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Title: Lack of relevant pharmacokinetic interactions between the new dual endothelin receptor antagonist macitentan and sildenafil in healthy subjects

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Body: Macitentan, a new potent, dual endothelin receptor antagonist (ERA), is a potential treatment for pulmonary arterial hypertension (PAH). As PAH treatment may involve combination therapy of an ERA with sildenafil, the mutual pharmacokinetic (PK) interactions were investigated using a randomised, 3-way crossover study design (AC-055-106). Twelve healthy male subjects were treated as follows: A) macitentan alone for 4 days (loading dose of 30 mg, thereafter 10 mg o.d.), B) sildenafil alone for 4 days (20 mg t.i.d. on Days 1–3 and 20 mg o.d. on Day 4), C) treatments A and B combined. Plasma concentrations of macitentan and its pharmacologically active metabolite ACT-132577 (A and C) and sildenafil and its N-desmethyl metabolite (B and C) were measured on Day 4. Tolerability was also assessed. The PK of macitentan was not affected (geometric mean ratios for C_{max} and AUC_{τ} close to 1.0 with 90% confidence intervals within 0.8–1.25 bioequivalence limits) by sildenafil while the exposure to ACT-132577 decreased (C_{max} 0.82 [0.76–0.89]; AUC_{τ} 0.85[0.80–0.91]). Exposure to sildenafil increased in the presence of macitentan (C_{max} 1.26 [1.07–0.89]; AUC_{τ} 1.15 [0.94–1.41]), while that to N-desmethylsildenafil was unaffected. All treatments were well tolerated but combined treatment resulted in a higher incidence of adverse events (most commonly headache) and decreased diastolic blood pressure. As no clinically relevant PK interactions were observed between macitentan and sildenafil, dose adjustment of either compound is not necessary during combined treatment.