PHARMACHEM LABORATORIES

DSM

Teavigo™

Green tea extract containing ≥90% of
Epigallocatechin gallate, a tea polyphenol (Ro 26-7624/000)

Statement on Safety for Use in Humans

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The safety data package on EGCG includes studies on genotoxicity, acute and repeated-dose toxicity, preliminary and definitive studies on reproduction/ developmental toxicity, studies on skin irritation / sensitization and ADME.

Interaction of EGCG with food constituents can decrease its systemic exposure in terms of AUC and peak concentrations (C_{max}). EGCG plasma concentration profiles were higher in animals fasted before administration of the compound when compared to pre-fed animals.

Relevant interactions of EGCG with concomitantly administered compounds / drugs metabolized mainly by cytochromes P450 are not to be expected.

A battery of mutagenicity studies was conducted with EGCG. No mutagenic activity was observed in one *in vitro* and three *in vivo* tests. Weak positive responses were observed in three *in vitro* tests. These positive responses are considered to be related to a mechanism observed also with other widely used nutrients, and are not considered to be relevant to human safety.

A thirteen-week study was done in rats with EGCG administered in the feed, at doses of 0, 50, 150 and 500 mg/kg body weight / day. The no-observed-effect level (NOEL) was 500 mg/kg.

A first 13-week study was done in dogs with EGCG administered once a day by capsule, four hours before the daily feeding, at doses of 0, 50, 150 and 500 mg/kg body weight / day. The No-Observable Adverse Effect Level (NOAEL) in this study in *fasted* dogs was 50 mg / kg body weight.

A second 13-week oral (capsule) toxicity study was conducted in dogs dosed twice a day, each time *after feeding*. The doses tested were 0, 50, 300 and 500 mg / kg body weight / day. Four dogs suffered accidental injuries and died or were found moribund (one high dose and three mid dose dogs) during the course of the study. There was no indication for a relationship of the morbidity/mortality to treatment. Treatment-related adverse effects observed during the study were vomiting and diarrhea. These clinical signs are early detectable in humans (nausea) and would be easily manageable. These findings have not been reported in human clinical trials at high doses (exposure) under fasted conditions.

EGCG did neither show a teratogenic potential up to the limit dose of 1000 mg/kg body weight nor a negative impact on reproductive performance up to 200 mg/kg body weight.

Protection measures against direct skin contact and inhalation of EGCG are recommended for workers' safety and product handling due to a potential for skin sensitization in man.

Considerations on safe daily doses in humans are based on the 13-week oral toxicity studies in rats and dogs with no evidence of organ toxicity at the highest doses tested (500 mg/kg/day). Given the average body weight (used for this type of calculations) of 60 kg for an adult person and a 100 fold margin of uncertainty (10x for extrapolation animal to man and 10x for interindividual differences in humans) daily doses of up to 300 mg are considered safe. Having in mind the design of the toxicity studies in dogs it is recommended to divide daily doses in two or more portions and to not take the product on an empty stomach.

The lower no effect level of 200 mg/kg body weight in the reproduction study arose due to an effect on suckling rats in the higher dosage groups. In the absence of information on EGCG secretion in milk, this may indicate that breast feeding women in particular should stay within a daily intake of 120 mg (200 mg/kg x 60 kg/100 = 120 mg). There was no indication that the newly weaned rats were more sensitive to EGCG, however the daily intake for children should be adjusted to take into account their lower body weight.

Roche Vitamins Ltd. has conducted several human studies in apparently healthy male volunteers with EGCG to evaluate safety and key pharmacokinetic parameters in man: a single ascending dose (SAD) and a multiple ascending dose (MAD). These three human studies translate into a total of 135 individuals which were exposed to EGCG up to an intake of 1600 mg/d (SAD) and of 800 mg/d up to 10 consecutive days (MAD). In these human studies no treatment-related clinically relevant adverse events or changes in clinical laboratory or vital signs were reported. EGCG was very well tolerated. No subjective complaints of gastric irritation were reported in these human studies even though EGCG was given in the fasting state.

As it is known from generally available literature that polyphenols in food and in tea in particular can reduce non-heme iron absorption, another human study was performed to investigate the effect of EGCG on fractional non-heme iron absorption. This study in 30 apparently healthy female volunteers was designed as a worse case scenario by selecting women with low iron stores. Two daily dosages were tested: 150 and 300 mg. The results showed that a daily dose of 300 mg EGCG reduced fractional non-heme iron absorption to a statistically significant extent, whereas a daily dose of 150 mg did not significantly affect non-heme iron absorption. The extent to which 300 mg of EGCG reduced fractional non heme iron absorption was much lower in this study than reported in the literature for black tea or similar compounds.

In addition, safety and tolerability and standard parameters of clinical chemistry of EGCG has been evaluated in the studies investigating various markers of

efficacy in humans. In all these studies EGCG was tolerated very well and considered safe at the intake given which was in general 300mg/d (one short term study 600 mg/d, one 8 week study 800 mg/d). The longest human study spanning 84 days at a daily intake of 300 mg EGCG is also without any clinically significant findings on safety and clinical chemistry which includes the assessment of liver enzymes.

However, it should be noted that in two patients who took a product aiding in weight management hepatitis was reported and judged by the consulted physician as possibly related to the intake of Teavigo. In these two cases Teavigo was recommended to be taken with or after meals 2 x 150 mg per day. After discontinuation of the product the individuals showed a rapid recovery. In this context a review published by the US Pharmacopeia (D.N. Sarma et al 2008, Drug Safety 31 (6), 469-484) on the "Safety of Green Tea Extracts" is worthy to mention. The paper reports 34 cases concerning undesired effects on the liver by various green tea extract products. Interestingly, also drinking of 4-6 cups of green tea has been reported to lead to hepatotoxicity (M. Jimenez-Saenz et al 2006, J. Hepatol 44, 616-617), which supports the view that catechins have a potential to lead in some individuals to hepatotoxicity even at an intake which millions of people consume on a daily basis and have been consuming for centuries (as the mechanism of this toxic liver response is not known and the incidence is considered very rare it is called an idiosyncratic reaction).

In summary, the results of the human studies show that the use of TEAVIGO in humans is considered to be safe and that TEAVIGO is bioavailable in humans. Iron status is unlikely to be adversely affected by TEAVIGO as an intake of 150 mg per day did not significantly change non-heme iron absorption even in individuals with poor iron status. However it is recommended that a maximum daily dose of 2 x 150 mg should not be exceeded and Teavigo should not be taken on an empty stomach. In view of the possibility of an idiosyncratic hepatotoxicity we recommend the following cautionary statement when using Teavigo in dietary supplements: "Take with food. Discontinue use and consult a healthcare practitioner if you have a liver disorder or develop symptoms of liver trouble such as abdominal pain, dark urine, or jaundice."

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