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Developmental Toxicity Evaluation of CKD-602, a New Camptothecin Anticancer Agent, in Rats

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CKD-602 is a newly developed camptothecin anticancer agent. Preclinical studies suggest that it may have greater antitumor activity and lower toxicity than other camptothecin anticancer agents. The potential of CKD-602 to induce embryotoxicity was investigated in the Sprague-Dawley rat. One hundred mated females (sperm in vaginal lavage = day 0) were distributed among three treatment groups and a control group. CKD-602 was administered intravenously at dose levels of 0 (vehicle), 0.005, 0.02 and 0.08 mg/kg/d to pregnant rats from days 6 to 15 of gestation. All dams were subjected to the caesarean section on day 20 of gestation. There were no signs of maternal toxicity or embryotoxicity at 0.005 and 0.02 mg/kg/d. At 0.08 mg/kg/d, reduced food intake, suppressed body weight and increased weight of spleen were observed in dams. An increase in the resorptions and dead fetuses, a decrease in litter size, fetal and placental weights were also found. In addition, various types of external, visceral and skeletal malformations occurred. Characteristic malformations included absent eye buldge, agnathia, dilated cerebral ventricle, anophthalmia, absent thoracic centrum, fused vertebral arch, fused rib, among others. Visceral and skeletal variations were observed. Retarded ossification of several skeletal districts and delayed ossification of sternebrae, metatarsals and sacrocaudal vertebrae were also observed. The results show that CKD-602 is embryotoxic and teratogenic at a minimally maternally toxic dose, i.e. at 0.08 mg/kg/d in rats. The no-observed-adverse-effect levels of CKD-602 are considered to be 0.02 mg/kg/d for dams and fetuses, respectively, in developmental toxicity study performed using rats.

Keyword : CKD-602, Anticancer agent, Developmental toxicity evaluation, Rats