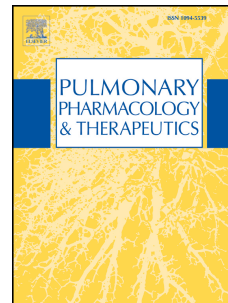


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Modeling of pharmacokinetics, efficacy, and hemodynamic effects of macitentan in patients with pulmonary arterial hypertension

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1 Modeling of pharmacokinetics, efficacy, and 2 hemodynamic effects of macitentan in patients with 3 pulmonary arterial hypertension

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10 Abstract

11 **Background:** Macitentan is the first endothelin receptor antagonist with demonstrated efficacy
12 on morbidity and mortality in pulmonary arterial hypertension (PAH) in the pivotal study
13 SERAPHIN.

14 **Methods:** The pharmacokinetics (PK) of macitentan and its active metabolite, ACT-132577,
15 were characterized in a population model. Efficacy and hemodynamics (pharmacodynamics, PD)
16 were related to PK based on PK/PD modeling.

17 **Results:** Sex, age, and body weight influenced the PK to a statistically significant extent. Model-
18 based simulations showed that these variables are clinically not relevant. Concomitant use of
19 PAH medication (PDE-5 inhibitors) did not influence macitentan trough concentration to a
20 relevant extent.

21 Efficacy and hemodynamics showed clear differences from placebo for macitentan
22 concentrations on 3 and 10 mg with consistent superior effects for 10 mg. After 6 months, PAH

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