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IN BRIEF

Embryotoxicity REMS Removal for Endothelin Receptor Antagonists

The FDA has removed the Risk Evaluation and Mitigation Strategy (REMS) requirement for the endothelin receptor antagonists ambrisentan (*Letairis*, and generics), bosentan (*Tracleer*, and generics), macitentan (*Opsumit,* and generics; *Opsynvi*), and aprocitentan *(Tryvio)* and the endothelin receptor antagonist and angiotensin II receptor antagonist sparsentan *(Filspari)* that was initially implemented because of a possible risk of embryofetal toxicity.[1]

Ambrisentan, bosentan, and macitentan are FDA-approved for treatment of pulmonary arterial hypertension (PAH), aprocitentan is approved for treatment of hypertension, and sparsentan is approved to slow kidney function decline in patients with primary immunoglobulin A nephropathy (IgAN).

The embryofetal toxicity REMS requirement for these drugs was based on studies in pregnant animals. Removal of the REMS requirement was based on an analysis in humans showing that exposure to an endothelin receptor antagonist during pregnancy was not associated with the congenital malformations observed in animal studies.[1]

All of these drugs still include a boxed warning in their labels about the risk of embryofetal toxicity associated with their use in animals. Pregnancy should be excluded before starting treatment with an endothelin receptor antagonist, and women with reproductive potential should use effective contraception while taking any of these drugs.

Because of increased risks of hepatotoxicity associated with their use, bosentan and sparsentan are still only available through a REMS program. ■

1. FDA Endothelin Receptor Antagonist REMS Information. FDA removes REMS requirements for embryofetal toxicity risk from all endothelin receptor antagonist medicines. July 3, 2025. Available at: https://bit.ly/44SAm6U. Accessed August 27, 2025.

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