APPLICATION FOR THE APPROVAL OF UROLITHIN A AS A NOVEL FOOD INGREDIENT IN THE EUROPEAN UNION

Pursuant to

Regulation (EU) No 2015/2283 of the European Parliament and of the Council of 25 November 2015 Concerning Novel Foods and Novel Food Ingredients

NON-CONFIDENTIAL SUMMARY OF THE APPLICATION

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SUMMARY

The subject matter of this application is urolithin A. Amazentis SA's ingredient is a synthetic version of urolithin A that is identical in structure to the compound formed endogenously following consumption of ellagic acid and ellagitannins. Ellagitannins are dietary polyphenols found in various fruits and berries (pomegranate, blackberries, strawberries, raspberries), nuts (walnuts, hazelnuts, acorns, chestnuts, pecans), muscadine grapes, and oak-aged wines and spirits.

Urolithin A is manufactured and purified in several steps to a well-defined and highly pure specification, requiring at least 97% purity. Urolithin A is then micronized to provide a more homogenous compound.

Urolithin A will be used as an ingredient in instant hot breakfast cereals [excluding processed cereal-based foods as defined under Regulation (EU) No 609/2013[1]], cereal bars, protein bars and nutrition bars targeting athletes, flavoured yogurts and yoghurt drinks [excluding baby food as defined under Regulation (EU) 609/2013], calorie/energy reduced puddings for adults, vitamin water, meal replacements for sports people and for weight loss (general weight loss and total diet replacements), nutrition drinks and powders, food supplements, and foods for special medical purposes, excluding products for infants and young children.

The absorption, distribution, metabolism, and excretion of ingested urolithin A was followed by dosing rats with ^{14}C labelled urolithin A. Following a single oral administration, the majority of radioactivity was excreted *via* the faeces; and by 72 hours, approximately all of the administered dose had been excreted in the faeces of males and females. The high levels of excretion in the faeces corresponded with the tissue distribution findings, which demonstrated the majority of the compound to be located in the gastrointestinal tract. During the same period, urinary excretion accounted for 1.3% of the administered dose in males and in females. Plasma concentration of radiolabelled urolithin A (aglycone and metabolites) peaked around three hours and then again around 6 or 7 hours. The glucuronide, sulphated and aglycone forms of urolithin A were major metabolites of urolithin A in both plasma and urine.

Urolithin A was not mutagenic as assessed in the bacterial reverse mutation test, at concentrations up to 5,000 µg/mL. Two independent *in vivo* micronuclei assays in rats were performed, following inconsistent results in the *in vitro* micronucleus assay. In both *in vivo* studies, no increase in micronuclei formation was observed following urolithin A treatment, neither with short-term dosing nor following 90-day dosing. The weight of evidence demonstrates the absence of genotoxic risk following systemic exposure to urolithin A.

The safety of urolithin A was investigated in a series of preclinical and clinical studies, which support the safety for its intended uses. Repeated dose 28-day and 90-day safety studies of urolithin A in rats did not demonstrate any toxicological effect in any of the parameters measured at all doses tested. Concentrations of urolithin A were administered at the highest levels achievable in the diet that would not affect food consumption and diet palatability (5% of diet). Treatment for up to 90 days with urolithin A did not result in any signs of reproductive or neurological toxicities in enhanced screening phases of repeated dose studies including analysis of spermatogenesis or oestrus cycles, ophthalmoscopic examinations, functional observatory battery screen, and motor activity assessments. The no-observed-adverse-effect level (NOAEL) was the highest dose tested, 5% urolithin A by weight in the diet, or 3,451 mg/kg body weight/day in males and 3,826 mg/kg body weight/day in females.

[1] Regulation (EU) No 609/2013 of the European Parliament and of the Council of 12 June 2013 on food intended for infants and young children, food for special medical purposes, and total diet replacement for weight control and repealing Council Directive 92/52/EEC, Commission Directives 96/8/EC, 1999/21/EC, 2006/125/EC and 2006/141/EC, Directive 2009/39/EC of the European Parliament and of the Council and Commission Regulations (EC) No 41/2009 and (EC) No 953/2009. OJ L 181, 29.6.2013, p. 35-56.

Using individual-based data from the United Kingdom (UK) National Diet and Nutrition Survey (NDNS) Rolling Programme (Years 1 to 6 [2008-2014]), it was determined that the estimated intake of urolithin A in the target population (*i.e.*, 18 years and over) was 6.0 and 16.2 mg/kg body weight/day at the mean and 95th percentile, respectively. In foods for particular nutritional use, whereby the foods would not be consumed as part of the normal diet (*i.e.*, they would replace entire meals or the entire diet, or would be consumed as part of a medically supervised diet), intakes based on the daily dose of 1,000 mg/day and default body weights were estimated to range between 13.2 and 14.0 mg/kg body weight/day in the target population. Thus, the margin of safety between the lowest NOAEL derived in the 90-day rat study (*i.e.*, 3,451 mg/kg body weight/day) and the highest estimated daily intake of urolithin A in the target population from the proposed conditions of use ranges from 213-fold (95th percentile intakes from conventional foods) to 261-fold (foods for particular nutritional use).

The totality of the presented data, including thorough safety assessments, highlights the safety and suitability of this ingredient for its proposed food uses.