

Reproductive and Developmental Toxicity Studies of Sapropterin Hydrochloride in Rats and Rabbits

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Summary

Sapropterin hydrochloride (SUN0588), a tetrahydrobiopterin, is a natural cofactor for phenylalanine hydroxylase (PAH). The reproductive toxicity and developmental toxicity of this compound were assessed following oral administration to Wistar rats and New Zealand White rabbits. A fertility study (administration before mating and during early pregnancy), a teratogenicity study (administration during organogenesis), and a peri- and post-natal study (administration during the late stage of gestation and during lactation) were conducted in rats. A teratogenicity study (administration during organogenesis) was also conducted in rabbits. The dosage levels were 4, 40 and 400 mg/kg/day in the three rat studies, and 6, 60 and 600 mg/kg/day in the rabbit study.

In rats, no effect on the reproductive performance of the parent animals or development of F1 offspring was observed at any dose tested, and the no observable effect level (NOEL) of SUN0588 for general toxicity and/or reproductive function of male and female rats, as well as for the growth and development of fetuses and offspring, was estimated to be 400 mg/kg/day.

In rabbits, decreases in body weight and in food and water consumption of dams were observed after the first administration of SUN0588 at the dose of 600 mg/kg/day, but no effect on fetal development was observed at any dose tested. NOELs were estimated to be 60 mg/kg/day for general toxicity in dams and 600 mg/kg/day for fetal development.

Key words

Sapropterin hydrochloride, Tetrahydrobiopterin cofactor, Reproductive and developmental toxicity studies, Rat, Rabbit