7800000G – ENERGEN™

Version: 23 - 22/DEC/2015

1. PRODUCT IDENTIFICATION

Trade Name:	ENERGEN™
Manufacturer:	PROVITAL
Responsible for the Safety Assessment:	Lourdes Mayordomo
Tf./Fax:	3493-7192350/7190294
e-mail:	l.mayordomo@provitalgroup.com
Kind of Raw Material:	Active Ingredient
Function of the Ingredient (PCPC Inventory):	Skin-Conditioning Agents - Miscellaneous, Adhesives, Viscosity Increasing Agents - Aqueous
Function of the Ingredient (UE Inventory):	Film Forming, Skin Conditioning, Viscosity Controlling
INCI approved in:	Registered in EU, USA, Japan
Japanese Name:	JCLS: --- Japanese translation available in PCPC.

2. PRODUCT COMPOSITION

Components Breakdown (INCI). Including actives, solvents, preservatives, antioxidants and other additives:

[EU]		CAS	EINECS
Glycerin	40 - 60 %	56-81-5	200-289-5
Aqua	40 - 60 %	7732-18-5	231-791-2
Sapindus Mukorossi Fruit Extract	1 - 2,5 %	---	---
Caesalpinia Spinosa Gum	1 - 2 %	39300-88-4	254-409-6
Preservatives			
Potassium Sorbate	0,2 - 0,3 %	24634-61-5 590-00-1	246-376-1
Sodium Benzoate	0,2 - 0,3 %	532-32-1	208-534-8

PCPC [CTFA]		CAS	EINECS
Glycerin	40 - 60 %	56-81-5	200-289-5
Water	40 - 60 %	7732-18-5	231-791-2
Sapindus Mukorossi Fruit Extract	1 - 2,5 %	---	---
Caesalpinia Spinosa Gum	1 - 2 %	39300-88-4	254-409-6
Preservatives			
Potassium Sorbate	0,2 - 0,3 %	24634-61-5 590-00-1	246-376-1
Sodium Benzoate	0,2 - 0,3 %	532-32-1	208-534-8

Impurities:

Heavy Metals (as Pb)	Less than 20 ppm.
Pesticides	No data available. Not expected to be found.

3. TOXICOLOGICAL INFORMATION

Data obtained in our own toxicological tests and/or bibliographical research

Animal testing:

This product has not been the subject of animal testing or retesting for cosmetic purposes by or on behalf of this

company.

General information:

Caesalpinia spinosa gum has been approved for use as a food ingredient by the Joint FAO/WHO Expert Committee on Food Additives, and this committee assigned a _not specified_ value for the acceptable daily intake (ADI) by man. This means that use of tara gum as a food substance does not represent a human health hazard, and, therefore, the establishment of an ADI in mg/kg body weight was not deemed necessary. (WHO Food Additives Series 21)

The Cosmetic Ingredient Review (CIR) Expert Panel concluded that the cosmetic ingredient Caesalpinia spinosa gum is safe in the present practices of use and concentration described in this safety assessment. (CIR Final Report on the Safety Assessment of Galactomannans as used in Cosmetics, March 6, 2012)

The CIR Expert Panel concluded that glycerin is safe in the practices of use and concentration described in the Safety Assessment of Glycerin as Used in Cosmetics, Final Report, December 2014, which include the toxicological data.

The following substances have the GRAS status ('Generally Recognized As Safe'): Glycerin (21CFR182.1320)

The CIR Final Report on Safety Assessment of Potassium Sorbate (JACT 7 (6): 837-80, 1988, confirmed 04/06) exists and includes all the toxicological data.

The CIR Final Report on Safety Assessment of Sodium Benzoate (IJT, 20(S3):23-50, 2001, reopened 06/10) exists and includes all the toxicological data.

Classification according to Council of Europe (*):

Non-classified.

*(1)- Non-recommended ingredients (2)-Ingredients which could not be assessed (3) –Recommended ingredients

Cytotoxicity:

ENERGEN (Cod. 7800): Neutral Red Release Assay performed using SIRC cell line. Results: CI50>50%, % of mortality at dilution 50% = 17%. Negligible cytotoxicity.

Saponins isolated from the fruits of Sapindus mukorossi didn't reported cytotoxic activity for platelets as assayed by lactate dehydrogenase (LDH) leakage. (J Nat Prod. 2006 May; 69 (5):763-7)

Sapindus mukorossi extracts tested at the doses of 10, 50 and 100 ug/ml didn’t caused cytotoxicity in primary hepatocytes monolayer cultures. (World J Gastroenterol. 2008; 14(6): 2566-2571)

Skin Irritation:

ENERGEN (Cod.78000): Patch Test on 10 volunteers, occlusive patch for 48 hours, product tested at 25%. Index of Primary Cutaneous Irritation = 0. The clinical cutaneous compatibility of this product may be judged "VERY GOOD"

The skin irritation potential of Caesalpinia spinosa gum was evaluated using rabbits NZW (3 males, 3 females). The gum (0.5 g/test site) was moistened with saline and applied to shaved, intact skin. Test sites were covered with a semi-occlusive wrap for 4 h. Reactions were scored according to the Draize scale at 4.5 h, 24 h, 48 h, and 72 h. Caesalpinia spinosa gum was non-irritating to the skin of rabbits. (CIR Final Report on the Safety Assessment of Galactomannans as used in Cosmetics, March 6, 2012)

Glycerin (RTECS no. MA8050000): Draize Test in the skin of rabbit, 500 mg, 24h, mild.

Glycerin (50% in water) was not irritating to subjects with dermatitis (n=420) when administered for 20-24h under occlusion. (Safety Assessment of Glycerin as Used in Cosmetics, Final Report, December 2014)

Skin Sensitization:

ENERGEN (Cod. 78000). Marzulli and Maibach's Method: Human Repeated Insult Patch Test. Study on 53 volunteers, product testes at 25%. No pathological irritation or sensitisation reaction significant of cutaneous intolerance was noted.

In a sensitization study, natural and synthetic glycerin were not sensitizing to white male guinea pigs (n=12). A moisturizer containing glycerin (65.9%) was not sensitizing in a modified Draize test (n=48). There was no reaction during either the induction or challenge phase. (Safety Assessment of Glycerin as Used in Cosmetics, Final Report, December 2014)

Eye Irritation:

ENERGEN (Cod. 78000): The Hen's Eggs Test on the Chorioallantoic Membrane (HET-CAM), product tested at 25%, Mean Irritation Index = 2.5. The trial product can be considered as WELL TOLERATED at the ocular level.

Glycerin (RTECS no. MA8050000): Draize Test eye rabbit = 500 mg/24h, mild.

Mutagenicity:

ENERGEN (Cod. 78000): Genic Mutation Bacteria In Vitro Test (Ames Test), using 5 strains of Salmonella

typhimurium (TA1535, TA1537, TA98, TA100 and TA102), both in the presence and absence of metabolic activation system (S-9). The product was tested at five dose levels between 0.00156 and 0.025 mg/plate. No significant increase in the number of revertants was noted in any of the strains. The trial product can be considered as: No mutagenic.

In bacterial and mammalian assays Caesalpinia spinosa gum was not found to be genotoxic. In the Ames test the gum up to 1,000 µg/plate ± metabolic activation caused no significant increase in revertant number. The micronucleous test in mice at a dose of 350 mg/kg showed also negative results. (CIR Final Report on the Safety Assessment of Galactomannans as used in Cosmetics, March 6, 2012)

Glycerin was not genotoxic in multiple Ames tests using multiple strains of Salmonella typhimurium up to 50mg/plate. It was not genotoxic in a cytogenetic assay, in a HGPRT assay, sister chromatid exchange assay using CHO cells, unscheduled DNA synthesis assay using rat hepatocytes, or a in vitro chromosome aberration test using CHO cells, up to 1.0mg/mL was tested in these studies. (Safety Assessment of Glycerin as Used in Cosmetics, Final Report, December 2014)

Moreover in two in vivo chromosome aberration assays, glycerin was not genotoxic when administered orally to rats at 1mg/kg or by injection into the abdomen at 1000/mg/kg. (Safety Assessment of Glycerin as Used in Cosmetics, Final Report, December 2014)

Acute toxicity:

Saponin, from Sapindus mukorossi (RTECS no. VQ1497500, Last Updated: 199806): LD50 p.o. mouse > 2821 mg/kg, LD50 i.p. mouse = 81 mg/kg

Sapindoside A (RTECS no. RK0177800, Last Updated: 199812): LD50 p.o. mouse > 4 g/kg, LD50 i.p. mouse = 1800 mg/kg

Tara Gum (RTECS nºMG1017000): LD p.o. rat and mice > 630 mg/kg

Glycerin (RTECS no. MA8050000): TDLo oral in human = 1428 mg/kg.

Glycerin (RTECS no. MA8050000): LD50 in rat: p.o. = 12600 mg/kg, i.p. = 4420 mg/kg, s.c. = 100 mg/kg, i.v. = 5566 mg/kg. LDLo in rat i.m. = 10 mg/kg, TDLo in rat i.m. = 5 g/kg.

Glycerin (RTECS no. MA8050000): LD50 oral mouse = 4090 mg/kg, LD50 i.p. mouse = 8700 mg/kg, LD50 s.c. mouse = 91 mg/kg, LD50 i.v. mouse = 4250 mg/kg, LD50 oral rabbit = 27 g/kg, LD50 i.v. rabbit = 53 g/kg, TDLo i.m. rat = 4 mL/kg, TDLo i.m. rat = 4000 mg/kg.

Subchronic and chronic toxicity:

Tara Gum (RTECS nºMG1017000): TDLo p.o. rat = 70 g/kg/14 D-C; TDLo p.o. mouse =168 g/kg/14 D-C; TDLo p.o.rat=1081500 mg/kg/103W-C; TDLo p.o. mouse =2163000 mg/kg/103W-C

In a 90-day oral feeding study, 50 rats of each sex were fed diets containing 0, 1, 2, or 5% Caesalpinia spinosa gum. There were no treatment-related differences in clinical chemistry parameters between the control group and any group fed Caesalpinia spinosa gum in the diet. Results of gross and microscopic examination of tissues were not indicative of changes related to Caesalpinia spinosa gum in the diet. (CIR Final Report on the Safety Assessment of Galactomannans as used in Cosmetics, March 6, 2012)

Groups of 10 F344 rats and 10 B6C3F1 mice of each sex were fed diets containing 0, 0.31, 0.63, 1.25, 2.50, or 5.0% Caesalpinia spinosa gum for 13 weeks. None of the mice or rats in any of the groups died during the feeding period. (CIR Final Report on the Safety Assessment of Galactomannans as used in Cosmetics, March 6, 2012)

Purebred Beagle dogs (3 per sex) were fed experimental diets containing 1% or 5% Caesalpinia spinosa gum for 90 days. No behavioural changes were reported, and hematological, urinalysis, and clinical chemistry results were unremarkable. There also were no gross or microscopic findings that were related to feeding with diets containing Caesalpinia spinosa gum. (CIR Final Report on the Safety Assessment of Galactomannans as used in Cosmetics, March 6, 2012)

Glycerin (RTECS no. MA8050000): TDLo oral rat = 96 g/kg/30d-I, TDLo oral mouse = 560 g/kg/8w-C, TDLo oral mouse = 2800 mg/kg/25w-C.

The NOAEL of glycerin in rats was between 115 and 2300 mg/kg when orally administered in water for 44days.The NOEL in dogs was 950 when orally administered for 3 days. (Safety Assessment of Glycerin as Used in Cosmetics, Final Report, December 2014)

In repeated dose toxicity studies with humans there were no signs of toxicity or effects on blood or urine production when subjects (n=14) were orally administered glycerin (1.3 - 2.2 g/kg/day) for 50 days.(Safety Assessment of Glycerin as Used in Cosmetics, Final Report, December 2014)

There were no treatment effects when glycerin (100%; 0.5 - 4mL) was administered to 30% of the body surfaces of rabbits for 45 weeks.(Safety Assessment of Glycerin as Used in Cosmetics, Final Report, December 2014)

The inhalation NOAEL was 0.167 for glycerin administered nose only for 5h/day, 5day/week for 13 weeks in rats.

(Safety Assessment of Glycerin as Used in Cosmetics, Final Report, December 2014)

Reproductive effects:

A multigeneration reproduction study on Caesalpinia spinosa gum was performed using groups of CD rats. The gum was administered to male and female rats at a dietary level of 5% through 3 successive generations. Litters were maintained until the end of lactation, at which time they were at least 21 days old. There were no consistent, statistically significant test substance-related adverse effects on any of the parameters evaluated. It was concluded that Caesalpinia spinosa gum did not have an adverse effect on reproductive performance or development of progeny. (CIR Final Report on the Safety Assessment of Galactomannans as used in Cosmetics, March 6, 2012)

The teratogenicity and embryotoxicity of Caesalpinia spinosa gum was evaluated in rats. Groups of 25 rats were fed with diets containing 0, 1.25%, 2.5% or 5% of the gum from days 6 to 16 of gestation. None of the animals died and there were no statistically significant differences in food consumption, body weight gain, general health, or behaviour between dams of control group and those that received the treatment. There was no evidence of test substance-related abnormalities after external, visceral, and skeletal examinations of fetuses were performed. Additionally, there were no differences in the sex ratios of fetuses or statistically significant differences in fetal body weights. It was concluded that Caesalpinia spinosa gum did not induce maternal toxicity, embryotoxicity, or teratogenicity. Based on results from this study and the preceding study, the NOAEL was considered to be > 5% in the diet (CIR Final Report on the Safety Assessment of Galactomannans as used in Cosmetics, March 6, 2012)

In a two-generation reproductive study in rats (n=10/sex), the administration of glycerin (0,20%; 2000mg/kg/day in drinking water) for 8 weeks before mating until weaning of pups produced no adverse effects on the reproductive efficiency of the parents (F0) or the development of the offspring (F1). (Safety Assessment of Glycerin as Used in Cosmetics, Final Report, December 2014)

When glycerin was administered orally to rats and mice on days 6 through 15 of gestation, there were no adverse effects observed in the dams. The NOAEL for maternal toxicity and teratogenicity was 1310 mg/kg/d for rats and 1280 mg/kg/d for mice. (Safety Assessment of Glycerin as Used in Cosmetics, Final Report, December 2014)

When glycerin was administered orally to rabbits (n=25) on days 6 through 18 of gestation, there were no adverse effects found in the dams. The NOAEL for maternal toxicity and teratogenicity was 1180 mg/kg/d. (Safety Assessment of Glycerin as Used in Cosmetics, Final Report, December 2014)

Other data:

Sapindus mukorossi has protective effect against experimental liver injury after oral administration in mice treated with carbon tetrachloride (CCl4), acetaminophen (AAP) and thioacetamide (TAA). (Lishizhen Medicine and Materia Medica Research, 2009-08)

Sapindus mukorossi extracts showed hepatoprotective activity in both in vitro and in vivo studies. Doses of 50 and 100 ug/ml showed protective activity in CCl4 damaged primary hepatocytes. Extracts at 2.5 mg/ml were found to have protective properties in rats with CCl4 induced liver damage. (World J Gastroenterol. 2008; 14(6): 2566-2571)

Tara Gum: Study in 50 F344 rats and 50 B6C3F1mice for 103 weeks at doses of 2.5% and 5% in diet. Product was not carcinogenic (Natl Toxicol Program Tech Rep Ser. 1982, 224:1-106)

4. ECOLOGICAL DATA

Biodegradability:

Glycerin (HSDB no. 492, revision: 20050624): Activated sludge test: 220 mg/l resulted in a COD of 97%; Test in a 5 days: BOD = 82%. Glycerin is considered an easily degradable substance.

Aquatic Toxicity:

Glycerin (HSDB no. 492, revision: 20050624): LC50 goldfish > 5000 mg/l/24h.

Glycerin: Multiplication inhibition test in algae (Microcystis aeruginosa) and protozoa (Entosiphon sulcatum): Toxicity threshold = 2900 mg/l and 3200 mg/l (HSDB no. 492, revision: 20050624).

Other data:

No data available.

5. CONCLUSION

The European cosmetics legislation (Regulation (EC) No 1223/2009) establishes the need to assess the safety of cosmetic products, taking into account the toxicological profile of the ingredients. To do this, in the case of possible systemic effects, it is necessary to obtain the NOAEL (no observed adverse effects level) for the calculation of MoS (margin of safety). The absence of these considerations shall be duly justified.

The NOAEL value, or else other data used for the same purpose (LOAEL, LD50, etc.), can only be calculated experimentally from toxicological studies that require the use of animals. Since Provital does not perform any animal testing, it has established a system to ensure the safety of its products without the need of NOAEL and the subsequent calculation of MoS. This systematic, in the case of natural complex substances (NCS) has been endorsed by international organisms and renowned toxicologists.

The safety of this ingredient is then established based on the following information: known uses of the active in different fields (medicine, food, cosmetics, etc.), profile of the chemical compounds of the ingredient and bibliographic toxicological information available for the active and its components. The integration and study of all these data allows for a conclusion on the safety of the ingredient.

The components of this product have registered adverse effects neither in its described uses nor in the historical marketing of this company. These data and the available toxicological information lead to the conclusion that the use of this product, under the normal conditions of cosmetic use, involves no risk for consumers.