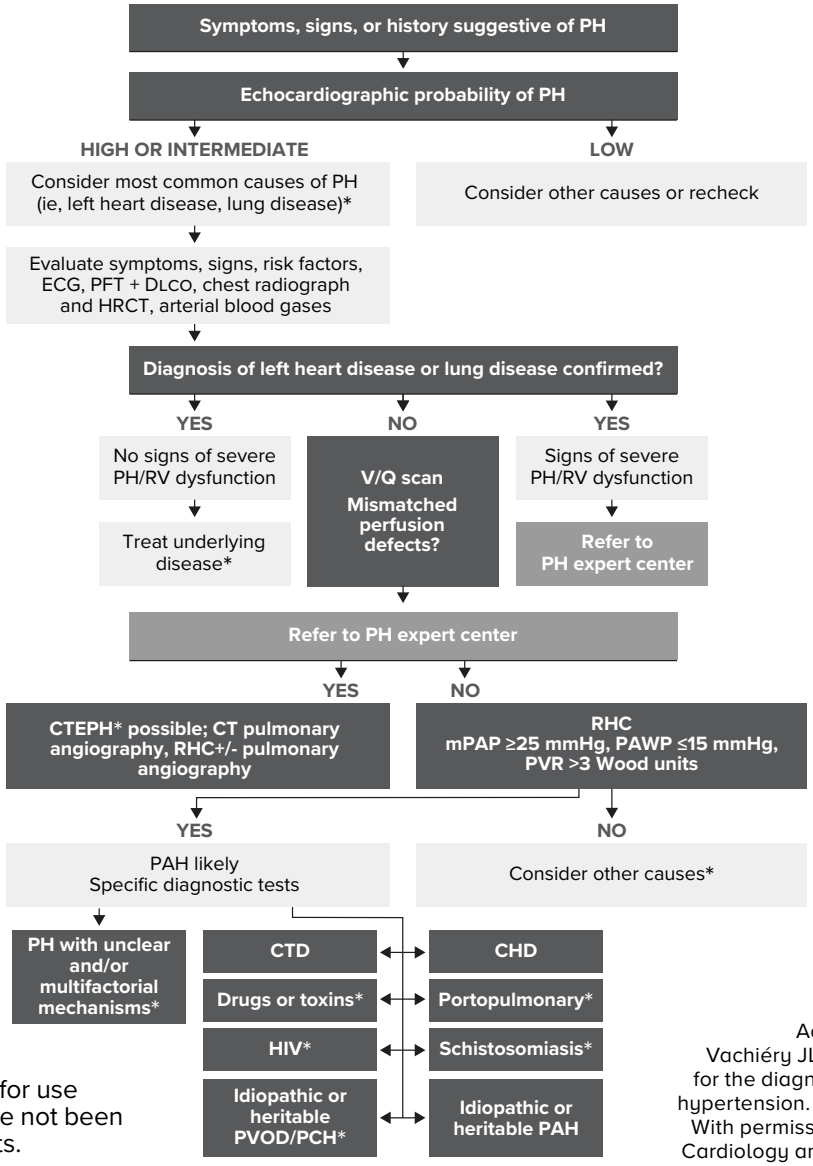
What steps can be taken if you suspect PAH?

The 2015 ESC/ERS Guidelines recommend diagnosing PAH through a stepwise approach

Follow the chart below to assist in the potential identification of PAH in your patients.

OPSUMIT® IS ONLY INDICATED FOR PAH (WHO GROUP I, FC II-III)

Diagnostic algorithm for PH from the 2015 ESC/ERS Guidelines[1]



*OPSUMIT® is not indicated for use and safety and efficacy have not been established in these patients.

Adapted from Galiè N, Humbert M, Vachiéry JL, et al. 2015 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension. *Eur Respir J.* 2015;46(4):903-975. With permission from the European Society of Cardiology and European Respiratory Society.

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 on pages 2 and 3 and please see full Prescribing Information, including BOXED WARNING.

IMPORTANT SAFETY INFORMATION (continued)

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.

Hypersensitivity: OPSUMIT® is contraindicated in patients with a history of a hypersensitivity reaction to macitentan or any component of the product.

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.

Notable requirements of the OPSUMIT® REMS Program include:

- 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.
- Pharmacies 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 >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).
- 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.

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 vs 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.
- 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 Veno-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.

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%).

IMPORTANT SAFETY INFORMATION (continued)

DRUG INTERACTIONS

- Strong inducers of CYP3A4 such as rifampin 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.
- Moderate dual inhibitors of CYP3A4 and CYP2C9 such as fluconazole and amiodarone are predicted to increase macitentan exposure. Avoid concomitant use of OPSUMIT® with moderate dual inhibitors of CYP3A4 and CYP2C9.
- Concomitant treatment of both a moderate CYP3A4 inhibitor and moderate CYP2C9 inhibitor with OPSUMIT® should also be avoided.

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Please see full Prescribing Information, including BOXED WARNING.

CHD=congenital heart disease; CT=computed tomography; CTD=connective tissue disease; CTEPH=chronic thromboembolic pulmonary hypertension; D_{LCO}=diffusing capacity of the lungs for carbon monoxide; ECG=electrocardiogram; ERS=European Respiratory Society; ESC=European Society of Cardiology; FC=Functional Class; HIV=human immunodeficiency virus; HRCT=high-resolution CT; mPAP=mean pulmonary arterial pressure; PAH=pulmonary arterial hypertension; PAWP=pulmonary artery wedge pressure; PCH=pulmonary capillary hemangiomatosis; PFT=pulmonary function tests; PH=pulmonary hypertension; PVOD=pulmonary veno-occlusive disease; PVR=pulmonary vascular resistance; RHC=right heart catheterization; RV=right ventricular; V/Q=ventilation/perfusion; WHO=World Health Organization.

Reference: 1. Galiè N, Humbert M, Vachiéry J-L, et al. 2015 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension: The Joint Task Force for the Diagnosis and Treatment of Pulmonary Hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS). *Eur Respir J*. 2015;46(4):903-975.