Opsynvi® (macitentan/tadalafil) – New orphan drug approval

- On March 25, 2024, Johnson & Johnson announced the FDA approval of Opsynvi (macitentan/tadalafil), for the chronic treatment of adults with pulmonary arterial hypertension (PAH, WHO Group I and WHO Functional Class [FC] II-III).
    - Individually, macitentan reduces the risk of clinical worsening events and hospitalization, and tadalafil improves exercise ability.
- PAH is a rare, progressive blood vessel disorder characterized by the constriction of small pulmonary arteries and elevated blood pressure in the pulmonary circulation that eventually leads to right heart failure.
    - An estimated 500 to 1,000 new cases of PAH are diagnosed each year in the U.S.
- Opsynvi contains macitentan, an endothelin receptor antagonist (ERA), and tadalafil, a phosphodiesterase 5 (PDE5) inhibitor.
    - Both macitentan and tadalafil are available as single-ingredients for PAH.
    - Opsynvi is the first fixed-dose combination containing an ERA and PDE5 inhibitor.
- The efficacy of Opsynvi was established in a double-blind, adaptive, randomized, active-controlled study in 187 patients with PAH (WHO FC II–III). Patients were randomized to receive Opsynvi, macitentan monotherapy, or tadalafil monotherapy. The primary endpoint was change from baseline in pulmonary vascular resistance (PVR) (expressed as the ratio of geometric means of end of double-blind treatment to baseline) vs. the individual component monotherapies after 16 weeks.
    - Treatment with Opsynvi resulted in a 29% reduction in PVR as compared to macitentan, and a 28% reduction in PVR as compared to tadalafil ($p < 0.0001$ for both comparisons).
- Opsynvi carries a boxed warning for embryo-fetal toxicity.
    - For all female patients, Opsynvi is available only through a restricted program called the Macitentan-Containing Products Risk Evaluation and Mitigation Strategy (REMS).
- Opsynvi is contraindicated in:
    - Pregnancy
    - Patients with a history of a hypersensitivity reaction to macitentan, tadalafil, or any component of the product
    - Patients who are using any form of organic nitrate, either regularly or intermittently
    - Patients with coadministration of GC stimulators such as riociguat.
- Additional warnings and precautions for Opsynvi include hepatotoxicity; hypotension; decreased hemoglobin; worsening pulmonary veno-occlusive disease; visual loss; hearing impairment; fluid retention; combination with other PDE5 inhibitors; decreased sperm count; and prolonged erection.
- The most common adverse reactions (≥ 10%) with Opsynvi use were edema/fluid retention, anemia, and headache/migraine.

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- For patients who are treatment-naïve to any PAH specific therapy or transitioning from ERA monotherapy, the recommended starting dose of Opsynvi is one 10 mg/20 mg tablet taken orally once daily with or without food for one week. If tolerated, Opsynvi should be up titrated to one 10 mg/40 mg tablet taken orally once daily with or without food as the maintenance dose.

- For patients transitioning from PDE5 inhibitor monotherapy or PDE5 inhibitor and ERA therapy in combination, the recommended dose of Opsynvi is one 10 mg/40 mg tablet taken orally once daily.

- Johnson & Johnson's launch plans for Opsynvi are pending. Opsynvi will be available as tablets containing macitentan 10 mg/tadalafil 20 mg and macitentan 10 mg/tadalafil 40 mg.

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