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PRECLINICAL TOXICITY STUDY OF A NEW PHOSPHODIESTERASE-5 INHIBITOR (II) FOUR-WEEK SUBACUTE TOXICITY STUDY IN RATS

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Toxic effects of a new phosphodiesterse-5 inhibitor, DA-8159, were investigated in Sprague-Dawley rats by repeated oral administration. Four groups of 10 male and 10 female rats were treated with DA-8159 at a dose of 0, 40, 80, or 320 mg/kg/day for 4 weeks. Clinical signs such as partially-closed eyes, decreased locomotor activity, prostration, teeth grinding and chromodacryorrhea were observed at the dose of 80mg/kg and 320mg/kg with a dose-relation. Reduced body weight gain were noted only in female rats of the highest group. There were no remarkable changes in food and water consumption, ophthalmoscopy, urinalysis and blood biochemical analysis attributed to the DA-8159 treatment. Hematology showed an increase in numbers of WBC and change in RBC related-parameters at 80 and 320mg/kg groups. At necropsy, there were no drug-related changes in all animals. Absolute and relative weights of liver, spleen and lung in female, and lung in male increased at the highest group. Histopathological examination revealed cholangiofibrosis and inflammation in the liver, infiltration of pulomary macrophage and alveolar wall thickening, megakaryocytic proliferation and the increase of hematopoiesis in bone marrow, and extrahematopoiesis in the spleen, which was more predominant in 320mg/kg group. In conclusion, the target organs of DA-8159 in 4-week repeated toxicity to rats were liver, bone marrow, spleen, lung and blood cells. Under the current test condition, the NOAEL was estimated to be 20mg/kg/day.