SAFETY EVALUATION OF UBIQUINOL IN RATS, DOGS AND HUMANS

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Ubiquinol (a reduced form of coenzyme Q₁₀) is the two-electron reduction product of ubiquinone (a oxidized form of coenzyme Q₁₀) and functions as an antioxidant in both mitochondria and lipid membranes. As part of the safety evaluation of ubiquinol, the genotoxic potential of ubiquinol was previously examined in a reverse mutation assay, chromosomal aberration test and bone marrow micronucleus test, and all results were negative. In this presentation, we report on two subchronic toxicity studies with rats and dogs and a clinical safety study in healthy subjects. These series of studies were conducted using KANEKA QH™ as the test article. KANEKA QH™ is the brand name of ubiquinol. In humans and most mammals, including dogs, the predominant form of coenzyme Q is coenzyme Q₁₀, whereas the primary form in mice or rats is coenzyme Q₉, which contains 9 isoprenoid units. Therefore, the subchronic toxicity of ubiquinol was evaluated and compared in Sprague-Dawley rats and beagle dogs. In the initial rat study, males and females were given ubiquinol at doses of 0, 300, 600 and 1200 mg/kg/day and ubiquinone as reference at 1200 mg/kg/day by gavage for 13 weeks. This was followed by the second study, where females were given doses of 75, 150, 200 or 300 mg/kg/day in order to determine the no-observed-adverse-effect level (NOAEL). In the dog study, the test material was administered to males and females at dose levels of 150, 300, and 600 mg/kg/day, and ubiquinone was included at 600 mg/kg/day. General condition, mortality, body weight, food and water consumption, ophthalmoscopy, urinalysis, hematology, blood biochemistry, gross findings, organ weight, and histopathological findings were examined.

There were no deaths or test article-related effects on body weight, food consumption, ophthalmology, urinalysis or hematology in rats. Slight prolongations of prothrombin and partial activated thromboplastin times were seen in male rats given 1200 mg/kg/day ubiquinol. Histopathological examinations revealed test article-related effects on the liver in female rats but not in male rats. Microgranuloma and focal necrosis with accumulation of macrophages in the liver were observed in the ubiquinol groups at 300 mg/kg/day and above. These findings were accompanied by increases in blood chemistry enzymes (ASAT, ALAT, and LDH), which suggested hepatotoxicity. As a result, microgranuloma and focal necrosis were judged to be the only adverse effects induced by the test article based on their
incidence and pathological characteristics, although they were not considered to be direct hepatic damage because no single hepatocyte necrosis was observed. These changes were thought to be the result of excessive uptake of ubiquinol by the liver, which exceeded the capacity for adaptive response to xenobiotics. Based on these findings, the NOAEL for ubiquinol in rats was estimated to be 600 mg/kg/day for males and 200 mg/kg/day for females.

In dogs, there were no deaths or ubiquinol-related toxicity findings during the administration period. No test article-related effects were observed in body weight, food consumption, ophthalmology, electrocardiogram, urinalysis, hematology, or blood chemistry. Histopathological examination revealed no effects attributable to administration of ubiquinol in any organs examined. Based on these findings, the NOAEL for ubiquinol in male and female dogs was estimated to be more than 600 mg/kg/day.

In the clinical safety study, 15 healthy volunteers (5 males and 5 females for the 150 mg dose and 5 males for the 300 mg dose) and 80 healthy volunteers (10 males and 10 females received placebo, and three groups of 20 each received 90 mg, 150 mg, and 300 mg daily doses of ubiquinol) were enrolled in the single-dose study and 4-week multiple-dose study, respectively. Standard laboratory tests for safety including hematology, blood clotting test, urinalysis and blood chemistry as well as physical examination, vital signs and electrocardiography were performed before administration on the day of treatment (day 0) as baseline and day 2 in the single-dose study. The same laboratory tests were performed before treatment, 2 and 4 weeks after starting treatment, and 2 weeks after completion of treatment in the 4-week multiple-dose study. No safety concerns or adverse events were noted on standard laboratory tests in both the single- and 4-week multiple-dose studies.

While the NOAEL for ubiquinol in female rats was lower than that established in dogs and male rats, it was shown that female rats exhibit a higher sensitivity to the accumulation of coenzyme Q$_{10}$ in the liver, a trend that likely results from gender-dependent differences in the expression of hepatic enzymes. As noted above, the predominant form of coenzyme Q in rats is coenzyme Q$_9$, and therefore the dog has a closer resemblance to humans with respect to endogenous coenzyme Q$_{10}$. The clinical dose of 300 mg/man (equivalent to 6 mg/kg/day for a person weighing 50 kg) used in this study is 1/100 of the NOAEL in the dog study. In conclusion, the chronic use of ubiquinol in dietary supplements at a daily dose level of up to 300 mg/man is expected to be safe in the clinical setting.

Keywords: coenzyme Q$_{10}$, ubiquinol, no-observed-adverse-effect level, safety, toxicity