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Subacute toxicities and toxicokinetics of CJ-10882, a type IV phosphodiesterase inhibitor, after 4-week repeated oral administration in dogs

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The subacute toxicity and toxicokinetics of a type IV phosphodiesterase inhibitor, CJ-10882, were evaluated after single (on the 1st day) and 4-week (on the 27th day) oral administration of the drug, in doses of 0 (to serve as a control), 2, 10 and 50 mg/kg/d, to male and female dogs (n = 3 for male and female dogs for each dose). During the test period, clinical signs, mortality, body weight, food consumption, ophthalmoscopy, urinalysis, hematology, serum biochemistry, gross findings, organ weight and histopathology were examined. The 4-week repeated oral doses of CJ-10882 resulted in salivation, vomiting, and atrophy of the thymus. The target organ was determined to be the thymus. The absolute toxic dose was 50 mg/kg/d and the level at which no adverse effects were observed was 10 mg/kg/d for male and female dogs.There were no significant gender differences in the pharmacokinetic parameters of CJ-10882 for each dose after both single and 4-week oral administration. The pharmacokinetic parameters of CJ-10882 were dose independent after a single oral administration; the time to reach a peak plasma concentration (Tmax) and the dose-normalized area under the plasma concentrationtime curve from time zero to 8 h in plasma (AUC08h) were not significantly different among three doses. The accumulation of CJ-10882 after 4-week oral administration was not notable at the toxic dose of 50 mg/kg/d. For example, after 4-week administration, the dose-normalized AUC08h value at 50 mg/kg/d (0.132 mg h/ml) was not significantly greater than that at 10 mg/kg/d (0.131 mg h/ml). After 4-week oral administration, the dose-normalized

Cmax and AUC08h at 50 mg/kg/d were not significantly higher and greater, respectively, than those after the single oral administration.

Key words: CJ-10882; subacute toxicities; toxicokinetics; 4-week oral administration; dogs